

**DECLARATION IN SUPPORT OF A CONVENTION
APPLICATION FOR A PATENT OR PATENT OF ADDITION**

(1) Here insert (in full) Name or Names of Applicant or Applicants

In support of the Convention Application made by⁽¹⁾.....
L'OREAL

(2) Here insert title of Invention.

for a patent..... for an invention entitled:⁽²⁾
COSMETIC OR PHARMACEUTICAL COMPOSITION BASED ON AN
AQUEOUS DISPERSION OF LIPIDIC SPHERULES

$\frac{I}{We}$ ⁽³⁾..... ANDRE VIOUT,

of⁽³⁾..... 14, rue Royale, 75008, Paris, FRANCE

(3) Here insert (in full) Address or Addresses

do solemnly and sincerely declare as follows:

1. $\frac{I}{We}$ am are the applicant for the patent.

2. The basic application as defined by Section 141 of the Act was.....
made in⁽⁴⁾..... France

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

on the..... 22nd..... day of..... April,..... 1986, by
..... L'OREAL

on the..... day of..... 19....., by

3. $\frac{I}{We}$ am are the actual inventors of the invention referred to in the basic application or

(5) Here insert full Name(s) and Address(es) of actual Inventor(s) if other than Applicant(s).

3.⁽⁵⁾..... Rose-Marie HANDJANI, of 24-26, rue de Cotentin,
75015 Paris, France and Alain RIBIER, of 16, rue Caffarelli,
75003 Paris, France

the actual inventors of the invention and the facts upon which $\frac{I}{We}$ am are entitled to make the application, are as follow:

(6) Full Name of actual Inventor or Inventors.

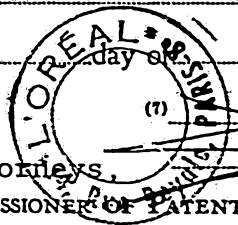
$\frac{I}{We}$ am are the assignee of the said⁽⁶⁾..... actual inventors

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at..... Paris

this..... 23rd..... day of..... November,..... 1989

(7) Signature of Applicant or Applicants.



ANDRE VIOUT

(12) PATENT ABRIDGMENT **(11) Document No. AU-B-72857/87**
(19) AUSTRALIAN PATENT OFFICE **(10) Acceptance No. 597361**

(54) Title
DISPERSION OF LIPIDIC SPHERULES

International Patent Classification(s)
(51)⁴ A61K 007/00 A61K 009/50

(21) Application No. : 72857/87 (22) Application Date : 17.04.87

(87) WIPO Number : WO87/06460

(30) Priority Data

(31) Number	(32) Date	(33) Country
86 05776	22.04.86	FR FRANCE

(43) Publication Date : 24.11.87

(44) Publication Date of Accepted Application : 31.05.90

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(56) Prior Art Documents
AU 580805 49006/85 A61K 009/50, 007/48, 031/785
WO 04880/85
EP 120722

(57) Claim

1. Cosmetic or pharmaceutical composition consisting of a dispersion, in an aqueous medium D, of lipidic spherules constituted by organized molecular layers encapsulating an aqueous phase E, the constituent lipid(s) of the said layers being ionic or nonionic amphiphiles, which is characterized in that the lipidic phase itself of the said spherules is combined with at least one lipoprotein free from any sulphhydryl functional group and chosen from mono- or polyacylated derivatives of amino acids or of polypeptides in which the acyl residue R-CO contains a C₁₃-C₁₉ hydrocarbon chain R, at least one of the functional groups which connects the polypeptide chain or the amino

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(10) 597361

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acid residue to the lipophile chain being an amide functional group, it being possible for the carboxylic functional groups of the polypeptide chain or of the amino acid residue to be partially or completely neutralized by one or more alkali metal cations, or an ammonium ion or substituted ammonium ion derived from an amine, the said lipo-protein(s) being present in a proportion of 1 to 15% by weight relative to the total weight of the said lipidic phase itself.



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DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(51) Classification internationale des brevets⁴ : A61K 7/00, 9/50	A1	(11) Numéro de publication internationale: WO 87/ 06460 (43) Date de publication internationale: 5 novembre 1987 (05.11.87)
(21) Numéro de la demande internationale: PCT/FR87/00128 (22) Date de dépôt international: 17 avril 1987 (17.04.87) (31) Numéro de la demande prioritaire: 86/05776 (32) Date de priorité: 22 avril 1986 (22.04.86) (33) Pays de priorité: FR (71) Déposant (pour tous les Etats désignés sauf US): L'OREAL [FR/FR]; 14, rue Royale, F-75008 Paris (FR). (72) Inventeurs; et (75) Inventeurs/Déposants (US seulement) : HANDJANI, Rose-Marie [FR/FR]; 24-26, rue du Cotentin, F-75015 Paris (FR). RIBIER, Alain [FR/FR]; 16, rue Caffarelli, F-75003 Paris (FR). (74) Mandataire: PEUSCET, Jacques; Cabinet Peuscet, 68, rue d'Hauteville, F-75010 Paris (FR).	(81) Etats désignés: AU, BE (brevet européen), CH, GB, IT (brevet européen), JP, NL, US. Publiée <i>Avec rapport de recherche internationale.</i> <div data-bbox="877 638 1268 795" style="border: 1px solid black; padding: 5px; text-align: center;"> This document contains the amendments made under Section 49 and is correct for printing. </div> <div data-bbox="933 840 1292 929" style="text-align: center;"> AU-LE 17 DEC 1987 </div> <div data-bbox="917 918 1228 1120" style="border: 1px solid black; padding: 5px; text-align: center;"> AUSTRALIAN 2 4 NOV 1987 PATENT OFFICE </div>	
(54) Title: DISPERSION OF LIPIDIC SPHERULES (54) Titre: DISPERSION DE SPHERULES LIPIDIQUES (57) Abstract <p>Cosmetic or pharmaceutical composition consisting of a dispersion in an aqueous medium D of lipidic spherules to the lipidic phase of which there is associated at least one lipoprotide free of sulphhydryle function selected amongst the mono- or polyacylated derivatives of amino acids or of polypeptides, wherein the acyle residue R-CO comprises a C₁₃-C₁₉, hydrocarbonated chain R, at least one of the functions which connects the polypeptidic chain or the amino acid residue to the lipophilic chain being an amide function, the carboxylic functions of the polypeptidic chain or of the amino acid residue being partially or completely neutralized by means of one or a plurality of alkaline cations, an ammonium ion or a substituted ammonium derived from an amine, said lipoprotide or lipoprotides being present in a ratio from 1 to 15% by weight based on the total weight of said lipidic phase.</p> (57) Abrégé <p>Composition cosmétique ou pharmaceutique consistant en une dispersion dans un milieu aqueux D, de sphérules lipidiques dont la phase lipidique est associée au moins un lipoprotide exempt de fonction sulfhydryle choisi parmi les dérivés mono- ou polyacylés d'amino-acides ou de polypeptides, dans lesquels le reste acyle R-CO comporte une chaîne hydrocarbonée R en C₁₃-C₁₉, au moins une des fonctions qui relie la chaîne polypeptidique ou le reste d'amino-acide à la chaîne lipophile étant une fonction amide, les fonctions carboxyliques de la chaîne polypeptidique ou du reste d'amino-acide pouvant être partiellement ou totalement neutralisées par un ou plusieurs cations alcalins, un ion ammonium ou un ammonium substitué dérivé d'une amine, ledit (ou lesdits) lipoprotide(s) étant présent(s) à un taux de 1 à 15% en poids par rapport au poids total de ladite phase lipidique propre.</p>		

DISPERSION OF LIQUID SPHERULES

The present invention relates to a composition for cosmetic use consisting of an aqueous dispersion of lipidic spherules.

5 It is known that certain lipids have the property of forming, in the presence of water, mesomorphic phases whose organization state is intermediate between the crystalline state and the liquid state. Among the lipids which give rise to mesomorphic phases it has already been
10 indicated that some can swell in aqueous solution to form spherules dispersed in the aqueous medium, these spherules consisting of multimolecular layers and preferably bimolecular layers.

Dispersions of lipidic spherules have already been
15 described in French Patent No. 2,315,991; these spherules are characterized by their leaflet structure consisting of a plurality of lipidic layers separated from each other by aqueous phase layers; they may thus be used to encapsulate water-soluble active substances in aqueous compartments included between the lipidic layers, and to protect
20 them against external conditions. The lipidic compounds which can be employed for forming such spherules may be ionic compounds, in which case liposomes are obtained, or nonionic compounds, in which case niosomes are obtained.

25 French Patents No. 2,485,921 and 2,490,504 have also described compositions consisting of an aqueous dispersion of spherules of the abovementioned type with a



dispersion of oil provided for in their outer aqueous phase. It has been found that, surprisingly, the presence of lipidic spherules made it possible to stabilize the dispersion of oil and that, in addition, a combined effect of the spherules and of the droplets of oil was obtained with such compositions.

French Patent Number 2,543,018, provides, furthermore, a process for the preparation of unilamellar lipidic vesicles having a mean diameter greater than 1,000 Å.

10 It will be stressed here that the aqueous dispersions of lipidic vesicles are of very particular interest in cosmetics, where they offer a considerable advantage when compared with the well-known use of emulsions, because they make it possible precisely to avoid the simultaneous use of an emulsifier and of an oil, a combination
15 which may be irritant to the skin. Furthermore, they make it possible to introduce hydrophilic substances into an essentially lipophilic medium, giving rise to a protective action of these substances in respect of various possible agents of change, such as oxidizing agents.
20

When liposomes or niosomes are prepared, various additives may be combined with the ionic or nonionic lipidic compounds, in order to modify the permeability or the surface charge of the spherules. A certain number
25 of these additives have been mentioned in this connection in the abovementioned French patents. It is known that the incorporation of molecules carrying electrical charges



in the walls of the vesicles, liposomes or niosomes affects the properties of these multilayers. The role of the charged lipids is to improve the stability of the vesicles by preventing their flocculation and, consequently, their fusion, even in the presence of electrolytes, and to permit the increase in the degree of encapsulation of water-soluble substances by increasing the thickness of the aqueous leaflets which separate the lipidic multilayers.

10 In order to improve the topical properties of these lipidic vesicles, it may be considered appropriate to incorporate in the lipidic phase which forms part thereof, compounds which have a beneficial effect on the cutaneous coating, such as polypeptides or compounds containing polypeptide fractions. However, it is known that, as a general rule, polypeptides have a destabilizing effect on the lipidic vesicles, with the inconvenient consequence of an increase in the permeability.

Surprisingly, the Applicant Company has found that the use of a specific group of lipoproteic compounds as additives to the lipidic phase of the spherules leads to the required improvement in the topical effect without the finding of a marked and prohibitive increase in the permeability, provided, however, that a specified range of proportions is adhered to in respect of these lipoproteins.

In parallel with this surprising maintenance of



the encapsulation capacity of lipidic vesicles, the dispersion stability effect is retained.

The lipoproteins according to the invention all have, on the one hand, a lipidic portion by which they are incorporated into the vesicular membrane and, on the other hand, a proteinic part which is directed towards the outside of the said membrane and which will thus be capable, during application to the cutaneous coating or to the hair, of acting directly on these.

The subject of the present invention is therefore the new industrial product constituted by a cosmetic or pharmaceutical composition consisting of a dispersion, in an aqueous medium D, of lipidic spherules constituted by organized molecular layers encapsulating an aqueous phase E, the constituent lipid(s) of the said layers being one or more ionic or nonionic amphiphile(s) which is characterized in that the lipidic phase itself of the said spherules is combined with at least one lipoprotein free from any sulphhydryl functional group and chosen from mono- or polyacylated derivatives of amino acids or of polypeptides in which the acyl residue R-CO contains a C₁₃-C₁₉ hydrocarbon chain R, at least one of the functional groups which connects the polypeptide chain or the amino acid residue to the lipophile chain being an amide functional group, it being possible for the carboxylic functional groups of the polypeptide chain or of the amino acid residue to be, where appropriate, partially or completely



neutralized by one or more alkali metal cations, or an ammonium ion or substituted ammonium ion derived from an amine, the said lipoprotein(s) being present in a proportion of 1 to 15% by weight relative to the total weight
5 of the lipidic phase itself.

In this definition, throughout the description, and in the claims, "lipidic phase itself" is the name given to the quantity of the lipids which constitute the walls of the vesicles.

10 Preferably, the acyl residue(s) of the lipoproteins employed is (or are) chosen from the palmitoyl, myristoyl, stearoyl, oleoyl, linoleoyl and linolenoyl residues.

The proteinic chain of the lipoproteins employed is derived particularly from collagen or from hydroxy-
15 proline.

Among the individual lipoproteins which can be employed for implementing the present invention, there may be mentioned the collagenic palmitoyl lipoamino acid, the O,N-dipalmitoyl derivative of hydroxyproline, hydroxy-
20 proline linoleate, sodium stearoylglutamate, collagen stearoyl tripeptide and collagen oleoyl tetra- and penta-peptide.

The range of proportions which is specified for the lipoproteins (1 to 15% by weight relative to the
25 lipidic phase itself) results from an optimum compromise between obtaining an appreciable cosmetic effect of the lipoproteins introduced and the retention of the

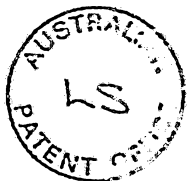


impermeability of the vesicles within acceptable limits. If the proportion of lipoproteins were chosen with a value of less than 1%, the cosmetic effect would no longer be observed. On the other hand, were this proportion to
5 exceed 15%, the permeability of the vesicles would be too high to enable them to be suitably used.

Any of the processes known previously and described may be employed in order to produce the dispersion of the lipidic spherules in the aqueous phase D.

10 It is possible, for example, to employ the process which consists in dissolving the lipids in a volatile solvent, in forming a thin film of lipids on the walls of a flask by evaporating the solvent, in introducing into the said flask the aqueous phase E to be encapsulated and
15 in agitating the mixture mechanically until a dispersion of spherules of the desired size is obtained; in this case, the aqueous phases D and E are necessarily identical.

It is also possible to employ the process described in French Patent No. 2,315,991, which consists
20 in forming a planar lamellar phase by introducing the aqueous phase to be encapsulated E into the liquid lipids at a temperature slightly above the melting temperature of the lipids, in then adding to the lamellar phase obtained an aqueous dispersion phase D, which may be identical or
25 not identical with the aqueous phase E, and in agitating vigorously, for example mechanically, in order to produce the conversion of the planar lamellar phase into a



dispersion, in the aqueous phase D, of lipidic spherules encapsulating the aqueous phase E. According to the means employed to produce the dispersion (ultradisperser, homogenizer and/or ultrasonics) and depending on the duration of agitation (from 15 minutes to a few hours), spherules are obtained, whose mean diameter varies approximately from 0.025 to 5 microns.

The abovementioned process is particularly suitable when it is desired to employ multilamellar spherules.

10 In the case where unilamellar spherules are desired, the process described in French Patent Number 2,543,018 may be employed to prepare them; according to this process, the lipids intended to form the leaflet of the vesicles are dissolved in at least one water-insoluble solvent;

15 the lipidic solution in the liquid state is packaged in a receptacle, at a pressure P_1 and at a temperature θ_1 ; the aqueous phase to be encapsulated E is packaged at a pressure P_2 and at a temperature θ_2 , and the lipidic solution is injected into the aqueous phase so that the

20 solvent(s) of the lipidic solution vaporize(s) on coming into contact with the said aqueous phase, the said injection being carried out at a reduced flow rate in order to form droplets initially, the pressure P_2 being lower than the pressure P_1 and lower than the vapour pressure

25 of the solvent(s) in the said droplets at the temperature θ_2 .

The lipoproteins according to the invention may



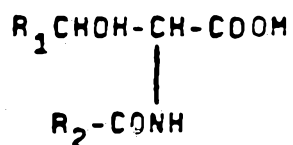
be added at any time before the formation of the vesicles, that is to say, during the passage through the formation of a lamellar phase, either before the preparation of the said lamellar phase, or after.

5 The lipids employed for the preparation of the spherules are ionic or nonionic amphiphiles of natural or synthetic origin comprising, per molecule, one or more linear or branched, saturated or unsaturated, hydrocarbon chain(s) containing particularly from 8 to 30 carbon atoms,
10 such as the oleyl, lanolyl, tetradecyl, hexadecyl, iso-stearyl, lauryl or alkylphenyl chains, and one or more hydrophilic group(s) taken from the hydroxyl, ether, carboxyl, phosphate and amine groups.

 Among the ionic amphiphiles, the use of natural
15 phospholipids (for example egg or soya lecithin or sphingomyelin), or of synthetic phospholipids (for example dipalmitoylphosphatidylcholine or hydrogenated lecithin) is preferred; it is also possible to employ amphoteric compounds containing two lipophile chains or a combination
20 of two long-chain organic ions of opposite signs, as well as anionic compounds.

 Among the anionic compounds, mention will be made of those described in the Luxembourg Patent Application No. 85/971 filed on 23 June 1985 and represented by the
25 formula:





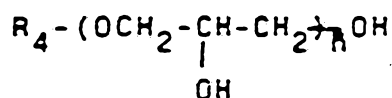
in which formula:

- R₁ denotes a C₇-C₂₁ alkyl or alkenyl radical;
- R₂ denotes a C₇-C₃₁ saturated or unsaturated hydro-
5 carbon radical; and
- M denotes H, Na, K, NH₄ or a substituted ammonium ion derived from an amine.

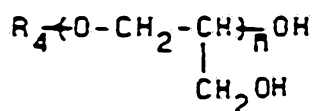
The anionic compounds defined in the preceding paragraph may be obtained by the preparative process re-
10 ferred to in French Patent Application 2,588,256.

In the case of the nonionic amphiphiles it is preferred that the hydrophilic groups should be polyoxy-
ethylenated or polyglycerolated groups, or groups derived
from esters of polyols, oxyethylenated or otherwise, or
15 else hydroxyamide derivatives. Advantageously, these nonionic lipidic compounds are chosen from the group consisting of

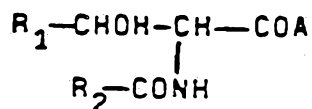
- linear or branched polyglycerol ethers, of formulae:



and



- respectively, \bar{n} being a mean statistical value of between 1 and 6, R_4 being a saturated or unsaturated, linear or branched aliphatic chain containing from 12 to 30 carbon atoms, the hydrocarbon radicals of Lanolin alcohols or the
- 5 2-hydroxyalkyl residues of long-chain α -diols;
- linear or branched polyglycerol ethers containing two fatty chains;
 - polyoxyethylenated fatty alcohols;
 - polyoxyethylenated sterols;
- 10 - polyol ethers;
- esters of polyols, oxyethylenated or otherwise and, in particular, polyoxyethylenated sorbitol esters;
 - glycolipids of natural or synthetic origin, for example cerebroside;
- 15 - hydroxyamides such as those described in Luxembourg Patent Application No. 85/971 filed on 23 June 1985 and represented by the formula:



in which formula:

- 20 - R_1 denotes a C7-C21 alkyl or alkenyl radical;
- R_2 denotes a C7-C31 saturated or unsaturated hydrocarbon radical;
 - COA denotes a group chosen from the following two groups:



- a residue CON-B
|
 R_3

B being a radical derived from mono- or poly-hydroxylated primary or secondary amines and

5 R_3 denoting a hydrogen atom or a methyl, ethyl or hydroxyethyl radical;

- COOZ , Z denoting the residue of a C_3 - C_7 polyol.

In a known manner, various other additives may be combined with the lipidic compounds in order to modify
10 the permeability of a surface charge of the spherules.
In this connection, mention will be made of the optional addition of long-chain alcohols and diols, of sterols, for example cholesterol and β -sitosterol, of long-chain amines, of hydroxyalkylamines, of polyoxyethylenated
15 fatty amines, of long-chain aminoalcohol esters, of their salts, of phosphoric esters of fatty alcohols, for example sodium dicetylphosphate and of alkylsulphates, for example sodium cetylsulphate, and of ionic derivatives of sterols.

From 0.5 to 25% by weight of amphiphile(s) relative to the total weight of the dispersion of spherules
20 to be obtained may be advantageously employed to form the dispersion of spherules.

Arrangements may be made for the walls of the spherules to contain at least one active liposoluble substance such as, for example, a keratolytic agent such as
25 retinoic acid, or an anti-inflammatory agent such as β -methasone 17-valerate, or else an antioxidant such as



vitamin E and its acetate or ascorbyl palmitate, which is of particular interest when topical applications are envisaged.

It is also possible to arrange for the aqueous phase E to be encapsulated in the spherules to be an aqueous solution of active substance, preferably isoosmotic relative to the phase D of the dispersion. The D and E phases may be identical.

The aqueous phase E encapsulated in the spherules or the outer aqueous phase D contains, for example, at least one water-soluble cosmetic substance taken from the group consisting of humectants such as glycerine, sorbitol, pentaerythritol, inositol, pyrrolidonecarboxylic acid and its salts; artificial tanning agents such as dihydroxy acetone, erythrulose, glyceraldehyde, γ -dialdehydes such as tartaric aldehyde, optionally combined with other skin-colouring agents; antisolar agents, antiperspirants, deodorants, astringents; freshening, tonic, cicatrizing, keratolytic or depilatory products; extracts of animal or plant tissues; perfumed waters, water-soluble colorants, antidandruff agents, antiseborrhoeic agents, oxidizing agents such as hydrogen peroxide, and reducing agents such as thioglycolic acid and its salts.

In the case of a composition which may be employed in pharmacy, the aqueous phase E encapsulated in the spherules or the outer aqueous phase D preferably contains at least one product taken from the group consisting of



vitamins, hormones, enzymes, such as superoxide dismutase, vaccines, antiinflammatories such as hydrocortisone, antibiotics and bactericides.

Provision may also be made for the aqueous phase
5 D surrounding the spherules to contain at least one water-immiscible liquid phase L dispersed in the said aqueous phase D. This water-immiscible liquid phase L may be an oil or a constituent taken from the group consisting of hydrocarbons, halogenated hydrocarbons, polysiloxanes,
10 organic acid esters, ethers and polyethers. Advantageously, the quantity of water-immiscible liquid phase L dispersed in the aqueous phase D is between 2 and 70% by weight relative to the total weight of the composition, the relative weight proportion of amphiphile lipid constituent(s) of spherules relative to the dispersed water-
15 immiscible liquid phase(s) being between 0.02/1 and 10/1.

The oil used in order to be dispersed in the aqueous phase D is advantageously taken from the group consisting of the esters of fatty acids and of polyols,
20 especially liquid triglycerides, and of esters of fatty acids and of branched alcohols of formula R_5-COOR_6 , in which formula R_5 denotes the residue of a higher fatty acid containing from 7 to 19 carbon atoms and R_6 denotes a branched hydrocarbon chain containing from 3 to 20 carbon
25 atoms. In such case, if the oil is an ester of fatty acids and of polyols, it is preferable that it be chosen from the group consisting of sunflower, corn, soya, marrow,



grapeseed, jojoba or sesame oils and glycerol tricapro-
caprylate; if, on the other hand, the oil is a higher
ester of fatty acids and of a branched alcohol, it is
preferable that the said oil be purcellin oil.

5 In order to form the water-immiscible liquid phase
L it is also possible to choose, advantageously, hexa-
decane, liquid paraffin, perhydrosqualene, perfluorotri-
butylamine, perfluorodecahydronaphthalene and volatile
silicone oil.

10 Provision may also be made for the aqueous phase
D, which surrounds the spherules, to contain at least one
adjuvant taken from the group consisting of opacifiers,
gelling agents, flavours, perfumes, sunscreens and color-
ants, it being possible for those of these adjuvants which
15 are liposoluble to be dissolved in the water-immiscible
liquid phase L dispersed in the aqueous phase D, in the
case where such a dispersion is employed.

 If the water-immiscible liquid dispersed and ad-
ded to the continuous aqueous phase which surrounds the
20 spherules is to contain dissolved adjuvants, the dis-
solving of these adjuvants is carried out before the dis-
persion is produced.

 Such adjuvants may be, for example, sunscreens,
such as 2-ethylhexyl para-dimethylaminobenzoate, or sub-
25 stances intended to improve the condition of dry or senile
skins, especially nonsaponifiable materials such as the
nonsaponifiable materials from soya, avocado, tocopherols,



vitamins E and F, and antioxidants.

The dispersion of oil in water which constitutes the outer medium of the dispersion of spherules may contain at least one additive, particularly a gelling agent or a perfume. The additive is added to the dispersion at the same time as the oil. The gelling agent may be introduced at a concentration ranging between 0.1 and 2%, these percentages being expressed on a weight basis relative to the total weight of the composition. Among the gelling agents which may be employed there may be mentioned cellulose derivatives such as hydroxyethyl cellulose, synthetic polymers, seaweed derivatives such as satragum or natural resins such as tragacanth. As gelling agents it is preferable to employ hydroxyethyl cellulose, the crosslinked polyacrylic acid sold by Goodrich under the trade name "Carbopol 940", satragum or else tragacanth.

When a composition containing a dispersion of water-immiscible liquid(s) is produced, it is found that this dispersion is stable without the use of emulsifier.

If the dispersion of spherules contains spherules of a number of types, for example niosomes and liposomes, the two types of spherules are prepared separately and the two dispersions are mixed.

In order to illustrate the subject of the present invention better an indication will now be given of the results of tests demonstrating that the introduction of lipoproteins according to the invention into the lipidic



phase of spherules in dispersion in water maintains a permeability and a degree of encapsulation which are wholly acceptable in the case of these spherules, as long as the upper limit of the specified range of the percentages of these lipoproteins is not exceeded.

5 These tests are summarized in the table below.



TABLE

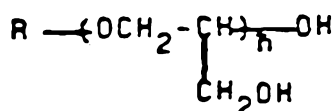
Lipidic phase consisting A, Ch and X, the weight ratio A/Ch being 1/1		Swelling with glucose in μ l per mg of lipidic phase	Permeability (%) after (n) days		
X	Weight percen- tage of X rel- ative to (A+Ch)		(n) = 0	(n) = 8	(n) = 15
B	5	9.1	0	3	8
	10	9.5	0	4	9
	15	8.5	1	9	14
	20 (*)	5.8	13	20	24
C	5	6.2	1	3	6
	10	6.7	1	25	34
	20 (*)	3.5	31	42	57
D	10	11.8	10	16	18
E	10	14.5	5	5	5
F	10	9.6	10	13	14
G	10	9.8	3	11	17

(*) Comparative experiment not forming part of the invention



In this table, the abbreviations A, Ch, B, C, D, E, F and G have the following meanings, respectively:

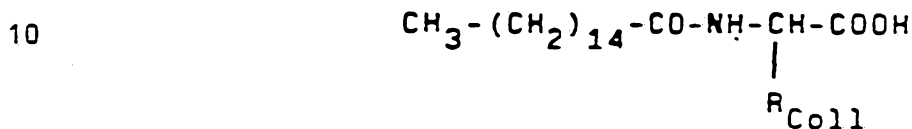
A = Nonionic lipid denoted by the following formula:



5 in which R = C₁₆H₃₃ and n is a mean statistical value equal to 3.

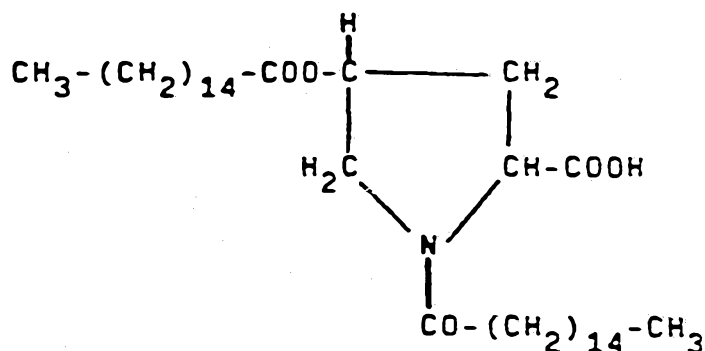
Ch = Cholesterol

B = Collagenic palmitoyl lipoamino acid, denoted by the formula:



in which R_{Coll} is the collagen polypeptide residue, this product being marketed by Rhone-Poulenc under The name "PCo".

15 C = The O,N-dipalmitoyl derivative of hydroxyproline, denoted by the formula:



of molecular weight 607, the lipidic and proteinic fractions representing 79 and 21% by weight respectively, this acid being marketed by Rhône-Poulenc under the name "D.P.H.P."

- 5 D = Hydroxyproline linoleate marketed under the name "Aminoefaderma" by Vevy.
- E = Sodium stearylglutamate marketed by Ajinomoto under the name "Acylglutamate H.S.11"
- F = Collagen stearyltripeptide marketed under the name
10 "Lexein A 200" by Inolex.
- G = Collagen oleoyltetra- and pentapeptide marketed under the name "Lamepon L P0" by Grünau.

A few examples of preparation making use of the invention and a few examples of formulation illustrating
15 the use of the dispersions of spherules according to the invention will be given below.

The preparation of the cosmetic or pharmaceutical formulations given in the examples below is carried out
in 1 or 2 stages.

20 In a first stage, an aqueous dispersion is manufactured according to the process described in French Patent 2,315,991.

The aqueous dispersion of lipidic spherules is prepared from:

- 25 - a nonionic or anionic or amphoteric amphiphile lipid,
- a lipoprotein containing one or more acidic



functional groups which are free or neutralized in the form of salts,

- a sterol, optional, and preferably cholesterol,
 - optional active substances of liposoluble nature
- 5 and/or of water-soluble nature and of demineralized water.

In a second stage, optional, depending on the cosmetic or pharmaceutical nature of the formulation, a water-immiscible liquid phase may be added to the outer medium.

10 It is also possible to add various cosmetic additives such as perfume and gelling agents, for example.

EXAMPLE 1: CARE CREAM FOR DRY SKINS

1st stage of preparation:

The following materials are weighed in a stainless steel beaker:

- nonionic amphiphilic lipid of formula $R-(OCH_2-\underset{\substack{| \\ CH_2OH}}{CH})_{\bar{n}}-OH$

- 20 (in which formula R is a hexadecyl radical and \bar{n} has a mean statistical value equal to 3)..... 3.5 g
- cholesterol..... 3.5 g

The mixture of these two materials is produced by melting at the temperature of 110°C under a nitrogen atmosphere, and then the temperature of the molten mixture is brought down to 80°C. 1 g of the collagenic palmitoyl



lipoamino acid marketed under the reference "PCO" by Rhône-Poulenc, of formula $\text{CH}_3-(\text{CH}_2)_{14}-\text{CO}-\text{NH}-\underset{\text{R}_{\text{coll}}}{\text{CH}}-\text{COOH}$

in which formula R_{coll} is a collagen polypeptide residue, is then added.

After the mixture of the three materials has been homogenized at the temperature of 80°C, 3 g of glycerine dissolved in 20 g of demineralized water are added.

The mixture obtained is homogenized at the temperature of 80°C.

The following materials are then added:

- methyl para-hydroxybenzoate
(stabilizer)..... 0.3 g
- demineralized water..... 22.5 g

The mixture is homogenized at the temperature of 80°C by means of a "Virtis" ultradisperser until the mean size of the vesicles obtained is 0.5 micron.

2nd stage of preparation:

25 g of sesame oil are added to the mixture obtained. The whole is subjected to the action of a "Virtis" ultradisperser until the globules of oil have a mean diameter of about 1 micron.

Lastly, the following materials are added:

- perfume..... 0.4 g
- crosslinked polyacrylic acid sold by Goodrich under the trade name "Carbopol 940"..... 0.4 g



- triethanolamine..... 0.4 g
- demineralized water..... 20.0 g

This cream, applied in topical use once daily in

5 dry-skinned individuals, gives satisfactory results after 20 days' application.

EXAMPLE 2: CARE BASE FOR FINGERNAILS

The following materials are weighed in a stainless steel beaker:

- 10 - nonionic amphiphilic lipid of
 formula P:
$$\text{---}\left(\text{OCH}_2-\underset{\substack{| \\ \text{CH}_2\text{OH}}}{\text{CH}}\right)_{\bar{n}}\text{---OH}$$

 (in which formula R is a hexadecyl radical and \bar{n} has a mean statis-
 15 tical value equal to 3)..... 8.5 g
- cholesterol..... 8.5 g

The mixture of these two materials is produced by melting at the temperature of 110°C under a nitrogen atmosphere, and the temperature of the molten mixture is then
 20 brought down to 70°C and 3 g of sodium stearoyl-glutamate sold by Ajinomoto under the name "Acylglutamate HS11" are added.

After the mixture of the three materials has been homogenized at the temperature of 70°C, 5 g of glycerine
 25 dissolved in 50 g of demineralized water are added. The mixture obtained is homogenized at the temperature of 70°C. The following materials are then added:



- methyl para-hydroxybenzoate
 (stabilizer)..... 0.3 g
- demineralized water..... 24.3 g
- perfume..... 0.4 g

5 The mixture is homogenized at the temperature of 70°C with the aid of a "Virtis" ultradisperser until the mean size of the vesicles obtained is about 0.3 micron.

10 After twice-daily application of the care base for fingernails, at the end of several days, a smoothing and a hardening of the surface of the fingernails are observed.

EXAMPLE 3: CONCENTRATE FOR THE TREATMENT OF IRRITATED SKINS

15 The following materials are dissolved in 200 ml of a solvent mixture (chloroform/methanol in the ratio 2/1) in a 1-litre round-bottomed flask:

- soya lecithin sold under the trade name "Epikuron E 200" by Lukas Meyer..... 12.0 g
- cholesterol..... 4.0 g
- DL- α -tocopherol..... 1.0 g
- hydroxyproline Linoleate (product marketed under the name "Amino-efaderma" by Vevy..... 1.5 g

25 The solvent is evaporated off with a rotary evaporator and the last traces of solvent are removed by



using a rotary pump for one hour. The combination of lipids obtained is placed in contact with 40 g of demineralized water mixed with 3 g of glycerine. The mixture is homogenized at the temperature of 40°C.

5 The following materials are then added:

- methyl para-hydroxybenzoate
(stabilizer)..... 0.3 g
- demineralized water..... 37.5 g
- perfume..... 0.7 g

10 The whole is subjected to the action of an ultra-disperser of the "Virtis" type until the mean size of the vesicles obtained is less than a micron.

The fluid dispersion obtained may be applied to the skin by spraying from a pump bottle.

15 This cream, employed as a topical application twice daily in subjects with an irritated skin affected by acne, reduces the irritation after one or two weeks' application.

EXAMPLE 4: LIPOSERUM FOR HARDENING THE SKIN

20 The following materials are weighed in a stainless steel beaker:

- nonionic amphiphilic lipid of
formula $R-(OCH_2-\underset{\substack{| \\ CH_2OH}}{\bar{n}}}{CH})_n-OH$

25 (in which formula R is a hexadecyl radical and \bar{n} is a mean statistical value equal to 3)..... 5.4 g



- cholesterol..... 5.4 g

The mixture of these two materials is produced by melting at the temperature of 110°C under a nitrogen atmosphere, and then the temperature of the molten mixture is brought down to 75°C and 1.2 g of a collagen stearoyl tripeptide marketed by Inolex under the trade name "Lexein A 200" is added. The mixture is homogenized at the temperature of 75°C.

A part of the aqueous phase consisting of the following is then added:

- glycerine..... 3.0 g

- demineralized water..... 17.0 g

- aqueous solution obtained by grinding animal placental tissues, marketed

by Gattefosse under the trade name

"Phyltherm"..... 20.0 g

The mixture obtained is homogenized at the temperature of 70°C.

The temperature is brought down to 60°C and 20 g of an aqueous solution containing 1% of monomethyl-trisilanol mannuronate sold by Exymol under the trade name "Algisium" are added. The mixture is homogenized at the temperature of 60°C with the aid of a "Vintis" ultra-disperser until the mean size of the vesicles obtained is about 0.5 micron. At this stage of manufacture, the dispersion is cooled to ambient temperature and its pH is adjusted to 5.5 by adding an aqueous 0.1 N sodium



hydroxide solution.

0.15 g of a stabilizer sold by Rohm and Haas under the trade name "Kathon CG", dissolved in 1 g of demineralized water, is then added. 10 g of an aqueous solution containing 5% of bovine serum albumin, marketed by Silab are then added. The mixture obtained is homogenized and 6 g of volatile silicone oil are added. The whole is subjected to the action of an ultradisperser until the globules of oil have a mean diameter of less than a micron.

10 Lastly, the following materials are added:

- polyglucose containing a linear chain sold by Alban Muller under the trade name "Amigel Poudre"..... 0.1 g
- demineralized water.....q.s..... 100 g

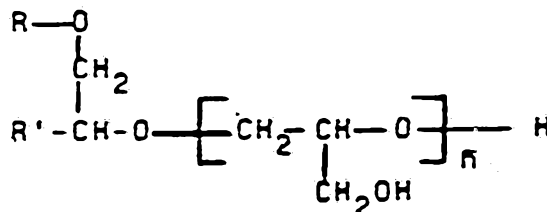
15 After application twice daily for 3 weeks, a hardening of the skin is noted.

EXAMPLE 5: MILK FOR THE CARE OF DRY SKINS

1st stage of preparation:

20 The following materials are weighed in a stainless steel beaker:

a) nonionic amphiphile Lipid of formula:



25 in which:

- R is a dodecyl radical;
- R' is an equimolar mixture of tetradecyl



and hexadecyl radicals; and

- \bar{n} has a mean statistical value determined by nuclear magnetic resonance equal to 5.5..... 7.0 g

5 b) collagenic palmitoyl lipoamino acid marketed under the reference "PCO" by Rhône-Poulenc, of formula $\text{CH}_3-(\text{CH}_2)_{14}-\text{CO}-\text{NH}-\underset{\text{R}}{\text{CH}}-\text{COOH}.....$ 1 g

10 in which R is an amino acid obtained by the hydrolysis of collagen.

After homogenization at 45°C, 3 g of glycerine dissolved in 20 g of demineralized water are added. The mixture obtained is homogenized at 90°C; 0.3 g of methyl para-hydroxybenzoate (stabilizer) dissolved in 37.4 g of 15 demineralized water are then added.

The mixture is homogenized at 40°C by means of a "Virtis" ultradisperser until the mean size of the spherules obtained is 0.2 micron.

20 1.3 g of aqueous normal sodium hydroxide solution are then added with stirring.

2nd stage of preparation:

15.0 g of sesame oil are added. The whole is subjected to the action of the "Virtis" ultradisperser so that the outer phase of the oil dispersion has globules of 25 oil whose mean diameter is about 1 micron.

Lastly, the following materials are added:

- perfume..... 0.4 g



- crosslinked polyacrylic acid sold under the trade name "Carbopol 940" by Goodrich..... 0.4 g
- triethanolamine..... 0.4 g
- 5 - demineralized water..... 13.8 g

This milk, applied in topical use once daily in dry-skinned subjects, gives satisfactory results after two weeks' application.

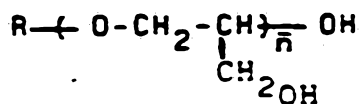
EXAMPLE 6 - CARE CREAM FOR SKINS AFFECTED BY ACNE

10 The whole preparation of this cream was carried out in the yellow light of a sodium vapour lamp.

1st stage of preparation:

The following materials are dissolved in 200 ml of a solvent mixture (chloroform/methanol in the ratio 15 1/1), in a 1-litre round-bottomed flask:

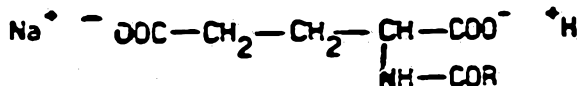
- nonionic lipid of formula:



in which R is a hexadecyl radical and n has a mean statistical value equal to 3..... 3.8 g

- cholesterol..... 3.8 g
- acyl glutamate HS11 marketed by Ajinomoto, of formula:

25



- where R is a stearyl radical..... 0.4 g
- retinoic acid sold by Roche under the trade name "Tretinoine"..... 0.025g

The solvent is evaporated off with a rotary evaporator and the last traces of solvent are removed with a rotary pump for 1 hour.

The combination of lipids obtained is placed in contact with 20.0 g of demineralized water mixed with 3.0 g of glycerine. The mixture obtained is homogenized at 80°C. 0.3 g of methyl parahydroxy-benzoate (stabilizer) dissolved in 38.675 g of demineralized water is then added.

The mixture is homogenized at 60°C by means of a "Virtis" ultradisperser until the mean size of the spherules obtained is about 0.3 micron.

15 2nd phase of preparation:

15 g of glycerol tricaprocaprylate are added.

The whole is subjected to the action of the "Virtis" ultradisperser so that the outer phase of the oil dispersion has oil globules whose mean diameter is about 1 micron.

Lastly, the following substances are added:

- perfume..... 0.4 g
- crosslinked polyacrylic acid sold under the trade name "Carbopol 940" by Goodrich..... 0.4 g
- 25 - triethanolamine..... 0.4 g
- demineralized water..... 13.8 g

This cream, employed in topical application twice



daily in subjects whose skin is affected by acne, enables appreciable improvement to be obtained after two weeks' application.

EXAMPLE 7 - AQUEOUS DISPERSION OF SPHERULES FOR FACE CARE

5 The following materials are weighed in a stainless steel beaker:

- nonionic amphiphile lipid employed in

Example 5..... 5.6 g

- cholesterol..... 1.6 g

10 - collagenic palmitoyl lipoamino acid marketed under the reference "PCO" by Rhône-Poulenc, of formula $CH_3-(CH_2)_{14}-CO-NH-CH-COOH$



in which R is an amino acid obtained by the

15 hydrolysis of collagen..... 0.8 g

After homogenization at 95°C, 5.0 g of glycerine dissolved in 20.0 g of demineralized water are added.

The mixture obtained is homogenized at 95°C.

20 0.3 g of methyl para-hydroxybenzoate (stabilizer), dissolved in 50.7 g of demineralized water, are then added.

The mixture is homogenized at 40°C by means of a "Virtis" ultradisperser until the mean size of the spherules obtained is 0.2 micron. 1.0 g of an aqueous normal sodium hydroxide solution is then added with stir-

25 ring.

Lastly, the following substances are added:

- perfume..... 0.2 g



- crosslinked polyacrylic acid sold under the trade name "Carbopol 940" by Goodrich..... 0.2 g
- triethanolamine..... 0.2 g
- 5 - demineralized water..... 14.4 g

This dispersion, employed in topical application for face care once daily, gives a highly satisfactory result after two weeks' application.

EXAMPLE 8 - VESICULAR CORTICOID PREPARATION

10 The following materials are weighed in a stainless steel beaker:

- nonionic amphiphilic lipid employed in Example 5..... 7.6 g
- collagenic palmitoyl lipoamino acid of formula
- 15 $CH_3-(CH_2)_{14}-CO-NH-\underset{\substack{| \\ R}}{CH}-COOH$

in which R is an amino acid obtained by the hydrolysis of collagen

- (marketed under the name "PCO" by Rhône-Poulenc)..... 0.4 g
- 20 - β -methasone 17-valerate (product marketed by Larks)..... 0.08 g

The mixture of these three products is produced by melting at 90°C. 20 g of demineralized water are added. The mixture obtained is homogenized at 90°C.

The following materials are then added:

- methyl para-hydroxybenzoate (stabilizer).... 0.3 g



- glycerine..... 5.0 g
- demineralized water..... 52.02g

The mixture is homogenized at 40°C by means of an ultradisperser of the "Virtis" type until the mean size of the vesicles obtained is 0.2 micron.

0.5 g of an aqueous normal sodium hydroxide solution is then added with stirring.

Lastly, the following materials are added:

- crosslinked polyacrylic acid sold under the trade name "Carbopol 940" by Goodrich..... 0.4 g
- triethanolamine..... 0.4 g
- demineralized water..... 13.3 g

This preparation, employed in topical application twice daily in subjects affected by dermatitis, enables an appreciable improvement to be found after a few days' application.

EXAMPLE 9 - AQUEOUS DISPERSION OF LIPIDIC VESICLES

The following materials are dissolved in 200 ml of a solvent mixture (chloroform/methanol in the ratio 1/1) in a 1-litre round-bottomed flask:

- nonionic amphiphilic lipid employed in Example 5..... 7.6 g
- collagenic palmitoyl lipoamino acid of formula $CH_3-(CH_2)_{14}-CO-NH-CH-COOH$

25

R

in which R is an amino acid obtained by the hydrolysis of collagen



- (marketed under the name "PCO" by Rhône-Poulenc)..... 0.4 g
- α -tocopherol acetate (product marketed by Roche)..... 0.2 g
- 5 - α -tocopherol (product marketed by Roche).... 0.2 g
- ascorbyl palmitate (product marketed by Roche)..... 0.4 g

The solvent is evaporated off with a rotary evaporator and the last traces of solvent are removed with a rotary pump for 1 hour. The combination of lipids obtained is placed in contact with 20 g of demineralized water. The mixture obtained is homogenized at 90°C.

The following materials are then added:

- methyl para-hydroxybenzoate (stabilizer).... 0.3 g
- 15 - glycerine..... 5.0 g
- demineralized water..... 50.8 g

The mixture is homogenized at 40°C by means of a "Virtis" ultradisperser until the mean size of the vesicles obtained is 0.2 micron.

20 0.5 g of aqueous normal sodium hydroxide solution is then added with stirring.

Lastly, the following materials are added:

- crosslinked polyacrylic acid sold under the name "Carbopol 940" by Goodrich..... 0.4 g
- 25 - triethanolamine..... 0.4 g
- demineralized water..... 13.8 g

This dispersion, employed in topical application



once daily in subjects who have a skin exhibiting some signs of aging, gives satisfactory results after four weeks' application.



CLAIMS

1. Cosmetic or pharmaceutical composition consisting of a dispersion, in an aqueous medium D, of lipidic spherules constituted by organized molecular layers encapsulating an aqueous phase E, the constituent lipid(s) of the said layers being ionic or nonionic amphiphiles, which is characterized in that the lipidic phase itself of the said spherules is combined with at least one lipoprotein free from any sulphhydryl functional group and chosen from mono- or polyacylated derivatives of amino acids or of polypeptides in which the acyl residue R-CO contains a C₁₃-C₁₉ hydrocarbon chain R, at least one of the functional groups which connects the polypeptide chain or the amino acid residue to the lipophile chain being an amide functional group, it being possible for the carboxylic functional groups of the polypeptide chain or of the amino acid residue to be partially or completely neutralized by one or more alkali metal cations, or an ammonium ion or substituted ammonium ion derived from an amine, the said lipo-protein(s) being present in a proportion of 1 to 15% by weight relative to the total weight of the said lipidic phase itself.

2. Composition according to claim 1, characterized in that the acyl residue(s) of the lipoproteins employed is (or are) chosen from the myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl and linolenoyl residues.

3. Composition according to either of claims 1 and



2, characterized in that the proteinic chain of the lipoproteins employed is derived from collagen or from hydroxyproline.

4. Composition according to claim 1, characterized in that the lipoprotein(s) employed is (or are) chosen from the group consisting of collagenic palmitoyl lipoprotein, the O,N-dipalmitoyl derivative of hydroxyproline, hydroxyproline linoleate, sodium stearylglutamate, collagen stearyl tripeptide and collagen oleoyl (tetra- or penta)peptide.

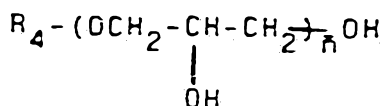
5. Composition according to one of claims 1 to 4, characterized in that the lipids intended to constitute the leaflets of the spherules are ionic or nonionic amphiphiles of natural or synthetic origin, containing, per molecule, one or more hydrophilic group(s) taken from the hydroxyl, ether, carboxyl, phosphate and amine groups.

6. Composition according to claim 5, characterized in that the ionic amphiphiles are taken from the group consisting of natural phospholipids such as egg or soya lecithin and sphingomyelin, synthetic phospholipids such as dipalmitoylphosphatidylcholine or hydrogenated lecithin, the amphoteric compounds and the anionic compounds.

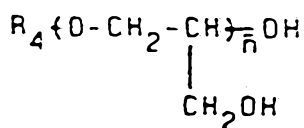
7. Composition according to claim 5, characterized in that the nonionic amphiphiles are taken from the group consisting of:

- linear or branched polyglycerol ethers, of formulae,

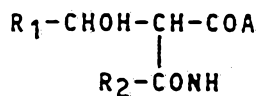




and



- respectively, \bar{n} being a mean statistical value of between
5 1 and 6, R_4 denoting a saturated or unsaturated, linear
or branched aliphatic chain containing 12 to 30 carbon
atoms, the hydrocarbon radicals of lanolin alcohols or
the 2-hydroxyalkyl residues of long-chain α -diols;
- linear or branched polyglycerol ethers containing two
10 fatty chains;
 - polyoxyethylenated fatty alcohols or polyoxyethylenated
sterols;
 - polyol ethers;
 - esters of polyols, oxyethylenated or otherwise;
 - 15 - glycolipids of natural or synthetic origin;
 - the hydroxyamides denoted by the formula:

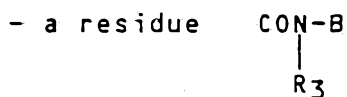


in which formula:

- 20 - R_1 denotes a $C_7 - C_{21}$ alkyl or alkenyl radical;
- R_2 denotes a $C_7 - C_{31}$ saturated or unsaturated hydro-
carbon radical;



- COA denotes a group chosen from the following two groups:



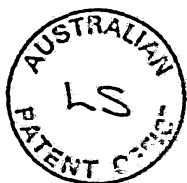
5 B being a radical derived from mono- or polyhydroxylated primary or secondary amines and R₃ denoting a hydrogen atom or a methyl, ethyl or hydroxyethyl radical;

- COOZ, Z denoting the residue of a C₃-C₇ polyol.

8. Composition according to one of claims 1 to 7,
10 characterized in that the amphiphiles intended to form the spherules are combined with additives taken from the group consisting of long-chain alcohols and diols, of sterols, of long-chain amines, of hydroxyalkylamines, of polyoxyethylenated fatty amines, of long-chain amino
15 alcohol esters, and their salts, of phosphoric esters of fatty alcohols, of alkyl sulphates, and of ionic sterol derivatives.

9. Composition according to one of claims 1 to 8,
20 characterized in that it contains from 0.5 to 25% by weight of amphiphile(s) constituting the walls of spherules, these percentages being expressed on a weight basis relative to the total weight of the composition.

10. Composition according to one of claims 1 to 9,
25 characterized in that the walls of these spherules contain at least one liposoluble substance such as, for example, keratolytic agents, antiinflammatory agents and antioxidant agents.



11. Composition according to one of claims 1 to 10, characterized in that the aqueous phase E encapsulated in the spherules is an aqueous solution of active substance(s), preferably isoosmotic relative to the phase D which surrounds the spherules.

12. Composition according to claim 11, characterized in that the aqueous phases D and E are identical.

13. Composition according to either of claims 11 or 12, characterized in that the aqueous phase E or the outer aqueous phase D contains at least one water-soluble cosmetic substance taken from the group consisting of humectants, artificial tanning agents, skin colouring agents, antisolar agents, sunscreens, antiperspirant agents, deodorants, astringents, freshening products, tonic products, cicatrizing products, keratolytic products, depilatory products, perfumed waters, water-soluble colorants, antidandruff agents, antiseborrhoeic agents, oxidizing agents, reducing agents and animal or plant tissue extracts.

14. Composition according to either of claims 11 or 12, characterized in that the aqueous phase E or the outer aqueous phase D contains at least one product taken from the group consisting of vitamins, hormones, enzymes, vaccines, antiinflammatories, antibiotics and bactericides.

15. Composition according to one of claims 1 to 14, characterized in that at least one water-immiscible liquid



phase L is dispersed in the aqueous phase D.

16. Composition according to claim 15, characterized in that it contains from 2 to 70% by weight of water-immiscible liquid phase L relative to the total weight of the composition, the relative weight proportion of amphiphile lipid constituent(s) of spherules relative to the dispersed water-immiscible liquid phase being between 0.02/1 and 10/1.

17. Composition according to either of claims 15 or 16, characterized in that the water-immiscible liquid phase L dispersed in the aqueous phase D is chosen from the group consisting of oils such as esters of fatty acids and of polyols, and esters of fatty acids and of branched alcohols of formula R_5-COOR_6 , in which formula R_5 denotes the residue of a higher fatty acid containing from 7 to 19 carbon atoms and R_6 denotes a branched hydrocarbon chain containing from 3 to 20 carbon atoms, hydrocarbons such as hexadecane, liquid paraffin or perhydrosqualene, halogenated carbides such as perfluoro-decahydronaphthalene, perfluorotributylamine, polysiloxanes, organic acid esters, ethers and polyethers.

18. Composition according to one of claims 1 to 17, characterized in that the aqueous phase D contains at least one adjuvant taken from the group consisting of opacifiers, gelling agents, flavours, perfumes, sun-screens and colorants.

19. Composition according to one of claims 15 to 18,



characterized in that the phase L contains at least one perfume and/or one or more liposoluble active substances.

20. Composition according to claim 19, characterized in that the liposoluble substance consists of a sunscreen,
5 a substance intended to improve the condition of dry or senile skins or an antioxidant.



INTERNATIONAL SEARCH REPORT

International Application No PCT/FR 87/00128

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, Indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC				
Int.Cl. ⁴ A61K 7/00;A61K 9/50				
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
Int.Cl. ⁴	A61K			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹				
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
X	WO, A, 85/04880 (UNIVERSITY OF TENNESSE RESEARCH CORP.) 7 november 1985 see page 3,lines 30-33;claims 1-5 -----	1,2,5-20		
X,Y	EP, A, 0120722 (PARFUMS CHRISTIAN DIOR) 3 October 1984 see page 3,lines 16-25;page 4,lines 4-18;claims -----	1-20		
A	GB, A, 2026340 (P.S.ASH) 6 February 1980 see page 1,lines 23-38;claims -----	1-20		
A	FR, A, 2315991 (L'OREAL) 28 January 1977 see claims 1,11,14,28 -----	1-20		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> ¹⁰ Special categories of cited documents: <ul style="list-style-type: none"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; vertical-align: top;"> <ul style="list-style-type: none"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family </td> </tr> </table>			¹⁰ Special categories of cited documents: <ul style="list-style-type: none"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	<ul style="list-style-type: none"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family
¹⁰ Special categories of cited documents: <ul style="list-style-type: none"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	<ul style="list-style-type: none"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family 			
IV. CERTIFICATION				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
8 July 1987 (08.07.87)	3 August 1987 (03.08.87)			
International Searching Authority	Signature of Authorized Officer			
European Patent Office				

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/FR 87/00128 (SA 16929)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 20/07/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8504880	07/11/85	EP-A- 0179126	30/04/86
		JP-T- 61501897	04/09/86
EP-A- 0120722	03/10/84	FR-A,B 2540381	10/08/84
		JP-A- 59152333	31/08/84
GB-A- 2026340	06/02/80	EP-A,B 0007714	06/02/80
		US-A- 4448765	15/05/84
FR-A- 2315991	28/01/77	NL-A- 7607210	03/01/77
		BE-A- 843300	23/12/76
		DE-A,B,C 2629100	20/01/77
		AU-A- 1539376	05/01/78
		GB-A- 1539625	31/01/79
		JP-A- 52006375	18/01/77
		CA-A- 1063908	09/10/79
		CH-A- 616087	14/03/80
		AU-B- 505843	06/12/79
		CH-A- 623236	29/05/81
		AT-B- 361893	10/04/81
		AT-B- 361896	10/04/81
JP-A- 56108528	28/08/81		
NL-A- 8102794	02/11/81		

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82

RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale N° **PCT/FR 87/00128**

I. CLASSEMENT DE L'INVENTION (si plusieurs symboles de classification sont applicables, les indiquer tous) ⁷		
Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB		
CIB ⁴ : A 61 K 7/00; A 61 K 9/50		
II. DOMAINES SUR LESQUELS LA RECHERCHE A PORTÉ		
Documentation minimale consultée ⁸		
Système de classification	Symboles de classification	
CIB ⁴	A 61 K	
Documentation consultée autre que la documentation minimale dans la mesure où de tels documents font partie des domaines sur lesquels la recherche a porté ⁹		
III. DOCUMENTS CONSIDÉRÉS COMME PERTINENTS ¹⁰		
Catégorie ⁶	Identification des documents cités, ¹¹ avec indication, si nécessaire, des passages pertinents ¹²	N° des revendications visées ¹³
X	WO, A, 85/04880 (UNIVERSITY OF TENNESSEE RESEARCH CORP.) 7 novembre 1985 voir page 3, lignes 30-33; revendications 1-5	1, 2, 5-20
X, Y	EP, A, 0120722 (PARFUMS CHRISTIAN DIOR) 3 octobre 1984 voir page 3, lignes 16-25; page 4, lignes 4-18; revendications	1-20
A	GB, A, 2026340 (P.S. ASH) 6 février 1980 voir page 1, lignes 23-38; revendications	1-20
A	FR, A, 2315991 (L'OREAL) 28 janvier 1977 voir revendications 1, 11, 14, 28	1-20

<p>⁶ Catégories spéciales de documents cités: ¹¹</p> <ul style="list-style-type: none"> « A » document définissant l'état général de la technique, non considéré comme particulièrement pertinent « E » document antérieur, mais publié à la date de dépôt international ou après cette date « L » document pouvant poser un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée) « O » document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens « P » document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée « T » document ultérieur publié postérieurement à la date de dépôt international ou à la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention « X » document particulièrement pertinent: l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive « Y » document particulièrement pertinent: l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier. « & » document qui fait partie de la même famille de brevets 		
IV. CERTIFICATION		
Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale	
8 juillet 1987	- 3 AUG 1987	
Administration chargée de la recherche internationale	Signature du fonctionnaire autorisé	
OFFICE EUROPEEN DES BREVETS	M. VAN MOL	

ANNEXE AU RAPPORT DE RECHERCHE INTERNATIONALE RELATIF

A LA DEMANDE INTERNATIONALE NO. PCT/FR 87/00128 (SA 16929)

La présente annexe indique les membres de la famille de brevets relatifs aux documents brevets cités dans le rapport de recherche international visé ci-dessus. Lesdits membres sont ceux contenus au fichier informatique de l'Office européen des brevets à la date du 20/07/87

Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office européen des brevets.

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevets	Date de publication
WO-A- 8504880	07/11/85	EP-A- 0179126	30/04/86
		JP-T- 61501897	04/09/86
EP-A- 0120722	03/10/84	FR-A, B 2540381	10/08/84
		JP-A- 59152333	31/08/84
GB-A- 2026340	06/02/80	EP-A, B 0007714	06/02/80
		US-A- 4448765	15/05/84
FR-A- 2315991	28/01/77	NL-A- 7607210	03/01/77
		BE-A- 843300	23/12/76
		DE-A, B, C 2629100	20/01/77
		AU-A- 1539376	05/01/78
		GB-A- 1539625	31/01/79
		JP-A- 52006375	18/01/77
		CA-A- 1063908	09/10/79
		CH-A- 616087	14/03/80
		AU-B- 505843	06/12/79
		CH-A- 623236	29/05/81
		AT-B- 361893	10/04/81
		AT-B- 361896	10/04/81
		JP-A- 56108528	28/08/81
NL-A- 8102794	02/11/81		

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voir Journal Officiel de l'Office européen des brevets, No. 12/82