CONVENTION APPLICATION FOR A PATENT

505843

L'OREAL,

of 14 Rue Royale,

75 Paris 8ème,

France,

hereby apply for the grant of a Patent for an invention entitled: (2)

"PROCESS FOR PREPARING AQUEOUS DISPERSIONS OF LIPID SPHERULES, AND AQUEOUS DISPERSIONS OF SUCH LIPID SPHERULES"

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

75.20456

for a patent or similar protection made in (4) France,

on 30th June, 1975,

Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys,

50 Queen Street, Melbourne, Victoria, Australia.

DATED this 28th day of June 1976

L'OREAL,

by

[Handwritten Signature]
COMMONWEALTH OF AUSTRALIA
Patents Act 1952-1962

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

In support of the Convention Application made by

L'OREAL

(herinafter referred to as the applicant) for a Patent for an inventor entitled:

PROCESS FOR PREPARING AQUEOUS DISPERSIONS OF LIPID SPHERULES, AND AQUEOUS DISPERSIONS OF SUCH LIPID SPHERULES

André VIOUT

of 14 Rue Royale, Paris, France

Do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in France on the 30th day of June 1975, by L'OREAL

3. GUY VANLERBERGHE, Montjay-La-Tour Commune de Villevaude 77, France; and ROSE-MARIE HANDJANI, 1 Place Saint Sulpice Paris 6ème, France

Are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the said GUY VANLERBERGHE and ROSE-MARIE HANDJANI

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, France this 23rd day of June 1976.
PROCESS FOR PREPARING AQUEOUS DISPERSIONS OF LIPID SPHERULES, AND AQUEOUS DISPERSIONS OF SUCH LIPID SPHERULES

CLAIM 1. Process for preparing a dispersion of aqueous liquid-containing spherules consisting of ordered molecular layers enclosing an aqueous phase which comprises bringing into contact at least one liquid lipid which is dispersible in water and has the general formula:

\[ X \rightarrow Y \]

in which \( X \) represents an ionic or non-ionic hydrophilic group and \( Y \) represents a lipophilic group, with an aqueous phase to be encapsulated by the spherules, the lipophilic/hydrophilic balance of the lipid being such that the lipid swells in the aqueous phase to be encapsulated so as to form a lamellar phase, agitating the mixture thereby to obtain a lamellar phase, adding a liquid dispersing agent in an amount greater than the amount of the lamellar phase obtained and agitating the resulting mixture vigorously...
for approximately from 15 minutes to 4 hours to obtain the dispersion.
Complete Specification for the invention entitled: "PROCESS FOR PREPARING AQUEOUS DISPERSIONS OF LIPID SPHERULES, AND AQUEOUS DISPERSIONS OF SUCH LIPID SPHERULES"
It is known that certain lipids possess the property of forming, in the presence of water, mesomorphic phases, the state of order of which is intermediate between the crystalline state and the liquid state. Amongst the lipids which give rise to mesomorphic phases, some have already been stated to be able to swell in aqueous solution to form spherules dispersed in the aqueous medium, these spherules consisting of multi-molecular layers and preferably of bi-molecular layers having an approximate thickness of 30 to 100 Å (see, in particular, the article by Bangham, Standish and Watkins, J. Mol. Biol., 13, 238 (1965)).

Hitherto it has only been possible to obtain lipid spherules consisting of concentric layers by using lipids containing an ionic hydrophilic group and a lipophilic group, and the processes of preparation which have been described entail the production of spherules having a mean diameter of less than 1,000 Å. The process for obtaining these spherules consists of producing a dispersion, of which the disperse phase contains the lipid substance capable of forming the spherules, and of subjecting this dispersion to a treatment with ultrasonics; to produce a dispersion which is subjected to ultrasonics, it is possible first to produce, by evaporation on a wall surface, a thin film of the lipid substance to be dispersed, then, secondly, to bring the continuous phase of the dispersion which is to be produced into contact with the wall surface thus coated, and finally, thirdly, to agitate the system so as to obtain the dispersion which is to be subjected to ultrasonics. In another
process, described in French Patent Application 2,221,122, it is also possible, in order to obtain the dispersion to be subjected to ultrasonics, to add the lipid intended to form the walls of spherules to an aqueous phase and then to heat the mixture gently and agitate it vigorously by vibration. The spherules consisting of concentric layers which are thus obtained, and which have a maximum diameter of about 1,000 Å, are in general called liposomes.

5. It has already been proposed to utilise the liposomes to enclose aqueous solutions containing active substances, in the aqueous compartments contained between the double layers of lipid, and thus to protect the encapsulated substances from the external conditions (see, in particular, the article by Sessa and Weismann, J. Lipid Res., 9, 310 (1968) and the article by Magee and Miller, Nature, Vol. 235 (1972)). Since the liposomes can have varying sizes within the range below 1,000 Å, it is possible to vary their ability to penetrate into the human body, and this has made it possible to envisage numerous pharmaceutical uses, all the more so since their external electrical charge can make it possible to select the site where they will become fixed (Biochem J. (1971), 124 p. 58 P). However, as far as cosmetics are concerned, the use of spherules of diameter less than 1,000 Å can cause some disadvantages because of the risk of penetration of the products through the skin. It is thus clear that at least for this type of application it would be desirable to be able to produce spherules of concentric lipid layers which have a diameter greater than 1,000 Å.
Furthermore, the currently known processes for obtaining liposomes containing active substances between their concentric lipid layers suffer from considerable disadvantages. In the first place, the active substance introduced into the continuous phase of the dispersion which is subjected to ultrasonics, is only encapsulated to a very small part between the lipid layers of the liposomes, because a very small part of the continuous phase of the dispersion finds itself trapped between the said layers. When it is desired to isolate the encapsulation liposomes it is necessary to pass the dispersion, which has been subjected to ultrasonics, over a separating column of the "Sephadex" type, in which case the liposomes are obtained in the form of an extremely dilute dispersion. As a result, on the one hand it is not possible in practice, with the known processes, to obtain a high concentration of liposomes and, on the other hand, the active substance is only encapsulated to a very low degree and is lost when eluting the separating column without it being possible in practice to recover it in a simple manner, thus resulting in a large increase in the cost price of the active substances encapsulated in the liposomes. It is thus desirable to have available a process for the manufacture of spherules with concentric layers which makes it possible to obtain a dispersion having a high concentration of a consequent reduction in the spherules with reduced loss of the product encapsulated between the layers of the spherules.

Finally, the processes of manufacture of liposomes which have been described hitherto mention that it is only
possible to use certain well-defined categories of lipids: in the art quoted above, the use of phospholipids, of lipids containing an ionic hydrophilic group and a lipophilic group, and of unsaturated fatty acids has been mentioned.

The object of the present invention is to provide a process for obtaining an aqueous dispersion of spherules of diameter less than or greater than 1,000 Å at high concentrations, the said spherules being capable of encapsulating active substances, with a high encapsulation yield. In this specification, the word "encapsulate" is used to indicate that there is an aqueous phase present within a capsule consisting of lipid spherules. The process according to the invention can be applied to ionic or non-ionic lipids and thus makes it possible to include non-ionic lipid compounds amongst the lipids capable of forming spherules.

The present invention provides a process for preparing a dispersion of aqueous liquid-containing spherules consisting of ordered molecular layers enclosing an aqueous phase which comprises bringing into contact at least one liquid lipid which is dispersible in water and has the general formula:

\[ \text{X} - \text{Y} \]

in which X represents an ionic or non-ionic hydrophilic group and Y represents a lipophilic group, with an aqueous phase to be encapsulated by the spherules, the lipophilic/hydrophilic balance of the lipid being such that the lipid swells in the aqueous phase to be encapsulated so as to form a lamellar phase, agitating the mixture thereby to obtain a lamellar phase, adding a liquid dispersing agent...
in an amount greater than the amount of the lamellar phase obtained and agitating the resulting mixture vigorously for approximately from 15 minutes to 4 hours to obtain the dispersion.

In a preferred embodiment, the weight ratio of the amount of aqueous phase to be encapsulated to the amount of lipids forming the lamellar phase is from 0.1 to 3; the aqueous phase to be encapsulated can be water or an aqueous solution of an active product; the weight ratio of the amount of dispersing liquid which is added to the amount of lamellar phase to be dispersed is from 2 to 100; the dispersing liquid and the aqueous phase to be encapsulated are preferably isotonic; the dispersing liquid is advantageously an aqueous solution; the agitation carried out as the last stage of the process is achieved by means of a vibratory agitator; the process is carried out at ambient temperature, or at a higher temperature if the lipid is solid at ambient temperature; where it is desired that the spherules obtained should have a mean diameter less than 1,000 Å, the dispersion of spherules can be subjected to a treatment with ultrasonics.

To form the lamellar phase, it is possible to use a single lipid or a mixture of lipids. The lipid or lipids,
which are used, contain or contain a long lipophilic chain comprising from 12 to 30 carbon atoms, which can be saturated or unsaturated, branched or linear; in particular, it is possible to choose oleyl, lanolyl, tetradecyl, hexadecyl, isostearyl, lauryl or alkylphenyl chains. If the hydrophilic group of the lipid which forms the lamellar phase is a non-ionic group, it is possible to choose, as the hydrophilic group, a polyoxyethylene, a polyglycerol, an oxyethyleneated or non-oxyethyleneated polyol ester or, for example, a polyoxyethyleneated sorbitol ester. If the hydrophilic group of the lipid which forms the lamellar phase is an ionic group, the hydrophilic group chosen can advantageously be an amphoteric compound containing two lipophilic chains or an association compound of two long-chain organic ions of opposite signs. Very satisfactory results have been obtained by using, as lipids which form the lamellar phase, polyglycerol ethers such as those which are described in French Patents Nos. 1,477,048 and 2,091,516 and in Certificate of Addition 94,928.

The aqueous phase which is chosen for encapsulation can contain active substances of all kinds and in particular substances which are of pharmaceutical or foodstuff value, or substances which are cosmetically active. The active substances can, for example, be the following, where cosmetics are concerned: products intended for the care of the skin and of the scalp, for example humectants, such as glycerol, sorbitol, pentaerythritol, inositol, pyrrolidonecarboxylic acid and its salts; artificial bronzing agents, such as
dihydroxyacetone, erythrulose, glyceraldehyde and \( \gamma \)-dialdehyde such as tartraldehyde (these products can optionally be associated with dyestuffs); water-soluble agents for protecting against sunburn; antiperspirants, deodorants, astringents, products having a freshening, tonic, cicatrising or keratolytic action, and depilatories; toilet waters; extracts of animal or vegetable tissues, such as proteins, polysaccharides and amniotic fluid; water-soluble dyestuffs, anti-dandruff agents, anti-seborrhoea agents, oxidising agents (bleaching agents) such as hydrogen peroxide, and reducing agents such as thioglycollic acid and its salts.

The following may be mentioned as pharmaceutical active substances: vitamins, hormones, enzymes (for example dismutase peroxide), vaccines, anti-inflammatory agents (for example hydrocortisone), antibiotics and bactericides.

It is obvious that lipids capable of stably encapsulating the aqueous phase will be chosen in accordance with the active substance contained in the aqueous phase to be encapsulated. In order that the lipids which constitute the lamellar phase should give stable spherules, it is necessary that there should be sufficient lateral interaction between the lipid chains which, placed side by side, constitute the strata or layers of the spherules, that is to say that the Van der Waals forces between the chains should ensure sufficient cohesion of the layers. This condition is satisfied in the case of the lipids having the characteristics indicated in the general definition of the process, given above. The lipids which can be used in
the process according to the invention belong to the category of the emulsifiers of the water-in-oil type.

The process according to the invention makes it possible to obtain dispersions of spherules which consist of non-ionic lipid compounds and which therefore form new compositions which make it possible to encapsulate active substances which can be used, for example, in pharmacy, in nutrition or in cosmetics. The use of non-ionic compounds to form the encapsulating spherules is of not insignificant value where it is desired to avoid a situation where the spherules have an electrically charged external surface.

According to an aspect of the present invention, there is provided a dispersion of spherules consisting essentially of ordered molecular layers enclosing an aqueous phase, said layers consisting of at least one lipid which is a non-ionic amphiphilic compound with a lipid chain, said lipid being dispersible in water, the spherules having a diameter of from 100 to 50,000 Å.

In a preferred embodiment, the spherules of the dispersion according to the invention contain an aqueous phase to be encapsulated; the non-ionic lipid compounds have a lipophilic/hydrophilic balance such that the compound swells in the aqueous phase to be encapsulated, forming a lamellar phase; the hydrophilic groups of the non-ionic lipid compounds are polyoxyethylenated groups, polyglycerolated groups, oxyethyleneated or non-oxyethyleneated polyol esters and, for example, polyoxyethyleneated sorbitol esters; the
non-ionic lipid compounds are preferably chosen from the
group consisting of:

The linear or branched polyglycerol ethers of the
respective formulae:

\[ R \rightarrow (OCH_2 CH OH CH_2)_n OH \]

and

\[ R \rightarrow (O CH_2 CH)_n OH \]

\[ \text{CH}_2 \text{ OH} \]

wherein \( n \) is an integer between 1 and 6, \( R \) is a linear or
branched, saturated or unsaturated aliphatic chain of 12 to
declared by the removal of \( \text{CH}_2 \text{OH} \) from a
30 carbon atoms, a hydrocarbon radical of lanolin alcohol,

or a 2-hydroxyalkyl radical derived from long-chain \( \alpha \)-diols;
polyoxyethyleneated fatty alcohols;

oxyethyleneated or non-oxyethyleneated polyol esters
and in particular the esters of polyoxyethyleneated sorbitol;
and

glycolipids of natural or synthetic origin, for
example the cerebrosides.

The continuous phase of the dispersion, which
surrounds the spherules, is an aqueous phase; the aqueous
phase encapsulated in the spherules is an aqueous solution of
active substance, preferably isotonic relative to the continuous
phase of the dispersion.

Various additives can be associated with the non-
ionic lipid compounds for the purpose of modifying the
permeability or the surface charge of the spherules. In
this context there may be mentioned the optional addition of
long-chain alcohols and diols, of sterols, for example cholesterol, of long-chain amines and of their quaternary ammonium derivatives, of dihydroxyalkylamines, of polyoxyethyleneated fatty amines, of esters of long-chain aminoalcohols, of their salts and their quaternary ammonium derivatives, of phosphoric acid esters of fatty alcohols, for example sodium dicetyl-phosphate, of alkyl-sulphates, for example sodium cetyl-sulphate, and of certain polymers, such as the polypeptides and the proteins.

According to another aspect of the present invention, there is provided a dispersion of spherules consisting essentially of ordered molecular layers enclosing an aqueous phase, said layers consisting of at least one lipid of the formula

\[ X -- Y, \]

where \( X \) denotes an ionic hydrophilic group and \( Y \) denotes a lipophilic group, the lipid being dispersible in water and the spherules having a diameter of approximately from 1,000 Å to 50,000 Å.

In a preferred embodiment, the aqueous phase to be encapsulated is an aqueous solution of an active substance; the active substances of the aqueous phase to be encapsulated are products having a cosmetic action; the continuous phase (i.e. the liquid in which the spherules are dispersed) of the dispersion is an aqueous phase; the ratio of the weight of the spherules relative to the weight of the continuous phase of the dispersion is from 0.01 to 0.5; and the continuous phase of the dispersion is advantageously iso-osmotic relative to the aqueous phase encapsulated in the spherules.

The active substances, which can be encapsulated in
the spherules of the two types of dispersion defined above, are extremely varied and correspond to those which have been indicated earlier for carrying out the process according to the invention. As a result, the compositions can be used in a variety of fields and in particular in pharmacy and in cosmetics.

The aqueous dispersions defined above are of very particular value in cosmetics because of the fact that the use of spherules of large size makes it possible to reduce the risk of these preparations passing through the skin.

It should be noted that the use of the aqueous dispersions according to the invention in cosmetics, whether dispersions containing non-ionic lipid compounds or dispersions containing ionic lipid compounds are concerned, offers a considerable advantage over the well-known use of emulsions. In fact, if it is desired to use preparations which simultaneously contain fatty substances and water, it is necessary, in order to ensure the stability of the emulsion, to use amphiphilic emulsifying compounds to ensure the stability of the dispersions. It is known that certain emulsifiers can have a relatively irritant effect when they are applied to the skin. It has been discovered, in the course of the work relating to the present invention, that this effect of the emulsifiers, for a given chemical structure, depends considerably on the form in which they are applied. Thus, it has been possible to demonstrate the fact that a water/oil emulsion composed of 42% of
perhydrosqualene. 8% of an emulsifier and 50% of water is highly irritant, whilst an 8% strength aqueous dispersion of the same emulsifier has an irritation index which is practically negligible. (Throughout this specification percentages are by weight unless otherwise stated.)

Accordingly, there is a synergistic irritation effect when an emulsifier and an oily phase are present. The aqueous dispersions according to the invention make it possible to avoid the simultaneous use of an emulsifier and an oil, which constitutes a considerable advance in the field of cosmetics.

It should be noted that it is possible to add to the dispersions of spherules according to the invention different auxiliary products, the object of which is to modify the presentation or organoleptic properties of the dispersions, such as opacifiers, gelling agents, aromas, perfumes or dyestuffs.

In general, the value of the dispersions according to the invention resides in the fact that they make it possible to introduce hydrophilic substances into an essentially lipophilic medium. As a result, under these conditions, the hydrophilic substances find themselves masked, resulting in a protection effect against various possible agents which cause deterioration, such as oxidising agents, digestive juices and, more generally, compounds which are reactive towards the encapsulated substances. The penetration and/or fixing of the active substances can be varied by varying the size of the globules and their electrical charge. Their action can also be varied (producing a delay effect). Furthermore, the fact that they
are masked makes it possible to suppress, or significantly to alter, their organoleptic properties, in particular the taste. Finally, the lipids used in these preparations in themselves possess a beneficial effect, for example an emollient effect, a lubricating effect, or the effect of glossiness.

In order that the object of the invention shall be better understood, several embodiments will now be described by way of purely illustrative and non-limiting examples.

EXAMPLE 1

500 mg of sorbitol triooleate oxyethyleneated with 20 mols of ethylene oxide (the product "Tween 85" marketed by Messrs. ICI Atlas) are brought into contact with 0.335 ml of an 0.7 M solution of sorbitol in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at ambient temperature.

Thereafter, 3 ml of a 1% strength aqueous solution of the product known by the tradename of "Carbopol 934" (a polyacrylic acid crosslinked by polyallylsucrose, sold by Messrs. "Goodrich") are added. The flask is placed on a shaker and is agitated vigorously for one hour.

The dispersion obtained is gelled; the diameter of the spherules is greater than 1 micron.

EXAMPLE 2

250 mg of oleyl alcohol oxyethyleneated with 10 mols of ethylene oxide (the product "Brij 96" marketed by Messrs. ICI Atlas) and 250 mg of oleyl alcohol oxyethyleneated with 2 mols of ethylene oxide (the product "Brij 92" marketed by Messrs. ICI Atlas) are intimately mixed in a 50 ml round
flask; the mixture obtained is then brought into contact with 1 ml of an 0.5 M solution of glycerol, and the whole is homogenised. The experiment is carried out at ambient temperature.

Thereafter, 20 ml of an 0.245 M solution of (NaCl, KCl) are added. The flask, placed on a shaker, is agitated vigorously for 1 hour.

The dispersion obtained is fluid and milky; the diameter of the spherules is about 1 micron.

**EXAMPLE 3**

500 mg of the product of the general formula

\[
R \left( \frac{OCH_2-CH}{\text{CH}_2\text{OH}} \right) \frac{\text{OH}}{\text{CH}_2\text{OH}}
\]

wherein R is the alkyl radical of hydrogenated lanolin alcohols and \( \bar{n} \) has a statistical average value of 3, are brought into contact with 0.220 ml of a 0.5 M solution of pentaerythritol in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at ambient temperature.

4 ml of water are then added. The flask, placed on a shaker, is agitated vigorously for 30 minutes.

The dispersion obtained has a milky appearance; the diameter of the spherules is greater than 1 micron.

**EXAMPLE 4**

500 mg of the product of the general formula

\[
R \left( \frac{OCH_2-CH}{\text{CH}_2\text{OH}} \right) \frac{\text{OH}}{\text{CH}_2\text{OH}}
\]
wherein R is the tetradecyl radical and n is equal to 2, are brought into contact with 0.75 ml of an 0.4 M solution of sorbitol in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at 40°C.

4 ml of water are then added. The flask, placed on a shaker, is agitated vigorously for 30 minutes. The dispersion obtained is clear after treatment with ultrasonics; the diameter of the spherules is less than 1 micron.

**EXAMPLE 5**

500 mg of the product of the general formula

\[
R - \left( \frac{OCH_2}{\text{CH}} \right)_n \text{OH}
\]

wherein R is the hexadecyl radical and n is equal to 2, are brought into contact with 0.335 ml of an 0.3 M solution of cysteine hydrochloride in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at 55°C.

Thereafter, 4.1 ml of an 0.145 M solution of \((\text{NaCl}, \text{KCl})\) are added. The flask, placed on a shaker, is agitated vigorously for 3 hours.

The dispersion obtained is practically limpid at 55°C; the diameter of the spherules is about 2 microns. On slowly cooling the dispersion to ambient temperature, a white opaque gel is obtained.

A sample of the dispersion taken at 55°C can be diluted with a solution, which may or may not be iso-osmotic,
containing a thickener such as gums or polymers; a slightly opaque solution is obtained, the dilution ratio being chosen in accordance with the appearance of the solution which it is desired to obtain.

EXAMPLE 6

500 mg of the product of the general formula

\[ R - \left( \frac{OCH_2-CH}{CH_2OH}_n \right) \frac{\text{OH}}{} \]

wherein \( R \) is the hexadecyl radical and \( n \) is equal to 2, are brought into contact with 10 ml of an 0.3 M solution of methionine in a 50 ml round flask placed in a waterbath at 55°C, and the mixture is homogenised. The experiment is carried out at 55°C.

The flask, placed on a shaker, is agitated vigorously for 3 hours at 55°C.

The dispersion obtained is limpid; the diameter of the spherules is about 1 micron. By cooling to ambient temperature, a white gel is obtained.

EXAMPLE 7

500 mg of the product of the general formula

\[ R - \left( \frac{OCH_2-CH}{CH_2OH}_n \right) \frac{\text{OH}}{} \]

wherein \( R \) is the alkyl radical of isostearyl alcohol and \( n \) has a statistical average value of 2, are brought into contact with 5 ml of water in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at
ambient temperature.

The flask, placéd on a shaker, is agitated vigorously for 4 hours.

The dispersion obtained is milky; the diameter of the spherules is about 5 microns.

The dispersion can be subjected to ultrasonics in order significantly to reduce the size of the spherules.

**EXAMPLE 8**

83.2 mg (200 µmols) of the product of the general formula

\[
R \cdot \left( \frac{OCH_2-CH}{CH_2OH} \right)^n \cdot OH
\]

wherein R is the alkyl radical of oleyl alcohol and n is equal to 2, are dissolved in 2 ml of a mixture of chloroform and methanol (in the ratio of 2:1) in a 50 ml round flask. The solvent is evaporated by means of a rotary evaporator and the last traces of solvent are removed by exposure to the reduced pressure from a vane pump for one hour.

10 ml of an 0.3 M solution of glucose are brought into contact with the lipid. The flask, placed on a shaker, is agitated vigorously for 4 hours. The experiment is carried out at ambient temperature.

The dispersion is subjected to ultrasonics for 20 minutes so as to reduce the diameter of the spherules to a value of less than 0.5 micron. The dispersion is then filtered over a column of "Sephadex G 50 coarse" gel swollen in a 0.145 M solution of (NaCl, KCl). The solution
obtained is slightly bluish.

**EXAMPLE 9**

58 mg of the product of the general formula

\[
R \cdot \left( \frac{OCH_2CH}{\text{CH}_2\text{OH}_n} \right) \text{OH}
\]

wherein R is the alkyl radical of isostearyl alcohol and \( \bar{n} \) is equal to 2, are intimately mixed with 58 mg of the product of the general formula

\[
R \cdot \left( \frac{OCH_2CH}{\text{CH}_2\text{OH}_n} \right) \text{OH}
\]

wherein R is the alkyl radical of "isostearyl" alcohol and \( \bar{n} \) is equal to 6, in a 50 ml round flask, and the mixture obtained is brought into contact with 10 ml of a 1 M solution of glucose. The experiment is carried out at ambient temperature. The flask, placed on a shaker, is agitated vigorously for 4 hours.

The dispersion obtained is very fine; the spherules have a diameter of about 1 micron. The dispersion can be subjected to ultrasonics for 30 minutes so as to reduce the size of the spherules to a value of less than 0.5 micron.

The dispersions which contain either spherules of diameter greater than 1 micron or spherules of diameter less than 0.5 micron are filtered over a column of "Sephadex G 50 coarse" gel swollen in an 0.475 M solution of (NaCl, KCl).

**EXAMPLE 10**

500 mg of tetraethylene glycol monolauryl ether are
brought into contact with 0.4 ml of an 0.3 M solution of glucose in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at ambient temperature.

5 ml of a 0.145 M solution of (NaCl, KCl) are then added.

The flask, placed on a shaker, is agitated vigorously for 15 minutes.

The dispersion obtained is limpid; the diameter of the spherules is about 1 micron.

**EXAMPLE 11**

500 mg of the product of the general formula

\[
R - \left( \frac{\text{OCH}_2\text{CH}_2\text{OH}}{\text{CH}_2\text{OH}} \right)_n \text{OH}
\]

wherein R is the hexadecyl radical and n has a statistical average value of 3, are brought into contact with 0.5 ml of a solution containing 50 mg/ml of "Croteine C" (a protein of molecular weight about 10,000, marketed by Messrs. "CRODA"), in a 50 ml round flask.

The mixture is homogenised. The experiment is carried out at 60°C.

4 ml of an 0.145 M solution of (NaCl, KCl) are then added.

The flask, placed on a shaker, is agitated vigorously for 3 hours.

The dispersion obtained is limpid; the diameter of the spherules is about 1 micron. On slow cooling to
ambient temperature, an opaque white gel is obtained.

**EXAMPLE 12**

300 mg of sphingomyeline are brought into contact with 0.350 ml of an 0.3 M solution of glucose in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at ambient temperature.

5 ml of an 0.145 M solution of (NaCl, KCl) are then added. The flask, placed on a shaker, is agitated vigorously for 2 hours.

The dispersion obtained is milky; the diameter of the spherules is about 2 microns.

The dispersion can be subjected to ultrasonics for 1 hour so as to reduce the diameter of the spherules.

**EXAMPLE 13**

300 mg of the product, obtained by molecular distillation, of the general formula

\[
R - \left( \frac{OCH_2-CH}{CH_2OH} \right)_n \text{OH}
\]

wherein \(R\) is the alkyl radical of oleyl alcohol and \(n\) is equal to 2, 150 mg of cholesterol and 50 mg of an amine of the general formula

\[
\text{RCOO(CH}_2\text{CH}_2\text{O)}_n\text{CH}_2\text{CH}_2\text{N}^{\text{C}_2\text{H}_5}\text{C}_2\text{H}_5
\]

wherein \(\text{RCOO}\) is the copra radical and \(n\) is a number between 2 and 5, are intimately mixed in a 50 ml round flask and the mixture obtained is brought into contact with 0.5 ml of an
0.3 M solution of sorbitol; the whole mixture is then homogenised. The experiment is carried out at ambient temperature.

4 ml of an 0.145 M solution of (NaCl, KCl) are then added.

The flask, placed on a shaker, is agitated vigorously for 4 hours.

The dispersion obtained is opalescent; the diameter of the spherules is about 2 microns.

**EXAMPLE 14**

425 mg of the product of the general formula

\[ R - \left( \frac{OCH_2-CH}{CH_2OH} \right)_n OH \]

wherein \( R \) is the alkyl radical of oleyl alcohol and \( n \) is a number equal to 2, and 75 mg of an amine of the following formula

\[ R - \left( \frac{OCH_2-CH}{CH_2OH} \right)_{\bar{n}} \text{OCH}_2\text{CHOH} - \text{CH}_2\text{N} \]

wherein \( R \) is the oleyl radical and \( \bar{n} \) has a statistical average value of 1, are brought into contact with 0.5 ml of an 0.3 M solution of glucose in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at ambient temperature.

4 ml of an 0.145 M solution of (NaCl, KCl) are then added.

The flask, placed on a shaker, is agitated vigorously
for 4 hours.

The dispersion obtained is opaque; the diameter of the spherules is greater than 2 microns.

The dispersion can be subjected to ultrasonics, whereupon the size of the spherules becomes less than one micron.

**EXAMPLE 15**

300 mg of sphingomyeline are brought into contact with 0.350 ml of an 0.3 M solution of ascorbic acid in a 50 ml round flask, and the mixture is homogenised. The experiment is carried out at ambient temperature.

2.650 ml of an 0.145 M solution of (NaCl, KCl) are then added. The flask, placed on a shaker, is agitated vigorously for 4 hours.

The dispersion obtained is milky; the diameter of the spherules is about 2 microns.

If desired, the dispersion can be filtered over a column of "Sephadex G 50 coarse" gel swollen in an 0.145 M solution of (NaCl, KCl).

**EXAMPLE 16**

142 mg of the Na salt of N²-(tallow alkyl)-N-dodecyl-N-(N',N'-diethylaminoethyl)-asparagine are dissolved in 2 ml of a mixture of chloroform and methanol (in the ratio of 2:1) in a 50 ml round flask. The solvent is evaporated by means of a rotary evaporator and the last traces of solvent are then removed by subjecting the product for one hour to the reduced pressure produced by a vane pump.

10 ml of an 0.3 M solution of glucose are brought
into contact with the lipid.

The flask, placed on a shaker, is agitated vigorously for 4 hours. The experiment is carried out at ambient temperature. The size of the spherules is about 1 micron. The dispersion is then filtered over a column of "Sephadex G 50 coarse" gel swollen in an 0.145 M solution of (NaCl, KCl).

EXAMPLE 17

80 mg of the product of the general formula

\[ R - \left( \frac{OCH_2}{CH_2OH} \right)_n OH \]

wherein R is the hexadecyl radical and n is equal to 2, 10 mg of cholesterol and 10 mg of dicetyl phosphate are dissolved in 2 ml of a mixture of chloroform and methanol (in the ratio of 2:1) in a 50 ml flask.

The solvent is evaporated by means of a rotary evaporator and the last traces of solvent are removed by exposure to the reduced pressure from a vane pump for 1 hour.

10 ml of an 0.15 M solution of the sodium salt of pyroglutamic acid are brought into contact with the lipids. The flask, placed on a shaker, is agitated vigorously for 2 hours on a waterbath at 55°C and is then cooled gradually until it has returned to ambient temperature.

The dispersion is subjected to ultrasonics for 1 hour at a temperature which is kept at near ambient temperature. The dispersion is then filtered over a column of "Sephadex G 50 coarse" gel swollen in distilled water.
The dispersion obtained is fluid and clear after treatment with ultrasonics; the diameter of the spherules is less than 1 micron.

**EXAMPLE 18**

240 mg of the product of the general formula

\[
R - \left( \frac{OCH_2-CH}{\text{CH}_2\text{OH}} \right)_n OH
\]

wherein \( R \) is the alkyl radical of hydrogenated lanolin alcohols and \( n \) has a statistical average value of 3, and 60 mg of cholesterol are mixed intimately in a 50 ml round flask.

The mixture obtained is brought into contact with 0.4 ml of an 0.15 M solution of the sodium salt of pyroglutamic acid and the whole mixture is homogenised. The experiment is carried out at 45°C. 4.6 ml of a 9% solution of sodium chloride are then added.

The flask, placed on a waterbath, is agitated vigorously by means of a shaker for 2 hours at 45°C and then whilst cooling gradually until it has returned to ambient temperature.

The dispersion obtained is fluid and milky; the diameter of the spherules is greater than one micron.

**EXAMPLE 19**

200 mg of the product of the general formula

\[
R - \left( \frac{OCH_2-CH}{\text{CH}_2\text{OH}} \right)_n OH
\]

wherein \( R \) is the hexadecyl radical and \( n \) is equal to 2, 25 mg of cholesterol and 25 mg of dicetyl phosphate are
intimately mixed in a 50 ml round flask; the mixture obtained is brought into contact with 0.3 ml of a 10% strength solution of tartraldehyde and the whole mixture is homogenised. The experiment is carried out at 55°C. 4.7 ml of an 0.145 M solution of (NaCl, KCl) are then added.

The flask, placed on a waterbath, is agitated vigorously by means of a shaker for 2 hours at 55°C and then whilst cooling gradually until it has returned to ambient temperature.

The dispersion obtained is gelled and has a slightly bluish appearance.

The simultaneous application to the skin of this dispersion of niosomes* and of an aqueous solution, of the same final concentration, of tartraldehyde, makes it possible to assess two effects of the niosomes*, which significantly intensify the colour developed and markedly improve the resistance of this colour to washing with water and with detergents.

Of course the embodiments described above in no way imply a limitation and can be modified in any desirable manner without thereby going outside the scope of the invention.
EXAMPLE 20

In a round 50 ml.-capacity flask, 300 mg of egg lecithin, 80 mg of cholesterol and 20 mg of dicetyl phosphate are dissolved in 3 ml of a mixture of chloroform and methanol in the ratio of 2 : 1.

The solvent is evaporated by means of a rotary vaporizer, whereupon the last traces of solvent are removed by subjecting the mixture of products for a period of 1 hour to the reduced pressure provided by a vane pump.

The lipidic film obtained is placed in contact with 5 ml of a 4% solution of salicylate of triethanolamine. A test is made at a temperature of 40°C.

The flask, placed on an agitator, is agitated vigorously for 2 hours at 40°C, after which it is gradually cooled until ambient temperature is reached.

The grains have a diameter of approximately 2 microns.

The dispersion can be subjected to ultrasonic rays in order to reduce the size of the grains to a value considerably less than 1 micron.

The dispersion can be filtered on a Sephadex gel column.

EXAMPLE 21

In a round 50 ml.-capacity flask, 190 mg of a product of general formula:

\[
R \left[ \begin{array}{c} OCH_2 \text{CH} \text{CH}_2 \text{OH} \\ \text{OH} \end{array} \right] \text{ } \text{ } \text{OH}
\]

wherein \( R \) denotes the alkyl radical of alcohols of hydrogenated lanoline, and \( n \) has a mean statistical value of 3.
100 mg of cholesterol, 20 mg of dicetyl phosphate are dissolved in 3 ml of a mixture of chloroform and methanol in the ratio of 2:1. The solvent is evaporated by means of a rotary vaporizer, whereupon the last traces of solvent are removed by subjecting the mixture of the products for 1 hour to the reduced pressure produced by a vane pump.

The lipidic film obtained is brought into contact with 5 ml of an 8.4% solution of triethanolamine salt of urocanic acid.

A test is made at a temperature of 70°C.

The flask, placed on an agitator, is agitated vigorously for 2 hours at 70°C, after which it is gradually cooled until ambient temperature is reached.

The dispersion is a liquid dispersion.

The grains have a diameter of approximately 1 micron.

**EXAMPLE 22**

In a round 50 ml.-capacity flask, 154 mg of hydrogenated egg lecithin, 40 mg of cholesterol and 10 mg of dicetyl phosphate are dissolved in 6 ml of a mixture of chloroform and methanol in the ratio of 2:1.

The solvent is evaporated by means of a rotary vaporizer, whereupon the last traces of solvent are removed by subjecting the mixture of the products for 1 hour to the reduced pressure produced by a vane pump.

The lipidic film obtained is brought in contact with 5 ml of a 2% solution of the potassium salt of methoxy-cinnamic acid.

A test is made at a temperature of 40°C.

The flask placed on an agitator is agitated vigorously for 2 hours at 40°C, after which it is gradually cooled until ambient temperature is reached.

The grains have an average diameter of 5 microns.
Of course the embodiments described above in no way imply a limitation and can be modified in any desirable manner without thereby going outside the scope of the invention.

The trade marks "TWEEN", "CARBOPOL", "SEPHADEX", "GOODRICH" and "BRJ" are Registered Trade Marks.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOW:-

1. Process for preparing a dispersion of aqueous liquid-containing spherules consisting of ordered molecular layers enclosing an aqueous phase which comprises bringing into contact at least one liquid lipid which is dispersible in water and has the general formula:
\[ X \rightarrow Y \]
in which, X represents an ionic or non-ionic hydrophilic group and Y represents a lipophilic group, with an aqueous phase to be encapsulated by the spherules, the lipophilic/hydrophilic balance of the lipid being such that the lipid swells in the aqueous phase to be encapsulated so as to form a lamellar phase, agitating the mixture thereby to obtain a lamellar phase, adding a liquid dispersing agent in an amount greater than the amount of the lamellar phase obtained and agitating the resulting mixture vigorously for approximately from 15 minutes to 4 hours to obtain the dispersion.

2. Process according to claim 1, in which the weight ratio of the amount of said aqueous phase to be encapsulated to the amount of said lipids forming the lamellar phase is from 0.1 to 3.

3. Process according to claim 1 or 2, in which the aqueous phase to be encapsulated is water.

4. Process according to claim 1 or 2, in which the aqueous phase to be encapsulated is an aqueous solution of an active product.
5. Process according to any one of claims 1 to 4, in which the weight ratio of the amount of said aqueous liquid dispersing agent to the amount of said lamellar phase is from 2 to 100.

6. Process according to any one of claims 1 to 5, in which said aqueous liquid dispersing agent and the aqueous phase to be encapsulated are isotonic.

7. Process according to any one of claims 1 to 6, in which said dispersing agent is an aqueous liquid.

8. Process according to any one of claims 1 to 7, which is carried out at a temperature at least equal to the melting point of the lipid.

9. Process according to any one of claims 1 to 8, in which the dispersion of spherules obtained is subjected to a treatment with ultrasonics such that the mean diameter of the spherules does not exceed 1000 Å.

10. Process according to any one of claims 1 to 9, in which the lipid contains a lipophilic chain having from 12 to 30 carbon atoms.

11. Process according to claim 10, in which the lipid contains an oleyl, lanolyl, tetradecyl, hexadecyl, isostearyl, lauryl or an alkylphenyl chain.

12. Process according to any one of claims 1 to 11, in which the hydrophilic group of the lipid is a non-ionic polyoxyethylene, polyglycerol or an oxyethylenated or non-oxyethylenated polyol ester group.
13. Process according to claim 10 in which the hydrophilic group is a polyoxyethylene.

14. Process according to any one of claims 1 to 11 in which the hydrophilic group of the lipid is an amphoteric compound containing two lipophilic chains or an association of two long-chain organic ions of opposite signs.

15. Process according to any one of claims 1 to 9, in which the lipid is a linear or branched polyglycerol ether of formula:

\[ R \quad - \quad \left( \text{OCH}_2 \text{CH} \text{OH CH}_2 \right)_{n} \quad \text{OH} \]

or

\[ R \quad - \quad \left\{ \text{O CH}_2 \text{CH}_n \quad \text{OH} \right\} \quad \text{OH} \]

\[ \text{CH}_2 \quad \text{OH} \]

wherein n is an integer from 1 to 6 and R is a linear or branched, saturated or unsaturated aliphatic chain comprising from 12 to 30 carbon atoms, a hydrocarbon radical derived by the removal of -OH from a lanolin alcohol, or a 2-hydroxy-alkyl radical of a long-chain \( \alpha \)-diol,

or a polyoxyethylenated fatty alcohol, an oxyethylenated or non-oxyethylenated polyol ester or a natural or synthetic glycolipid.

16. Process according to claim 15 in which the lipid is a polyoxyethylenated sorbitol ester or a cerebroside.

17. Process according to claim 12, 15 or 16 in which the non-ionic lipid is used in conjunction with a long-chain alcohol or diol, a sterol, a long-chain amine or a quaternary ammonium derivative thereof, a dihydroxyalkylamine, a
polyoxyethylenated fatty amine, an ester of a long-chain
aminoalcohol or a salt or quaternary ammonium derivative
thereof, a phosphoric acid ester of a fatty alcohol, an
alkyl-sulphate, a polypeptide or a protein.

18. Process according to claim 17 in which the non-
ionic lipid is used in conjunction with cholesterol, sodium
dicetyl-phosphate or sodium cetyl-sulphate.

19. Process according to any one of the preceding
claims in which the aqueous phase to be encapsulated contains
at least one cosmetic agent which is a humectant, an
artificial bronzing agent, erythrulose, glyceraldehyde
or an γ-dialdehyde, a water-soluble anti-sunburn agent,
an antiperspirant, a deodorant, an astringent, a product
having a freshening, tonic, cicatrising or keratolytic
action, a depilatory, a toilet water, an extract of animal
or vegetable tissues, a water-soluble dyestuff, an anti-
dandruff agent, an anti-seborrhoeic agent, an oxidising
agent or a reducing agent.
20. Process according to claim 19, in which the cosmetic agent is glycerol, sorbitol, pentaerythritol, inositol, a pyrrolidone carboxylic acid or a salt thereof, dihydroxyacetone, a protein, polysaccharide or amniotic fluid, hydrogen peroxide or thioglycollic acid or a salt thereof.

21. Process according to any one of claims 1 to 18, in which the aqueous phase to be encapsulated contains at least one vitamin, hormone, enzyme, vaccine, anti-inflammatory agent, antibiotic or bactericide.

22. Process according to claim 2., in which the aqueous phase to be encapsulated contains dismutase peroxide or hydrocortisone.

23. Process according to any one of the preceding claims in which the dispersion contains at least one opacifier, gelling agent, aroma, perfume or dyestuff.

24. Process according to claim 1, substantially as described in any one of Examples 1 to 5 and 11 to 23.

25. A dispersion of aqueous liquid-containing spherules whenever prepared by a process as claimed in any one of the preceding claims.

26. A dispersion of spherules consisting essentially of ordered molecular layers enclosing an aqueous phase, said layers consisting of at least one lipid which is a non-ionic amphiphilic compound with a lipid chain, said lipid being dispersible in water, the spherules having a diameter of from 100 to 50,000 Å.
27. A dispersion according to claim 26, in which the lipid has a lipophilic/hydrophilic balance such that the compound swells in the aqueous phase thereby forming a lamellar phase.

28. A dispersion according to claim 26 or 27, in which the lipid is as defined in claim 12, 15 or 16.

29. A dispersion according to any one of claims 26 to 28, in which the lipid is present in conjunction with a substance as defined in claim 17 or 18.

30. A dispersion of spherules consisting essentially of ordered molecular layers enclosing an aqueous phase, said layers consisting of at least one lipid of the formula

\[ X---Y \]

wherein \( X \) denotes an ionic hydrophilic group and \( Y \) denotes a lipophilic group, the lipid being dispersible in water and the spherules having a diameter of approximately from 1,000 Å to 50,000 Å.

31. A dispersion according to claim 30, in which the encapsulated aqueous phase is an aqueous solution of an active substance having a cosmetic action.

32. A dispersion according to claim 30 or 31, in which the ratio of the weight of the spherules relative to the weight of the aqueous liquid dispersing agent is from 0.01 to 0.5.

33. A dispersion according to any one of claims 26 to 32, in which the aqueous liquid dispersing agent is isotonic relative to the encapsulated aqueous phase.
34. A dispersion according to any one of claims 26 to 33, which has one or more of the features of the dispersion prepared by the process of any one of claims 16 to 22.

DATED THIS 1ST DAY OF AUGUST, 1979.

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