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(54) Title: NON-AQUEOUS COLLOIDAL FORMULATION

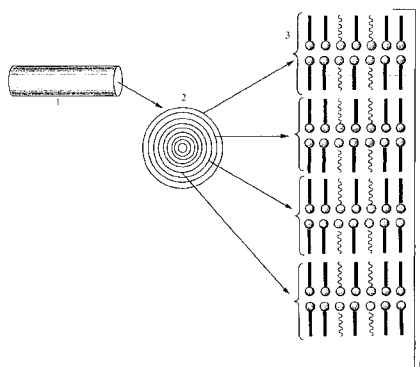


Fig 1

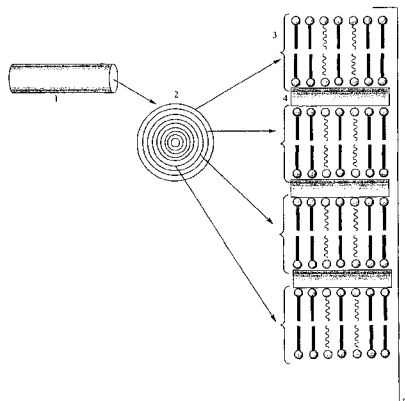


Fig 2

(57) Abstract: The invention relates to formulations, such as a gel, which are non-aqueous, colloidal, consisting of a first and a second component as defined in the specification and having a particular structure as defined in the specification; methods of manufacturing such formulations; oral care compositions and topical / transdermal compositions containing such formulations; methods of manufacturing such compositions and to the use of these formulations and compositions in cosmetics, pharmaceuticals, nutrition and dietary.



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Non-aqueous colloidal formulation

The invention relates to formulations, such as a gel, which are non-aqueous, colloidal, containing tubulosomes as defined herein; methods of manufacturing such formulations; oral care compositions and topical / transdermal compositions containing such formulations; methods of manufacturing such compositions and to the use of these formulations and compositions in cosmetics, pharmaceuticals, nutrition and dietary.

Vesicles have become the vehicle of choice in drug and cosmetic delivery. Different types of carriers of pharmaceutical and cosmetic importance are known in the art. They are particulate, polymeric, macromolecular and cellular carrier. Particulate type carrier, which is also known as colloidal carrier system, includes lipid particles (low and high density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles and vesicles.

A common problem that all water containing dentifrice gel/cream compositions, particularly tooth-pastes, suffer from is that on a longer storage, the inorganic ingredients undergo hazardous, as well as undesired synthetic, chemical reactions with the organic ingredients therein, and water actually stipulates and facilitates such reactions. It is known that an aqueous medium facilitates oxidative/reductive degradation of other ingredients which are easily susceptible towards redox reactions (such as alcohols, glycols, dyes, vitamins, enzymes, flavoring agents, coloring agents) if an oxidizing/reducing ingredient is incorporated.

It is also known that hydrogels require substantial amounts of preservatives, which is disadvantageous, e.g. in case of oral administration.

The present invention aims to overcome one or more or of the problems associated with known formulations containing active ingredients. Particularly, they
5 leak additives / active ingredients from the vesicles (liposomes / niosomes) of such formulations, they can't efficiently solubilize and transport difficult hydrophilic and lipophilic substances/additives, they can't form gels, they need aqueous gel / emulsion.

10

US 4812306 and US5264205 disclose certain anhydrous gel formulations, and teach that the main challenge towards composing a non-aqueous dentifrice gel/cream is to form an anhydrous gel/cream/emulsion,
15 which is consistent in nature, stable in storage, and has appropriate flow properties (viscosity, thixotropy, yield value) and a pleasant surface-texture.

Biju et al (Indian J Pharm Sci 2006;68:141-53) provide an overview on Vesicular systems, also
20 disclosing limitations and problems of the formulations known in the field.

Karthikeyan et al. (Pharmainfo, 2008, vol.6, issue 6) provide an overview on non-ionic surfactant based vesicles ("Niosomes") as a potential ocular drug
25 delivery system.

Thus, it is an aim of the present invention to mitigate at least some of these drawbacks of the prior art. In particular, it is an aim of the present invention
30 to provide further formulations and compositions with improved properties.

These objectives are achieved by a formulation as defined in claim 1 and compositions as defined in
35 claims 8 and 11. Further aspects of the invention are disclosed in the specification and independent claims,

preferred embodiments are disclosed in the specification and the dependent claims.

5 The present invention will be described in more detail below. It is understood that the various embodiments, preferences and ranges as provided / disclosed in this specification may be combined at will. Further, depending of the specific embodiment, selected definitions, embodiments or ranges may not apply.

10

Where the plural form (e.g. compounds, additives, surfactants) is used, this includes the singular (e.g. a single compound, a single additive, a single surfactant). Where the singular is used, (e.g. a compound, a surfactant) this does not exclude the plural (e.g. that more than one compound / surfactant is present).

15

For the sake of brevity, the disclosures of the publications cited in this specification are herein incorporated by reference.

20

As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

25

Unless otherwise stated, the following definitions shall apply in this specification:

A "formulation" relates to a combination of two or more components which are not intended as a product to the end-user but rather a commercial intermediate to manufacture such end-products. The nature of the formulation basically determines the appearance of the end-product, i.e. gel or emulsion.

30

A "composition" relates to a combination of two or more components which are intended as a product to the end-user. Compositions according to this invention contain a formulation as described herein and one or more

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additives. Such additives basically determine the nature of the composition, i.e. a topical / transdermal composition or an oral care composition.

5 An "additive" is any component, other than used for obtaining the formulation as defined above, which is useful in obtaining a composition as defined above.

10 The term "colloid", also in the context of colloidal formulation, is well known in the field. A colloid is a broad category of mechanical mixtures where one substance is dispersed evenly throughout another giving rise to a bi-phase non-crystalline substance consisting of nano-particles. A colloidal system comprises of two separate phases: a dispersed phase (internal phase) and a continuous phase (dispersion medium).
15 The average diameter of the dispersed phase particles approximately ranges between 5 and 200 nanometers. Such particles are normally invisible to an optical microscope, but their presence can be confirmed by ultra-
20 microscopy or electron microscopy. Some colloids are translucent due to the Tyndall effect, which is the scattering of the visible light by particles in the colloid. Other colloids may be opaque or have a slight color. The dispersed phase particles or droplets are
25 largely affected by the surface chemistry present in the colloid. Because the average size of the dispersed phase particles may be difficult to measure, and because colloids have the appearance of solutions, colloids are sometimes identified and characterized by their properties.
30 There are eight different types of colloid, each of which has a different name according to the identity of the dispersed phase and the phase acting as the dispersion medium. A gas suspended in a liquid or solid is called foam. A liquid dispersed in a different liquid is
35 called an emulsion. A liquid dispersed in a solid is called a solid emulsion. A solid or liquid suspended in a gas is called an aerosol. A solid suspended in a liquid

is called a sol although a high concentration of solid is also called a paste. A solid suspended in a solid is called a solid suspension. There are several important forces of interaction that interplay among the colloidal particles attributing to overall stability (or instability) of the colloidal system. Major forces are as follows: i) Excluded Volume Repulsion; ii) Electrostatic interaction; iii) van der Waals forces; iv) entropic forces; v) Steric forces.

10 The term "surfactant" is well known in the field. Surfactants are surface active compounds that reduce the surface tension of a liquid and interfacial tension between two liquids by adsorbing at the interfaces of liquid-gas and liquid-liquid, respectively. 15 Therefore, they facilitate the formation of liquid film at the interface by allowing the dispersion medium (liquid) be spread easily. Surfactants are usually organic compounds that are amphiphilic due to coexistence of hydrophilic and lipophilic groups, often referred to as "heads" and "tails", respectively. Surfactant solutions may contain a disordered phase of free monomers (molecules and/or ions, "nM") and an ordered phase of aggregates (micelles, vesicles, etc., "M"_n), through self-assembling above a critical concentration and 25 temperature, in equilibrium. A surfactant can be classified by the presence of formally charged groups in its head. A non-ionic surfactant has no charge groups in its head. The head of an ionic surfactant carries a net charge (negative = anionic; positive = cationic; head with two oppositely charged groups = zwitterionic). 30

 In the context of the present invention, "surfactant family" refers to a group of surfactants belonging to a given set of H_xT_y, where H and T denote particular head and tail groups that are extended by digital numbers of x and y, respectively, to form a family 35 in which each surfactant is identified as a member of it. Exemplary surfactants which may be used for the

inventive formulations are identified in table 1 (see end of specification).

The term "micelle" is well known in the field. A micelle is an aggregate of surfactant molecules dispersed in a liquid colloid. Geometrical orientation of the head-tail groups in monomers in such an aggregate depends on the polarity of the dispersing medium. In an aqueous or polar medium, monomer units assemble in such a fashion that the head groups form the outer surface, surrounded by the polar solvent molecules, while the liophilic tails are sequestered in the inner core or centre region. This type of micelle is called normal phase or typical micelle. In a non-polar medium/solvent, the hydrophilic heads are sequestered in the core/centre region and the liophilic tails are extended away from the core region. This type of micelle is known as reverse/inverse micelle. A micelle may form when surfactant molecules aggregate to form particles suspended in solution, which is a colloid, nonetheless. Since micelle forms colloid by the association of a discrete number of components, it is often called an "association colloid".

The term "vesicle" is well known in the field. Vesicles are uni- or multi-lamellar aggregates composed of bi-layers of amphiphilic molecules. They are, in general, spheroid. Phospholipids, cholesterol and surfactants are known to form vesicles in aqueous medium. Surfactant vesicles are analogous to surfactant micelles in molecular structural sense. The bi-layer comprises of either typical (head groups are pointing towards both the exterior as well as interior polar solvent, while tail groups of both layers are sequestered face one another) arrangement of the amphiphilic molecules or reverse. "Liposomes" and "niosomes" are vesicles that have been used as carriers of various drugs. Liposomes are simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecules with double

- 7 -

liophilic tails. There are a number of components present in liposomes, with phospholipid and cholesterol being the main ingredients. The type of phospholipids includes phosphoglycerides and sphingolipids, and together with
5 their hydrolysis products. Niosomes are similar vesicular aggregates that stems from non-ionic surfactants instead of phospholipids in an aqueous medium.

The term "gel" is well known in the field. Generally, gels are an intermediate state of matter, containing both solid and liquid components. The solid
10 component comprises a three-dimensional network of interconnected aggregates (typical/reverse vesicles) or molecules which immobilizes the liquid continuous phase. Hydrogels have an aqueous continuous phase, and organo-
15 gels have an organic solvent as the liquid continuous phase. Gels may also be classified based on the nature of the bonds involved in the three-dimensional network. In chemical gels, strong covalent bonds comprise the gel network, and in physical gels, the hydrogen bonds,
20 electrostatic and van der Waals interactions, which are relatively weaker.

The present invention will be better understood by reference to the figures.

25 Fig. 1 shows an idealized inverse tubulosome structure of an inventive formulation, wherein the dispersing medium is substantially non-polar or liophilic. In this figure, 1 shows a tubulosome vesicle in perspective view, 2 shows the cross section of this
30 tubulosome, 3 shows an enlarged view of this cross section identifying a stacked, bi-layered surfactants; n denotes the number of stacking.

Fig. 2 shows an idealized typical tubulosome structure of an inventive formulation, wherein the
35 dispersing medium is substantially polar or hydrophilic. In this figure, 1 shows a tubulosome vesicle in perspective view, 2 shows the cross section of this tubulosome,

3 shows an enlarged view of this cross section identifying stacked, bi-layered surfactants; n denotes the number of stacking; 4 denotes hydrophilic interior.

Fig. 3 shows a known spherical liposome / ni-
osome vesicle 1; its idealized 3D structure 2, its 2D
cross-section 3. In 3, typical bilayer lamella (e.g.
phospholipid nonionic surfactant) 4, hydrophilic core 5,
lipophilic interior 6, and surrounding aqueous medium 7
are shown.

10

The invention may be more fully appreciated
by reference to the following description, including the
glossary of terms given above and the concluding exam-
ples.

15

Thus, in a first aspect, the invention re-
lates to a non-aqueous colloidal formulation comprising
of a first and a second component wherein said first
component is an amphiphilic, non-ionic surfactant; said
second component is a water-free, liquid, organic
dispersing medium.

20

Preferred embodiments and various aspects of
this first aspect of the invention are explained below.

25

In an advantageous embodiment, the invention
relates to a formulation which is a gel (i.e. solid /
liquid phase) or an emulsion (i.e. liquid / liquid
phase). Depending on the selection of first and second
component, the formulation may be a gel selected from the
class of i) organogels, ii) pure amphiphilic gels, iii)
mixed amphiphilic gels and iv) co-gels.

30

This inventive formulation is engineered to
accommodate various additives either solubilizing over a
wide range of solubility or suspending, retain the
chemical functionalities of additives, transport and

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deliver the additives to target site through a range of possible administration methods. Without being bound to theory, it is believed that this is due to the formation of a stable isotropic, visco-elastic association colloid.

5 Such colloid comprises multi-lamellar bi-layer stacked tubular vesicle (tubulosome) carriers of amphiphilic surfactants. Such tubulosome carriers constitute the skeleton of a three dimensional gel network to immobilize the solvent/liquid medium thereby, which is consistent,

10 stable on storage with high shelf-life. Such colloids are easy to manufacture at industrial scale, offer broad range of adjustable viscosity and gel-flow properties (rheology, yield point/value, thixotropy), are capable to accommodate various additives (through solubilizing the

15 hydrophilic ones in the hydrophilic interior of tubulosomes, the liophilic ones in the liophilic interior of tubulosomes as well as in the continuous solvent and suspending the particles of the insoluble ones within the 3D gel network), are suitable towards oral-care /

20 dentifrice applications and topical / transdermal applications onto skin. The swollen tubulosomes are capable in transporting the entrapped additives / drugs through osmotic diffusion, and hence ensure / stipulate sustained release at site-specific target. This non-

25 aqueous tubulosome based gel / association colloid technology thus offers a unique way to preserve the chemical functionalities of the ingredients thereby, and to selectively as well as sustainably deliver them to the target site through a number of administration methods.

30

The first component, referred to above, is also referred to as the "gelator" or "gelling agent". The invention particularly relates to a formulation as described herein, wherein said first component is a

35 solid, amphiphilic, non-ionic surfactant. Preferred is one or a combination of solid surfactants, belonging to non-ionic, zwitterionic, anionic and cationic classes of

surfactants, with a melting point (MP) ranging between 35 - 80°C, more preferably between 45 - 70°C, and most preferably between 50 - 65°C. Non-ionic and zwitterionic surfactant classes are more preferable, while the non-ionic class is most preferable. Said surfactant is particular preferably selected from the mono- and poly-ester families of Sorbitan, Glycerol, Glycol, polyalkylglycol and fatty alcohols (with hydrocarbon chain with at least 12 carbon atoms and higher) with fatty acids such as lauric acid, palmitic acid, stearic acid, oleic acid, cocoic acid, ricinolic acid, tallic acid, etc; mono- and poly-substituted amine oxides of fatty alcohols, mono- and poly-substituted alkanolamides; Ethylene Oxide (EO)/Propylene Oxide (PO) block copolymers (such as $[EO]_x[PO]_y[EO]_x$, $[PO]_x[EO]_y[PO]_x$); alkylamine ethoxylates (such as $CH_3-[CH_2]_1-N[EO]_m[EO]_n$); Polyethyleneoxide (PEG) ethers of fatty acids etc. Further, said solid, amphiphilic non-ionic surfactant may be selected from the group consisting of mono- and poly-esters, wherein the acid component of said ester is selected from the group consisting of behenic acid, eicosadic acid and isostearic acid ; the alcohol component of said ester is selected from the group consisting of glycol, glycerol, polyglycols and poly-glycerols; particularly Polyglyceryl-10 Behenate / Eicosadioate; Glyceryl Behenate / Eicosadioate and Glyceryl tribehenate / Isostearate / Eicosadioate.

The second component, referred to above, is also referred to as "dispersing medium". In the context of the present invention, dispersing media includes liquids without surfactant properties as well as liquids with surfactant properties.

Liquids with surfactant properties: A wide variety of liquid surfactants / classes of surfactants may be used as a second component. Such surfactants include non-ionic, anionic, cationic, zwitterionic surfactants.

- 11 -

Non-ionic surfactants: are preferably based on the mono- and poly- ester families of Sorbitan, Glycerol, Glycol, polyalkyl-glycol and fatty alcohols (with hydrocarbon chain with at least 12 carbon atoms and higher) with fatty acids such as lauric acid, palmitic acid, stearic acid, oleic acid, cocoic acid, ricinolic acid, tallic acid, etc; mono- and poly-substituted amine oxides of fatty alcohols, mono- and poly-substituted alkanolamides; Ethylene Oxide (EO)/Propylene Oxide (PO) block copolymers (such as $[EO]_x[PO]_y[EO]_x$, $[PO]_x[EO]_y[PO]_x$); alkylamine ethoxylates (such as $CH_3-[CH_2]_1-N[EO]_m[EO]_n$); Polyethyleneoxide (PEG) ethers of fatty acids; etc. For the avoidance of doubt, liquid non-ionic surfactants serve as "second component" as defined herein, while solid, non-ionic surfactants serve as "first component" as defined herein.

Anionic surfactants: are preferably based on sulfate, sulfonate and carboxylate anions. Particular preferred are Alkali metal salts of fatty acids, such as Sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, other alkyl sulfate salts, Sodium laureth sulfate (also known as sodium lauryl ether sulfate SLES), Alkyl benzene sulfonate, Sodium Lauroyl Sarcosinate.

Cationic surfactants: are preferably based on quaternary ammonium cations. Particular preferred are Cetylpyridinium chloride (CPC) and other halides, Benzalkonium chloride (BAC) and other halides, Benzethonium chloride (BZT) and other halides, Cetyl trimethylammonium bromide (CTAB) (hexadecyl trimethyl ammonium bromide), and other alkyltrimethylammonium salts, Polyethoxylated tallow amine (POEA).

Zwitterionic surfactants: Particular preferred are Dodecyl betaine; Cocamidopropyl betaine; Dodecyl dimethylamine oxide; Coco amphoteric glycinate; betaine oxides, alkyl amine oxides.

Liquids without surfactant properties: A wide variety of organic liquids without surfactant properties

may be used as a second component in the inventive formulations. Such organic liquids include vegetable oils such as corn oil, cottonseed oil, soybean oil, olive oil, sesame oil, sunflower oil and castor oil. Such organic liquids also include derivatives of vegetable oils (such as alcohols, esters, alkoxylates of vegetable oils); particularly long chain synthetic esters such as isopropyl myristate, ethyl oleate, ethyl myristate, etc.; Such organic liquids also include acyclic and cyclic alkanes (higher than five carbon) such as hexane, octane, decane, dodecane, tetradecane, hexadecane, octadecane, cyclohexane, cis and trans decalines, Such organic liquids also include polyalkenes, such as polyisodecene, polyisobutene, polybutene, etc.; Such organic liquids also include cyclic and acyclic alkenes such as squalene.

In the context of the present invention, the structure of the inventive gels may be described as (1) pure amphiphilic gel; (2) Organogel; (3) Mixed amphiphilic gel; and (4) Co-gel. (1) Pure amphiphilic gel: This type comprises gels where the first component comprises one or more solid amphiphilic surfactants and the second component comprises or consists of a liquid amphiphilic surfactant. (2) Organogel: This type comprises gels where the first component comprises one or more solid amphiphilic surfactants and the second component comprises one or more liquids without surfactant properties. (3) Mixed amphiphilic gel: This type comprises gels where the first component comprises one or more solid amphiphilic surfactants and the second component comprises two or more liquid amphiphilic surfactants. (4) Co-gel: This type comprises those gels wherein the second component is a mixture of an organic liquid without surfactant properties and a liquid amphiphilic surfactant.

- 13 -

Organogels (2) have revealed the surfactant aggregates to form rod-like tubular clusters. The clusters associate with each other through junction points due to van der Waals and electrostatic dispersion interactions (including weak to strong hydrogen bondings) constructing a 3-D network that immobilizes the solvents and acts as the skeleton of the gel. As the sol phase cools and the solvent-surfactant affinities decrease, doughnut shaped, interface- (membrane) bound, inverse toroidal vesicular structures have been seen to form as surfactant gelator molecules self-assemble. The toroids are short-lived structures, existing only at the gelation temperature. Further cooling results in their conversion into tubules. Gel microstructure is affected upon incorporation of a relatively higher hydrophilic surfactant, such as polysorbate 20, polysorbate 40, pluronic, PEG-80 Sorbitan Laurate, etc. Organogels spiked with the hydrophilic surfactants comprise star-shaped clusters of the surfactant tubules. The molecules of spiking hydrophilic surfactants are revealed to participate in formation of mixed inverse bi-layers, which is comparable to mixed reverse micelle, and thus formation of tubular aggregates, tubulosomes, by stacking.

Amphiphilic gels (1); (3) consist of tubules that become more numerous with increasing gelator concentration. In contrast to rod-like clusters in surfactant organogels, the tubulosomes are clustered into star- or flower-shaped structures with a diameter of order 8-100 μ m in the amphiphilic gels as in cases of organogels spiked with a hydrophilic surfactant. In amphiphilic gels, tubules are revealed to be the aggregates of concentrically stacked sheets of mixed surfactant bi-layers with solvent embedded interiors. The mixed typical tubulosomes possess higher number of binding sites that stipulate multidimensional clusterification through inter-vesicular association interactions to

produce star or flower shaped clusters in amphiphilic gels, compared to mono-dimensional clusterification to rod-like clusters in organogels. Higher binding sites attribute to more compact structure of the gel network and hence to greater stability. The clusterification proceeds through fractal growth yielding a 3D gel network, which is essentially a volume fractal, as sol phase cools down. Fractal growth through higher binding sites gives rise to higher fractal dimensionality to the offspring clusters, and hence to the resulting gel network as well. Higher fractal dimensionality attributes to the higher stability and chemical reactivity to the amphiphilic gels, compared to the organo gels with relatively lower fractal dimensionality. In contrast to star- or flower-shaped clusters of tubulosomes in the majority of the disclosed amphiphilic gels, the clusterification of the tubulosomes proceeds through unidirectional (mono-dimensional) fashion yielding tubular or fibrous network when the liquid medium/solvent of the amphiphilic gel is a very thick viscous substance, such as Polysorbate 60 (semi-solid at room temperature) and Span 20 (thick viscous liquid at room temperature).

The toroids and rod-like clusters in organogels, and tubular/fibrous and star/flower shaped clusters in amphiphilic gels are composed of stacked bi-layer lamella of surfactant molecules, in a fashion similar to well-known vesicles, liposomes and niosomes. This arrangement is retained upon gelation and therefore, the tubules in gel network are comprised of concentric sheets of bi-layers ("Tubulosome"). This is a unique feature of present invention. The disclosed tubulosomes exactly match to the functional properties of the liposomes and niosomes, although they are more efficient to solubilize the hydrophilic as well as liophilic substances/additives and do not require sophisticated and expensive preparation routes. The active ingredients can be swollen by the

tubulosomes which span the entire skeleton of the organo- and amphiphilic-gels, giving rise to swollen tubulosomes and thus attributing to huge enhancement in solubilizing power and stability of the disclosed gel formulations. As
5 a result, these swollen tubulosomes largely boost the bioavailability of the active ingredients as well as enable the disclosed gels permeating the active ingredients into and/or through the skin. These make them attractive carrier vehicles in cosmetic and drug industry
10 for oral, topical and transdermal applications.

In the context of the present invention, the closed association model states that above a critical temperature (Krafft temperature) and a critical concentration (critical aggregation concentration, CAC)
15 monomers nM of a surfactant in a given bulk solution / medium / sol-phase spontaneously self-assembles / aggregates to form aggregates (either typical in which head groups point toward aggregate-solvent interface, or
20 reverse/inverse in which tail groups point towards aggregate-solvent interface) of equal size, but below CAC and/or Krafft temperature monomers are retained in the bulk phase.

25 It is important to identify a fundamental property (or a group of them) that underpins towards predicting the functional properties, including efficiency, selectivity (formation of emulsions of type, viz. water-in-oil W/O, oil-in-water O/W, water-in-oil-in-water
30 W/O/W and oil-in-water-in-oil O/W/O, formation of gels of type, viz. hydrogel and organogel, formation of microemulsions of type, viz. W/O, O/W, W/O/W, O/W/O and others, detergency, foaming capacity, nature of micelles, viz. typical, reverse/inverse, appearance or optical proper-
35 ties, and the like) and stability of the resulting associated colloids, of surfactants across various families with different chemical structures.

In the present invention, a group of predicting properties, including CMC, aggregation number (N), melting point, molecular packing parameter (P) and hydrophilic-lipophilic balance (HLB) of a surfactant are formulated towards its appropriate application. Tailoring a particular trade-off combination of these properties casts a surfactant to yield the desired associated colloid system with satisfactory properties and stability.

The co-existence of two opposite types of behavior (hydrophilic and hydrophobic / lipophilic) inside the same molecule is the origin of local constraints which lead to spontaneous aggregation into microscopic labile structures observed with surfactants in solution / dispersion in oil (organic solvent/medium) or water (polar solvent). Within individual surfactant families, increases in efficiency, selectivity, or activity often do correlate with increasing hydrocarbon tail length. This effect can be understood in terms of an increasing hydrophobicity of the surfactant, which may reflect its improved ability to form aggregates (micelles, vesicles) and solubilize hydrophobic substances. Increasing chain length and branching tails largely improve a surfactant's affinity towards forming aggregates. It is therefore prognosticated that the hydrophilic-lipophilic balance (HLB) is a characteristic property of a surfactant. The HLB was originally developed as a scale to classify the relative effectiveness of non-ionic surfactants towards forming stable emulsions at room temperature. Griffin proposed an empirical formula to evaluate the HLB number of a surfactant molecule through calculating the total molecular weight fraction of hydrophilic part in a given molecule:

$$HLB = 20 * MH / M$$

Where MH is the sum of molecular weights of the hydrophilic portion of the molecule, and M is the total molecular weight of the whole molecule, giving a

- 17 -

result on an arbitrary scale of 0 to 20. An HLB value of 0 corresponds to a completely hydrophobic/liophilic molecule, and a value of 20 corresponds to a molecule totally hydrophilic. In this sense, HLB value can be used to select a surfactant molecule for a particular functional role:

HLB value 0 to 3 : an anti-foaming agent

HLB value 4 to 6 : a W/O emulsifier

HLB value 7 to 9 : a wetting agent

10 HLB value 8 to 18 : an O/W emulsifier

HLB value 13 to 15 : a typical detergent

HLB value 10 to 19.5 : solubilizer or O/W microemulsifier

Each lipophilic ingredient used in O/W emulsion/sol has a "required" HLB number, which can be determined through a simple experiment of forming stable emulsion with a standard surfactant of known HLB number. In other words, the HLB value of the surfactant that provides the lowest interfacial tension between the unique oil and water phases is the "required" HLB of the oil. HLB number of the surfactants can be alternatively measured through chromatographic experiments. In table 1 and 2 we report the HLB numbers and required HLB numbers of various surfactants and liophilic substances, respectively.

A mixture of surfactants (surfactant blend) of different families and/or classes (with different HLB values) is known to be advantageous, over a single surfactant, in practical formulation of stable association colloid systems, especially in industrial end uses, since an appropriate surfactant blend is often able to provide lowest interfacial tensions. Depending on the concentration fraction, three situations can arise:

The molecules of the surfactant (B), which is present in low concentration, can adsorb at the interface of the aggregates (vesicles, micelles) of the other surfactant (A), which is present in solution / dispersion

in much higher concentration. This leads to an overall lowering in interfacial tension between aggregate and solvent due to the relaxation in repulsions among the head groups of the aggregates, and due to lowering the contact between inner hydrophobic core and water in case of typical vesicles / micelles. This adsorption also results in lowering aggregate-aggregate repulsion, which enhances the over kinetic stability of the colloid system against coalescence.

10 If A and B are present in bulk solution with comparable concentration and above the CMC, they often increase the resulting CMC of the blend and produce mixed aggregates (vesicles, micelles) with lower size, which are thermodynamically, as well as kinetically more stable than the bigger aggregates. Formation of smaller aggregate promotes formation of more aggregates in solution / dispersion. If one of these surfactants has lower HLB due to its larger liophilic tail group, it promotes in-core solvation of the liophilic materials in liophilic interior of vesicles and typical micelles and raises overall attractive aggregate-aggregate and aggregate-solvent interactions in a liophilic or substantially low polar solvent / medium. The surfactant with higher HLB in this pair, promotes aggregate-solvent (solvation) interactions in substantially hydrophilic solvent/medium, while in liophilic or substantially low polar solvent/medium it promotes formation of more reverse/inverse aggregates (vesicles, micelles) with smaller size.

 There is a third possibility that one of these two surfactants is dissolved in the interior/core of the vesicle / micelle of other one, giving rise to a swollen vesicles / micelle, which always promotes formation of more vesicles / micelles and hence attributes to the thermodynamic stability of the system. Interfacial tension is much lower in a swollen aggregate (vesicles, micelle).

It is in this context important to mention that application of surfactant blend of two or more surfactants has revealed to elevate the temperature of phase inversion and cloud point of sol and emulsion phases and broaden the phase transition temperature of sol-to-gel (gel-to-sol) process of the association colloids of present formulation. Therefore, such association colloids possess remarkable stability toward coalescence and syneresis (the tendency of the liquid components to separate from solids) or phase separation and significantly long shelf-life.

HLB number of a surfactant blend can be easily computed through summing the concentration fraction times the HLB number of the surfactant components. Likewise, total "required" HLB number of a mixture of liophilic ingredients can be calculated by summing the concentration fraction times its required HLB number for all liophilic components. HLB numbers of the components can either be theoretical or experimentally measured. Matching total HLB number of surfactant (surfactant blend) with total HLB requirement of a liophilic substance (a mixture of liophilic substances) yields largest entrapment of the additives within vesicles as well as most stable swollen aggregates (swollen tubulosomes) in sol phase association colloids.

In the original definition, HLB was meant to be a specific property based solely on the chemical structure of a surfactant. Each functional group was assigned a specific value based on correlation of emulsion properties for various surfactants. Thus, HLB was thought to be independent of intensive variables such as temperature or ionic strength. However heating a gel phase of an association colloid leads to sol phase and cooling a sol phase leads to gel phase back; the temperature at which this phase transition occurs is called phase transition temperature. Likewise, heating an oil-

in-water emulsion or sol phase leads to phase inversion, or formation of a water-in-oil emulsion/reverse sol phase; the temperature at which this occurs is the phase inversion temperature, and is common to many nonionic surfactant emulsions and sols. These phase transition and inversion can be interpreted as a consequence of the increase in relative hydrophobicity of nonionic surfactants (the surfactant starts to get dissolved in the oil or liophilic interior of vesicle/micelle) with temperature or ionic strength, which in turn leads to a change in aggregate curvature and ultimately packing about the aggregate-solvent interface. So, although HLB may include specific structural information about a given surfactant, its interpretation in terms of other physical properties is somewhat limited.

One parameter that has been successfully used to categorize surfactant aggregate and resultant phase structure for various systems is the molecular packing parameter (P), which is defined as:

$$P = v / (a * l)$$

where v is the volume of the hydrocarbon (hydrophobic) chain (tail group), l the length of the chain and a the cross-section area of the head group (hydrophilic). "a" can be determined from the CAC/CMC measurements, while for single chain hydrocarbon tails, one can estimate v and l as:

$$v = 27.4 + 26.9 * n$$

$$l = 1.5 + 1.255 * n$$

where the units for v and l are angstrom³ and angstrom, respectively, and n the number of hydrocarbon units in the chain within the model assumption that the chain is at maximal extension for which it remains fluid. However, the properties of the chain are not greatly influenced by the type of head group for a given surfactant, and thus these correlations hold reasonably well for a wide range of ionic, zwitterionic, and nonionic surfactants. In case of typical aggregate, the head

groups are always located at the hydrophilic solvent-hydrocarbon interface, but some solvent-hydrocarbon contact remains and cannot be avoided. Complete coverage by head groups would require a close proximity between them which is incompatible with their mutual repulsion. Because of its minimum area for a given volume, the spherical shape is the best way to minimize this contact area. Aggregates are thus expected to be spherical whenever it is sterically possible. To avoid this solvent-hydrocarbon contact, solvent molecules are expelled from the liophilic interior which is composed of dry hydrocarbon of constant density. It has been shown that spherical micelles can grow up to a maximum value of aggregation number (N_{sph}) and any further growth induces a shape deformation. This limit is calculated on purely geometrical grounds and is strongly dependent on the value of l ; any surface roughness increases N_{sph} sharply. It is obvious that most of a sphere, volume sits close its surface; a radius increase of 26% doubles the volume. A radius increase by $2.35\text{\AA}$ results in an increase of N_{sph} from 56 to 82 for a hydrophobic chain with 12 carbon atoms. The ratio of the area per head group (a) to the average section of the hydrophobic part (v/l), which is the molecular packing parameter P , defines the spontaneous curvature R_{sph} of the interface. P is the fundamental geometric quantity for structural descriptions. Its value has to be kept in mind for any surfactant-solvent couple. A value of P higher than 1 indicates a spontaneous bending of the interface towards oil (hydrophobic / liophilic medium / solvent), while a value lower than 1 indicates a spontaneous bending towards water/hydrophilic medium/solvent (typical micelles). For concentrated solution/dispersion, such as micro-emulsions and surfactant gels, the qualitative estimate of R_{shp} is no longer sufficient, since oil-water (hydrophilic-liophilic) has to be characterized by two curvatures on each point. P depends on the surfactant chemical structure (l and v)

and on surface repulsions between the head groups (a). The desired curvature (and thus type of aggregate) may be obtained upon a correct choice of the surfactant molecule and solvent conditions (type of solvent, ionic strength, etc), using P as a guide. P values can be used to estimate the aggregate shape based on the geometry of the monomer, such as a value between 0 and $1/3$ corresponds to spherical shape, $1/3$ and $1/2$ corresponds to cylindrical shape (for single chain tail groups, and the aggregate can be flexible), $1/2$ and 1 corresponds to lamellar shape (for single as well as double chain tail groups, and the aggregate can be flexible), and a value higher than 1 corresponds to reverse/inverse micelles in substantially liophilic or non-polar solvent/medium.

Small aggregates are obtained with ionic and zwitterionic surfactants, while large ones are made up with non-ionic or ionic surfactants under conditions of high ionic strength, since size is controlled by the repulsion interactions between head groups at the interface. When repulsions increase, "a" increases and hence P decreases resulting in generation of smaller aggregates. As a consequence, size and critical aggregation concentration (CAC) are related: surfactants with low CAC aggregate into large aggregates, the higher the CAC, the smaller the aggregates. Therefore, a continuous size increase (and CAC decrease) is observed as salt is added in ionic surfactant sol phase. The same effect is obtained when surfactant solution is concentrated.

Large aggregates: The area per head group in an ellipsoid being less than that of a sphere, the transition to large aggregates occurs upon a reduction of inter-head group repulsions. It may be caused by salt or surfactant addition, or solubilization. Aggregate growth is then controlled by entropy and a large polydispersity is expected in sol phase. Because of the limited length of a surfactant molecule, at least one dimension of larger aggregates is equal to twice this length, leading

to cylinders with spherical end caps or lamellae with toroidal rims. Such aggregates may be flexible. Energetically unfavorable edges can be avoided upon formation of toroids from cylinders or vesicles from lamellae, but the energy reduction may be compensated by a decrease of deformation entropy. The transition from rigid to flexible aggregates as well as the persistence length of coiled aggregates depends on the nature of the surfactant molecules. The strength of interfacial interactions governs the variation of area per head group and thus flexibility. When flexibility is strongly hindered as in during non-ionic gel formation from sol phase, interacting rods are observed, resulting in a viscoelastic behavior of the medium.

Solvation: solvent penetration in the vesicular interiors and interface thickness: High HLB Amphiphilic solvent molecules surround typical vesicles (tubulosomes) and some solvent molecules are bound to the hydrophilic groups at the surface as well as in the hydrophilic interiors of the multi-lamellar structure of the vesicle. Therefore, lamellar embedded as well as interfacial solvent molecules attribute greatly to the stability of tubulosomes and to overall stability of the gels. Low HLB solvent molecules though surround and bind to liophilic surface of the reverse/inverse vesicles (tubulosomes), their embedding into the liophilic interiors of the lamellar structure is rather fewer. This ascribes the relatively lower stability of tubulosomes, stemming from reverse bi-layer stacking compared to the ones stemming from typical bi-layer stacking (Figs 1 and 2), and hence the overall much greater stability and shelf-life of amphiphilic gels over the organo gels. The de-solvation of the interface as well as lamellar interiors is necessary for two vesicles to merge (coalescence) and requires the de-solvation energy, which is much higher than that of uni-lamellar vesicles and micelles. Therefore, multi-lamellar vesicles, such as

tubulosomes are more efficient in entrapping additives against coalescence.

The term "tubulosome" shall be explained in further detail below: On a micro-level, the inventive formulation according to this aspect may be considered an isotopic association colloid wherein tubulosomes furnish a three-dimensional network, particularly a network of linked clusters that spans the entire volume as a skeleton. The term tubulosomes is chosen to describe tubular shaped, multi-lamellar vesicles comprising of stacked bi-layers of amphiphilic surfactant molecules. Idealized tubulosome structures are shown in figures 1 and 2.

As the dispersion of the said first and second components is heated, along with vortexing, at least 5°C above the melting point of said first component, the surfactant molecules form a "sol" phase, which upon gradual cooling with vortexing stipulates tubular shaped, concentric stacked bi-layer vesicles ("tubulosomes"), of the surfactant molecules near the phase transition temperature. Formed tubulosomes, which remain soluble in the sol phase within the range of phase transition, aggregate further into clusters, which establish linkage through junction points to construct a 3D network over the volume, as temperature drops down further, giving rise to viscoelastic/thickening property to the formulation.

It is thus understood that the term "formulation" relates to an association colloid (such as a gel) while "tubulosomes" are the structural unit of such association colloid. It is believed that tubulosomes aggregate / associate through van der Waals and electrostatic interactions to form clusters which are tubular shaped in Organogels, and star- or flower- shaped in all disclosed amphiphilic classes of gels (pure gels, mixed

gels and co-gels) and in organogels spiked with one or more solid and / or liquid hydrophilic surfactants.

For a successful formation of tubulosomes, it was found by the present inventors, that the first component has to be a) insoluble (or substantially insoluble) in the second component at room temperature (e.g. 20 - 25°C) and b) fully miscible in the second component when heated above its melting point of the first component. Upon heating, the combination of first and second component form a sol phase (due to solubility / insolubility balance). It was found that tubulosomes are not formed when such sol phase is not obtained.

Further, the tubulosomes can be either "typical" (or "regular"), in which head groups in bi-layer point towards the polar/substantially hydrophilic liquid continuous medium, or "inverse" ("reverse"), in which lipophilic tail groups in bi-layer point towards lipophilic (hydrophobic)/substantially low polar continuous medium/solvent. According to the present invention, the tubulosomes of the formulation exhibit inverse geometrical orientation of the surfactant molecules in organogels, while typical orientation in all classes of amphiphilic gels.

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The inventive compositions, comprising such tubulosome structure, prove to be superior when compared to other formulations comprising known vesicles, such as niosomes. The inventive formulations are thus useful to replace the known formulations containing Liposomes and Niosomes; particular in pharmaceutical and cosmetic compositions. First, tubulosomes are considered a self gel forming agent, while niosomes are incapable of forming a gel or thicken a formulation. This avoids the addition of a further component. Second, the entrapment of additives into tubulosomes does not require an extra step (it occurs in the sol phase), while niosomes must be

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loaded in an extra step. This avoids one manufacturing step, which is often sensitive and difficult for scale-up.

5 In a further advantageous embodiment, the invention relates to a formulation as described herein wherein said first component is a liquid, amphiphilic, non-ionic surfactant.

10 In a further advantageous embodiment, the invention relates to a formulation as described herein wherein said second component is selected from the group consisting of vegetable oils, and derivatives of vegetable oils, such as alcohols, esters, alkoxylates; long
15 chain synthetic esters such as isopropyl myristate, ethyl oleate, ethyl myristate, etc.; acyclic and cyclic alkanes (higher than five carbon) such as hexane, octane, decane, dodecane, tetradecane, hexadecane, octadecane, cyclohexane, cis and trans decalines, etc.; and alkene squalene.
20 Particularly preferred are vegetable oils selected from the group of cottonseed oil, soybean oil, corn oil, sesame oil, olive oil, castor oil and sunflower oil, and the long chain synthetic esters selected from the group consisting of ethyl olate and ethyl myristate and
25 isopropyl myristate. Such formulations may be referred to as an "Organo-Gel".

 In a further advantageous embodiment, the invention relates to a formulation as described herein
30 wherein said second component is selected from the group consisting of liquid, non-ionic surfactants. Said liquid non-ionic surfactant is preferably selected from the mono- and poly- ester families of Sorbitan, Glycerol, Glycol, polyalkyl-glycol and fatty alcohols (with
35 hydrocarbon chain with at least 12 carbon atoms and higher) with fatty acids such as lauric acid, palmitic acid, stearic acid, oleic acid, cocoic acid, ricinolic

- 27 -

acid, tallic acid, etc; mono- and poly-substituted amine oxides of fatty alcohols, mono- and poly-substituted alkanolamides; Ethylene Oxide (EO)/Propylene Oxide (PO) block copolymers (such as $[EO]_x[PO]_y[EO]_x$,
5 $[PO]_x[EO]_y[PO]_x$); alkylamine ethoxylates (such as $CH_3-[CH_2]_l-N[EO]_m[EO]_n$); Polyethyleneoxide (PEG) ethers of fatty acids; etc. Such formulations may be referred to as a "Pure Amphiphilic Gel" (if one of said surfactants is used) or as a "Mixed Amphiphilic Gel" (if two or more of
10 said surfactants are used).

In a further advantageous embodiment, the invention relates to a formulation as described herein wherein said second component is a combination of (i)
15 organic solvents/liquids as defined herein, and (ii) liquid, non-ionic surfactants as defined herein. Such formulations may be referred to as a "Co-Gel".

In a further advantageous embodiment, the invention relates to a formulation as described herein wherein the said first component is present in concentration range of 0.1 to 50, preferably 1 to 40, more preferably 5 to 35, and most preferably 10 to 30 %weight/weight (%first/second w/w) to the said second component.
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In a further advantageous embodiment, the invention relates to a formulation as described herein wherein a low net HLB value of the first component (3.5-7.5, more preferably 4.5-7) and higher net HLB value (4-20, more preferably 8-18, most preferably 15-17) of the
30 second component (wherein a liquid surfactant or a blend of surfactants comprises the solvent) are combined. Such formulations yield best outcome towards commercial applications. For example, Sorbitan monostearate (Span 60; HLB=4.7, MP=55.2C) gels all solvents herein at lower MCG,
35 compared to Sorbitan monopalmitate (Span 40; HLB=6.7; MP=47.8).

In a further advantageous embodiment, the invention relates to a formulation as described herein wherein the second component is selected from the group of vegetable oils, synthetic esters, acyclic and cyclic alkanes (with more than 6 carbon atoms), alkene sequale-
5 nes and liquid non-ionic surfactant with HLB ranging between 15 and 20. Particularly preferred liquid non-ionic surfactants are a member from polyoxyethelene PEG
10 (O-CH₂-CH₂)₂₀ sorbitan ester family (including monolaurate (Polysorbate 20/ Tween 20), monopalmitate (Polysorbate 40/ Tween 40), and monoolate (Polysorbate 80/Tween 80) with concentration ranging between 1 and 5%. Such formulations may be referred to as a "spiked-gel".

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In a further advantageous embodiment, the invention relates to a formulation as described herein comprising an additional viscosity modifier, preferably selected from the group consisting of natural clays,
20 synthetic clays and combinations thereof, such as Thixogel. Such modifier may be added to enhance the viscosity, if required.

In a second aspect, the invention relates to
25 compositions comprising a formulation as described herein.

Compositions according to the invention contain a formulation as described herein and one or more
30 additional components ("additives"). Such additives are known per se in the field. The type and amount of additives determines the intended use of the composition. Thus, such compositions may relate to the field of cosmetics, pharmaceuticals, nutrition and / or dietary.
35 Particularly, such compositions are oral care compositions or topical / transdermal compositions. Further,

such compositions may be in the form of a gel or an emulsion.

Typically, due to the aim of the invention,
5 the compositions as described herein do only contain small amounts of water ("essentially water free composition") or do not contain water ("water free composition"). This, in turn requires that the additives used are either water free or and additional water-removing
10 step is applied when manufacturing a composition according to the invention. A composition according to the invention thus contains preferably less than 5wt% water, preferably less than 1wt% much preferred less than 0.2wt%.

15

Thus, in one embodiment, the invention relates to an oral care composition, such as a dental cream, dental gel, dental/oral ointments and dental lozanes, comprising a formulation as described herein.
20 Such composition typically contains additives, including an abrasive, a mild detergent or foam forming/stabilizing agent, an anhydrous humectants, a thickening agent, a flavouring agent, a sweetening agent, a colouring agent, an anti-tarter agent, a nutrient agent, an oral isotonic agent, a polishing agent, an anti-carious agent, an anti-
25 plaque agent, a bleaching/oxidizing agent, an enzyme.

In an advantageous embodiment such oral care composition additionally comprises anti-microbial, anti-
30 fungal, anti-bacterial, dental mineralizing agents and / or preservatives.

In an advantageous embodiment, the invention relates to an oral care composition as described herein additionally comprising bleaching agents, in particular
35 peroxides.

Preferred peroxides are Hydrogen Peroxide, PVP-Hydrogen Peroxide, Alkaline Earth Metal Peroxides, group 12 metal peroxides, Urea Peroxide (Carbamide Peroxide), Alkali Metal Percarbonates, Alkali Metal Persulfates, Alkali Metal Perborates and alkali metal and alkali earth metal Monoperthalates. Other bleaching/oxidising agents are Hypochlorites, such as alkali metal hypochlorites, alkaline earth metal hypochlorites and group 12 metal hypochlorites; Chlorites, such as alkali metal chlorites, alkaline earth metal chlorites and group 12 metal chlorites; Chlorates, such as alkali metal chlorates, alkaline earth metal chlorates and group 12 metal chlorates; Clathrates of Chlorine dioxide (ClO_2) and alkali metal oxoborates.

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In a further advantageous embodiment, the invention relates to an oral care composition as described herein additionally comprising enzymes. The enzymes useful in the practice of this invention are catalytically active protein substances within the class of hydrolases, which break down or hydrolyze proteins (proteases), carbohydrates (carbohydrases), fatty substances (lipases), or complexes of these types of substances. These enzymes and the crude enzyme preparations containing them are obtained from natural sources or by the action of microorganisms on an appropriate medium having a nitrogen source and a carbon source. For example the microorganism *Bacillus subtilis* when cultivated in a medium containing a protein, such as soybean meal, and glucose, produces a proteolytic enzyme suitable for use in accordance with the invention. One useful protease thus prepared has an activity of about 2.4 million units per gram at pH 7 when assayed against a casein substrate as described hereinafter.

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Among the proteases useful in accordance with this invention are: Alcalase (trademark) a hydrolytic enzyme preparation whose major activity is proteolytic.

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- 31 -

It is derived from *Bacillus subtilis* and is obtainable from Novo Industri A/S. Purification of the commercial detergent- grade material is desirable before use in an oral preparation. Maxatase (trademark) obtainable from
5 Chas. Pfizer, Inc. Protease AP-100 (trademark) obtainable from Monsanto Chemical Company. Prolase 300 a trademark of the Wallerstein Company. trypsin may be derived from bovine or porcine pancreas. chymotrypsin may be derived from bovine, chicken, or turkey pancreas. Papain may be
10 obtained from the milky latex of the Papaya tree. ficin may be obtained by extraction from the fruit of a tropical fig tree. bromelin produced by the family Bromeliaceae obtainable from pineapple and pineapple plant. M-Zyme derived from a microbiological source. Has
15 keratinase activity. Rhozyme P-11 (trademark) derived from fungal sources. Obtainable from Rohm and Hass.

Among the useful carbohydrases are: dextranase may be derived from *Aspergillus* sp. cellulase may be derived from *Myrothecium verrucaria* Cellzyme A a crude
20 cellulolytic enzyme system. alpha-amylase, beta-amylase, and mixtures thereof may be obtained from *Bacillus subtilis*. Mylase 100 (trademark) derived from *Aspergillus oryzae*. Obtainable from the Waller- stein Company. Mylase W (trademark) a mixture of amylase, dextranase and other
25 enzymes derived from a fungal source. Obtainable from the Wallerstein Company. Amylase L-661 (trademark) obtainable from Premier Malt Products, Inc. Fungal Amylase (trademark) obtainable from the Marschall Division of Miles Laboratories, Inc.

30 Among the lipases useful in the invention are: Lipase 4000 (trademark) may be derived from *Aspergillus oryzae*. Lipase B (trademark) Lipase 448 (trademark) a relatively pure lipolytic enzyme derived from hog pancreas. One gm digests 448 gm of fat (av. mw = 840) per
35 hour at pH 7.8 and a temperature of 37° C. Obtainable from Nutritional Biochemicals Corp. are gastric lipase, pancreatic lipase and plant lipases.

Preferred concentration of enzyme (a mixture of them) ranges between 0.001% and 20%, preferably 0.1% and 10%, more preferably 0.5% and 5%, most preferably 1% and 3%.

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In a further advantageous embodiment, the invention relates to an oral care composition as described herein additionally comprising a source of zinc ions and enzymes, particularly a source of zinc ions and a
10 protease, a carbohydrase, and / or a lipase. Without being bound to theory, it is believed that dental plaque and calculus can be greatly reduced by contacting the teeth for a relatively short time with a combination of zinc ions and an enzyme, which may be a protease, a
15 carbohydrase, or a lipase, or mixtures thereof. The combination of zinc salt with various enzymes has been found experimentally to be so active as an antiplaque and anticalculus agent to demonstrate practical efficacy for the control of plaque and calculus formation, i.e. to be
20 effective under oral hygiene regimens.

In a further advantageous embodiment, the invention relates to an oral care composition as described herein additionally comprising lytic Bacterio-phages of
25 oral bacterias. Preferred are bacterio-phage of *Streptococcus mutans*, such as Phage M102, Phage E10, Phage F1, or mixtures thereof. Without being bound to theory, it is believed that the disclosed dentifrice composition containing disclosed co-gel and lytic bacterio-phages
30 provide an effective means in controlling / subsiding oral plaque (S. Mutan/Plauq count) and hence a new remedy against tooth disorder and discolouration problems due to well known acid dissolution of HCA.

35 In a further advantageous embodiment, additives may be added to the inventive oral care compositions are explained below:

Preferred abrasives are anhydrous fumed silica, anhydrous silica, Brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$), Kaolin, Aragonite, Calcite, white Pearl powder, Baking Soda and Calcium carbonate.

5 Preferred anhydrous humectants are anhydrous Glycerol, anhydrous Propylene Glycol, Polyethylene Glycols (PEG 400, 600, 800, 1000, 1200, etc.), hydrogenated vegetable oils, D-Sorbitol, vegetable oils, etc.

Preferred mild detergent is Zwitterionic Sur-
10 factant such as Cetyl Betain, Cocamidopropyl betaine, Dodecyl betaine, betaine oxides, alkyl amine oxides, etc., or a Nonionic Surfactant such as Alkyl poly(ethylene oxide), Poloxamer, Cetyl Alcohol, Oleyl Alcohol, Cocamide MEA, cocamide DEA, cocamide TEA.
15 Preferred mild detergent is a polysorbate ester such as Polysorbate 20, Polysorbate 60, Polysorbate 80, etc. Preferred mild detergent is a poloxamer (Pluronic, Synperonic).

Preferred thickening agents are Carbopol or
20 Carober, fatty acid mono- and poly- ester of mono- and poly-glycols and their amide or oxide derivatives, such as Glyceryl MonoStearate, Ceto Stearyl Stearate, Ethylene Glycol MonoStearate, Poly Glyceryl Stearate, Glyceryl Mono Laurate, Glyceryl Mono Palmitate, Glyceryl Mono
25 Oleate, Coco Mono Ethanolamide, Ethylene Glycol Di Stearate, Propylene Glycol MonoStearate, PEG Mono Laurate, PEG Mono Stearate, Cetyl Palmitate, Stearyl Stearate, Coco Di Ethanolamide, Butyl Stearate, 2 Ethyl Hexyl Stearate, 2 Ethyl Hexyl Palmitate, etc. Said
30 abrasive agents with low abrasivity serve as thickening agents.

Preferred flavoring agents are Peppermint Oil, Spearmint Oil, Orange Oil, Anise Oil, Wintergreen Oil, Birch Oil, Freshmint flavor, Herbal Flavor, Lemon
35 oil, Green Apple flavor, etc.

Preferred sweetening agents are either natural such as xylitol, Dihydrochalcones, Cyclamate,

Dextrose, Sorbitol, Levulose Thaumatine, D-Tryptophan, etc., or synthetic such as Potassium Acesulfame, Sodium Saccharin, Aspartame, etc.

Preferred anti-tarter agents are Alkali Metal Pyrophosphates, Disodium dihydrogen Pyrophosphates, Dipotassium dihydrogen Pyrophosphates, 1-Azocycloheptane-2,2-diphosphonate (AHP), Ethane-1-hydroxy-1,1-diphosphonate, Alkali metal salts of Polyphosphate, Phosphocitrate salts, Polyacrylates, Polycarboxylates, Alkali Metal Alkali-Earth Metal salts of EDTA, Zinc Chloride, Polyphosphonates, Polyepoxysuccinates, Nitrotriacetic Acid and its Salts of Alkali Metals, Ethylenediaminetetraacetic acid (EDTA), Alkali Earth Metal Salts of Citrate etc., or a mixture thereof.

Preferred nutrient agents are Ascorbic Acid (Vitamin C) and its salts of Alkali Metals and Alkali Earth Metals, Tocopherol (Vitamin E) and its acetate precursors, Phyloquinone (Vitamin K), Vitamin B (B1, B5, B6, B12), Vitamin A and its Retinoid precursors, Vitamin P, Vitamin H, etc., or a mixture thereof.

Preferred oral isotonic agent is sodium chloride (NaCl).

Preferred polishing agents are titanium oxide, zirconium oxide, zinc oxide, aluminum oxide, etc.

Preferred anti-cariogenic agents are a fluoride agent such as alkali metal fluorides, ammonium fluoride, alkali metal monofluorophosphates, etc., dental mineralizing agents such as water soluble salts of calcium, including glycerophosphate, nitrate, propionate, maleate, etc.

Preferred anti-plaque agent is Polyamino-propyl Biguanide, which is a gentle and effective antimicrobial substance that acts against tough gram negative bacteria as well as gram positive bacteria, yeast and fungi over a wide range of pH, 4-10. Other anti-plaque agents are said bleaching/oxidizing agents, naturally occurring substance such as Xylitol, Thymol, Eucalyptol,

Euganol, Oil of Colve, Sweet Birch Oil, Wintergreen Oil, D-Limonene, Mentha Paprita L oil, Spearmint oil, etc., synthetic substances such as Methyl Paraben, Ethyl Paraben, Propyl Paraben, Domiphen Bromide, Salicylanide, 5 Zinc ions, Stannous ions, Octenidine, Delmopione, Octapinol, etc.

Preferred pH Buffering agents, are Alkali Metal Salt of mono-, di- and tri-basic Phosphate or mixtures thereof.

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In a further embodiment, the invention relates to skin care composition, such as a skin cream, beauty cream, shower gel, shampoo, lozanes, and ointments comprising a formulation as described herein 15 (collectively: "cosmetic compositions"). For such compositions, non-ionic surfactants are preferred over ionic surfactants. It is believed that they are less skin irritant, less allergic and more pharmaceutically accepted.

20

Such skin care composition may contain rheology modifiers. The viscosity, surface texture, thixotropy, surface-feeling, etc., of the inventive compositions can further be optionally modified by incorporation of 25 such rheology modifier, such as Carbopols or Carbomers, natural and synthetic waxes, gums and clays, and diluting by a suitable humectant.

In further embodiment, the invention relates 30 to a topical and/or transdermal delivery vehicle gel composition as described herein additionally comprising one or more pharmaceutically active ingredients. The disclosed topical / transdermal compositions are capable in accommodating, transporting and delivering to the 35 target lipophilic as well as hydrophilic active ingredients, such as enzymes, co-enzymes, vitamins, precursors of vitamins, anti-bacterial/anti-microbial agents

- 36 -

(collectively: "pharmaceutical compositions") Such composition may also contain additives, e.g. oxidizing/bleaching, flavoring, coloring agents, etc.

5 Preferred active ingredients are in particular one or more folate antagonists, immunosuppressive, disease-modifying antirheumatic drug (DMARD), in particular Methotrexate and its pharmaceutically accepted derivatives such as orotate, γ -glycine-tris, γ -glycine-
10 tris monopalmitate, γ -glycine-tris dipalmitate, γ -glycine-tris tripalmitate, etc. Preferred concentration ranges between 0.01 and 10%, more preferably 0.1 and 5% and most preferably 0.25 and 1%. Compositions may additionally (but not limited to) contain another DMARDs
15 drugs such as azathioprine, ciclosporin (cyclosporine A), Cyclophosphamide, D-penicillamine, leflunomide, minocycline, sulfasalazine, gold salts, hydroxychloroquine, etc., tumor necrosis factor alpha (TNF- α) blockers such as, etanercept, infliximab, adalimumab, etc., Interleukin
20 1 (IL-1) blockers such as anakinra, monoclonal antibodies against B cells such as rituximab, T cell activation blocker such as abatacept, Anti-inflammatory agents (steroidal and non-steroidal) such as glucocorticoids, non-steroidal anti-inflammatory drug NSAIDs (salicylates,
25 arylalkanoic acids, 2-arylpropionic acids, N-arylanthranilic acids, pyrazolidine derivatives, oxicams, COX-2 inhibitors, Sulphonanilides, Licofelone, Omega-3 fatty acids, etc.) and analgesic agents such as opiates, acetaminophen, diproqualone, lidocaine, an A₃ adenosine
30 receptor (A₃AR) agonist such as N⁶ - (3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide, 2-chloro-N⁶ - (3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide, etc.

In an advantageous embodiment, the disclosed
35 topical transdermal vehicle compositions provides an excellent delivery system for Methotrexate to treatment for autoimmune disorder diseases, in particular RA,

psoriatic arthritis, psoriasis, scleroderma, polymyositis, lupus and systemic lupus erythematosus, directly on the local diseased spots / sites with much enhanced topical bioavailability, as compared to niosomal and emulsion composition of prior art, overcoming most of the major side-effects as well as risk of cytotoxicity / tissue-toxicity / organ-toxicity, which are associated with oral route administration of Methotrexate including anemia, neutropenia, nausea, vomiting, renal disorders, hepatitis, gastrointestinal disorders, mucositis, lung disorder, etc. Clinical studies exhibit that disclosed topical „tubulosomal“ methotrexate gel compositions have better absorption, permeation/penetration through the skin as well as longer dermal-residence due to sustained release of methotrexate, and that the disclosed compositions (0.1%, 0.2% and 0.25% MTX gel) did not produce any significant irritation or sensitization on human volunteers, subject to daily once a day basis administration for four weeks period. Liposomal as well as niosomal systems, are believed to be unsuitable for transdermal delivery, because of their poor skin permeability, breaking of vesicles, leakage of drug, aggregation, and fusion of vesicles.

In a further advantageous embodiment, the invention relates to a topical transdermal gel vehicle compositions as described herein additionally comprising a non-steroidal anti-inflammatory drug NSAID, in particular but not limited nimesulide, which targets a number of key mediators of the inflammatory process such as, COX-2 mediated prostaglandins, free radicals, proteolytic enzymes and histamine. Preferred concentration of NSAID is 0.01-20%, more preferably 0.5-10%, most preferably 1-6%. Additionally, an A₃ adenosine receptor (A₃AR) agonist such as N⁶ - (3-iodobenzyl)-adenosine- 5'-N-methyluronamide, 2-chloro-N⁶ - (3-iodobenzyl)-adenosine- 5'-N-methyluronamide, etc., can be incorporated to composi-

tion with preferred concentration 0.001-0.1%. Additionally TNF- α blockers such as, etanercept, infliximab, adalimumab, etc. with concentration 0.001-0.1%, Interleukin 1 (IL-1) blockers such as anakinra with 0.001-
5 0.1%, monoclonal antibodies against B cells such as rituximab 0.001-0.1%, T cell activation blocker such as abatacept with concentration 0.001-0.1% may be incorporated. The disclosed topical transdermal gel vehicle compositions can also be used in treatment to RA and
10 related inflammatory conditions, such as psoriatic arthritis, psoriasis, SLE, etc.

In an advantageous embodiment, the invention relates to a topical transdermal gel/ointment composition
15 as described herein additionally comprising lipolysis agent Lipase, an activator of lipolysis and a blocker of dephosphorylation of cyclic adenosine monophosphate (cAMP). Preferred lipase agent is from *Candida rugosa*, *Candida cylindracea*, Lipase B, etc., with concentration
20 0.001-20%. Preferred activator is cAMP with concentration 0.001-10%. Preferred cAMP-Phosphodiesterase blocker is paraxanthine with concentration 0.001-10%. Additionally/optionally, other cAMP-Phosphodiesterase blockers such as pheophylline, Caffeine, Aminophylline, etc., can
25 be incorporated. Additionally/optionally a phosphate donor, which also activates Lipase, can be incorporated. Optionally, an appetite suppressant agent such as Ephedrine can be incorporated. Optionally an inhibitor of glucose-6-phosphate dehydrogenase such as extract of
30 Andiroba can be incorporated in concentration 0.01-10%. Additionally/optionally a promoter of cellular cAMP such as Forskolin, which acts through activating protein kinase A (PKA) and hence adenylyl cyclase enzyme, can be incorporated in concentration 0.01-10%. Optionally,
35 Clenbuterol, Yohimbine or its precursors, viper venom, nutrient, flavouring and colouring agents can be incorporated.

- 39 -

This transdermal gel / ointment composition is suitable for the reduction of unwanted fat, particular for unwanted fat located in the hypodermis. Therefore, such compositions are suitable for therapeutic treatment of obesity, adiposis and / or for cosmetic shaping of the body, particular for shaping abdomen, hip and/or buttock of a person in need thereof. This is achieved by fat reduction / burning. The invention thus also relates to the use of such compositions and to the manufacture of a medicament for such indications. Without being bound to theory, it is believed that said composition, when topically applied onto the skin, is being absorbed by the epidermis, followed by osmotic spreading through the dermis and hypodermis, respectively, as a result of which the swollen tubulosomes, encapsulating the ingredients, permeate through the epidermis and dermis, and delivers the entrapped ingredients into hypodermis due to osmotic dilution and subsequent selective absorption by the adipocytes, which are called fat cells. The absorbed lipase molecules thereby are being activated by an activator and locally stimulate the lipolysis of triglycerides (break/hydrolyze the lipid bonds of triglyceride) to produce mono-glycerides and free fatty acids which subsequently enter into the oxidative citric acid cycle in mitochondria to yield ultimately Adenosine Triphosphate (ATP) and carbon dioxide and water as bi-products and release energy. Thus, the processes of catabolism of the lipids, which are contained in the adipocytes located in the hypodermic layers, is accomplished. As a result, reduction in fat content in the fat cells, production of extra ATP as well as free energy, and keratolytic softening of skin (as well as skin wound healing due to accelerated regeneration of cells) are achieved upon regular use of the said composition. An activator of lipolysis, such as, cyclic adenosine monophosphate (cAMP), which is believed to be an activator of Lipase enzyme through the protein kinase mediated phosphate

group transfer, and hence stimulate overall lipolysis. Blocker of dephosphorylation/promoter of cAMP inhibits the action of cAMP-Phosphodiesterase enzyme and activates adenylyl cyclase which promotes formation of cAMP from
5 ATP/GTP. In consequence, the present invention provides a composition that supports lipolysis and the use of such compositions in the treatment of lipolysis - related diseases, disorders and/or conditions.

10 In a further advantageous embodiment, the invention relates to a topical vehicle pharmaceutical composition as described herein additionally comprising an analgesic/local anesthetic/antiarrhythmic agent/drug, in particular Lidocaine (Lidocaine hydrochloride monohy-
15 drate). Lidocaine alters depolarization in neurons, by blocking the fast voltage gated sodium (Na^+) channels in the cell membrane. With sufficient blockade, the membrane of the presynaptic neuron will not depolarize and therefore fails to transmit an action potential, leading
20 to its anesthetic effects. Careful titration allows for a high degree of selectivity in the blockage of sensory neurons, whereas higher concentrations will also affect other modalities of neuron signaling. Disclosed Lidocaine gel compositions have shown to have improved bioavail-
25 ability, as compared with 3% topical bioavailability in prior art, towards topically relieve itching, burning and pain from skin inflammations and towards topical dental anesthesia in minor dental surgeries. Other such analge-
30 sic agents are prilocaine, bupivacaine and ropivacaine. Preferred concentration of Lidocaine (hydrochloride monohydrate derivative) is 0.001-25%, more preferably 0.01-10%, most preferably 0.25-5%. The disclosed topical gel compositions can also be used in treatment to early
35 stage of RA and related inflammatory conditions, such as psoriatic arthritis, psoriasis.

In an advantageous embodiment, the invention relates to a topical transdermal gel / ointment vehicle composition as described herein additionally comprising Omega-3 fatty acids in concentration 0.1-20%. Such composition is particularly suitable for the treatment of atopic dermatitis and RA.

In a third aspect, the invention relates to the manufacture of formulations as described herein. Formulation according to this invention may be prepared by processes that, though not applied hitherto for the components of the present invention where they thus form new processes, are known *per se*.

Hence, the invention relates to a method for manufacturing a formulation as described herein comprising the steps of: combining component 1 and 2, preferably by vortexing; heating the obtained mixture at least 5°C above the melting point of component 1, preferably over a water-bath suited with a thermostat; maintaining the temperature for a period from 10 min to 10 hrs, preferably with occasional vortexing; slowly cooling down the obtained mixture.

A general procedure for manufacturing the inventive formulation may be given as follows: (1) The solid gelators and the liquid medium are mixed, (2) The mixture is heated to a fixed temperature, at least 5°C above the melting point of the gelators, by means of thermostat regulated water-bath until the gelator has completely dissolved/dispersed to give a sol phase, (3) The sol phase is then kept at the same temperature for time span ranging from 30 minutes to 2 hour, allowing the stable formation of the sol phase, (4) The resulting sol is then allowed to cool down by standing at room temperature for overnight (preferable cooling time is from 8 to 36 hours), (5) At gelator concentrations above a minimum

threshold, which is called minimum gelation concentration (MGC), the sol phase sets to an opaque, smooth, semi-solid gel as it cools down to room temperature.

5 Gelation, which is defined as the transition from a sol to a gel state, is considered successful in this context, if, upon inversion of the vial, sample does not flow perceptibly.

Minimum Gelation Concentration (MGC): The lowest concentration of gelator which causes gelation at
10 room temperature (20°C) is taken as the MGC. Gelator-solvent mixtures containing increasing concentrations of gelator have been prepared and observed gel formation in order to determine MGC. At very low concentration of gelators, a white (or pale) fibrous gel mass is formed
15 within the solvent. The fibrous mass within the solvent becomes denser with increasing surfactant gelator concentration until whole solvent is gelled. An increase in gelator concentration is expected to cause a gradual increase in the viscosity of the bulk sample due to an
20 isotropic dispersion of the increasing number of linked clusters of the tubulosomes of surfactant-gelator in the solvent until gelation occurred at a critical concentration. As sol phase is cooled, the gelator solubility in the solvent is reduced, resulting in reduced gelator-
25 solvent affinity and enhanced aggregate-aggregate interactions, which conduce formation of a coherent network of interconnected clusters throughout the liquid phase, thus immobilizing it. In very low polar solvents/substantially liophilic mediums, aggregate-
30 aggregate interactions are stronger than solvent-aggregate affinities, resulting in a preferential ordered flocculation of the clusters to form a 3-D network within the solvent. Such a gel network, which is anisotropically dispersed in the solvent, is then able to gel the solvent
35 only in parts, and a fibrous gel mesh is observed within the excess solvent, which is not accommodated in or immobilized by the gel network. In relatively higher

polar solvents, such as corn oil, isopropyl myristate, etc., the aggregate-aggregate interactions required for entanglement and formation of a 3-D network seem to be less favored, probably because of relatively stronger solvent-aggregate attractions, which promotes an isotropic dispersion of the gelator aggregates in the solvent and consequently a progressive increase in the sample viscosity is observed upon increasing the gelator concentration until critical gelling concentration is reached.

In case of organo-gels, wherein a second surfactant with relatively high HLB is incorporated in low amount ($\leq 5\%$ w/w), it has reduced the CGC (critical gelling concentration) and MGC of the surfactant gelator, presumably due to enhancing the solubility of the gelators in the solvent via forming mixed reverse tubulosomes.

In a fourth aspect, the invention relates to the manufacture of compositions as described herein. Compositions according to this invention may be prepared by processes that, though not applied hitherto for the the components of the present invention where they thus form new processes, are known *per se*.

Hence, the invention relates to a method for manufacturing a composition as described herein comprising the steps of providing a formulation as described herein and combining it with one or more additives to obtain the desired composition.

General procedure for manufacturing a non-aqueous oral care composition containing an oxidizing/bleaching agent:

A. Disperse a non-aqueous gelling agent (and optionally a thickener agent, if required) into the liquid dispersion medium, which is either with or without surfactant

- 44 -

property , or a mixture thereof, containing humectants, flavoring, sweetening and coloring agents.

- 5 B. Heat the obtained suspension / mixture / dispersion at a constant temperature 5⁰C greater than the melting point of gelling agent (which is the "first component" as defined above) with constantly stirring at a moderate propeller speed ranging between 100 rpm and 1200rpm (preferably 300rpm and 1000 rpm, most preferably between 600 and 800 rpm) for 10 minutes to 5 hours, preferably
10 for 30 min to 3 hours, most preferably for 1 to 2 hours. Allow the obtained composition to cool down to room temperature while constantly stirring with lower propelling speed ranging between 100 rpm and 600rpm, preferably between 300 and 400rpm to obtain a gel.
- 15 C. The stirring is withdrawn to let the obtained gel settle down for 10 minutes to 10 hours, preferably for 30 minutes to 5 hours, most preferably for 1 to 2 hours.
- D. Add the abrasives during vacuum milling, if required.
- F. Add foaming agent during milling, if required.
- 20 G. Add polishing agent, oral isotonic agent and the oxidizing/bleaching agent as a batch process, if required.

25 General procedure for manufacturing a non-aqueous oral care composition containing an enzyme and/or bacteriophage:

- A. Disperse a non-aqueous gelling agent (and optionally a thickener agent, if required) into the liquid dispersion medium, which is either a liquid (non-ionic) surfactant
30 or a vegetable oil, or a mixture thereof, containing humectants, flavoring agent, sweetening agent, coloring agent and the enzyme (a mixture of enzymes).
- B. Heat the obtained suspension/mixture/dispersion at a constant temperature 5⁰C greater than the melting point
35 of gelling agent (which is the "first component" as defined above) with constantly stirring at a moderate propeller speed ranging between 100 rpm and 1200rpm

(preferably 300rpm and 1000 rpm, most preferably between 600 and 800 rpm) for 10 minutes to 5 hours, preferably for 30 min to 3 hours, most preferably for 1 to 2 hours.

C. Allow the obtained composition to cool down to room
5 temperature while constantly stirring with lower propelling speed ranging between 100 rpm and 600rpm, preferably between 300 and 400rpm to obtain a gel (If the enzyme and/or bacteriophage or a group of them which are not compatible to high temperature needed for gelation, they
10 can be added in this stage when during cooling the temperature reaches to about 40°C as a batch).

D. The stirring is withdrawn to let the obtained gel settle down for 10 minutes to 10 hours, preferably for 30 minutes to 5 hours, most preferably for 1 to 2 hours.

15 E. Add the abrasives during vacuum milling, if required.

F. Add foaming agent during milling, if required.

G. Add polishing agent and oral isotonic agent as a batch process, if required.

20 In a fifth aspect, the invention relates to the use of formulations and compositions as described herein.

Hence, the invention relates in one embodiment
25 ment to the use of a formulation as described herein for manufacturing a composition as describes herein, in particular for the manufacture of a cosmetic product, pharmaceutical product, nutrition product or dietary product, very particularly a topical / transdermal
30 product or an oral care product.

The invention relates in a further embodiment to the use of a composition as described herein in cosmetics, pharmaceuticals, nutrition and/or dietary. The
35 invention relates in a further embodiment to a composition as described herein as pharmaceutical.

To further illustrate the invention, the following examples are provided. These examples are provided with no intention to limit the scope of the invention.

5 Analytics:

Phase Transition Temperature: The inventive organogels and amphiphilic gels are thermoreversible. They melt on heating to the sol phase which can once again be gelled upon cooling without any appreciable
10 change in gel properties. The gel-to-sol and/or sol-to-gel phase transition temperatures have been obtained through measuring the melting points using a standard melting point apparatus. The gel is introduced into the capillary tube of 100mm length and 1.4mm outer diameter,
15 by dipping the tube into the gel to obtain a sample of approximately 0.5cm in length within the tube. The sample is then drawn up the tube to approximately 0.3cm from the lower end of the tube using a syringe. The gel filled tubes are then placed in the melting point apparatus, and
20 the temperature is increased with a constant rate of 1°C/min. The gel phase transition temperature is taken as the temperature at which the gels melt into an isotropic liquid (sol) that flows down the capillary tube. In order to increase the precision in measurement, five samples of
25 a gel are used to obtain an average.

 The cohesion of the gel network stems from the binding strength of cross-links between the aggregates in a gel. Gel to sol phase transitions involve breakdown of the cross-links/junctions, disaggregation of
30 the gelator clusters, de-stacking of the tubulosomes, and dissolution of the surfactant bi-layer assemblies into the solvent. All these events do not occur simultaneously, and require different amounts of energy-intake. Therefore, the phase transition does not take place at a
35 single temperature but over a range, typically 3-5°C, for a gel belonging to organogel or amphiphilic gel-class disclosed herein. Consequently, broad phase transition

temperatures correspond to homogeneous microstructure within the gel for organogels and amphiphilic gels. The phase transition temperature of all organogels and amphiphilic gels are below the melting point of the gelators. This is a universal property of the organogels and amphiphilic gels, and can be understood by the fact that relatively much higher energy is required to break the close-pack lattice in solid state than to break the supra-molecular associations in gel state of a gelator.

Increasing the gelator concentration leads to an increase in phase transition temperature, reflecting more cohesive 3D network of gelator aggregates and the number of cross-links between aggregates such that more energy is required for the sol-to-gel transition. The higher phase transition temperature with increased HLB of solvent reflects a stronger network, and is due to higher gelator-gelator affinities compared to gelator-solvent affinities as the solvent HLB increases. However, phase transition temperature does not correlate to solubility-insolubility balance of the gelator in a solvent based on HLB. For example, Span 40 gels possess lower phase transition energy than Span 60 gels, although the latter is more insoluble in a hydrophilic solvent. Therefore, the phase transition temperature correlates much better to the melting point of the solid surfactant gelator, while the melting points of the solid surfactant gelators correlate well to their HLB numbers; lower the HLB, higher the melting point.

The increase in phase transition temperature on storage for organogels and amphiphilic gels attributes from a greater number of and/or stronger junction points. Often a stronger gel network is formed among the tubular clusters over the time.

Gel lifetime: Gel lifetime is taken herein as the duration between gel preparation and gel syneresis. Syneresis is a result of the contraction of the solid

network of tubulosome clusters stipulating the release of the trapped liquid solvent, which was initially accommodated within the gel network, and thus the separation of two phases. Syneresis is expected to take place in the gels comprising larger aggregates. The larger pore size that exists between the large aggregates indicates that the liquid phase is not held very tightly/efficiently within the gel network by capillary (cohesion) forces and that it may separate out (get un-enveloped). Five samples of each gel have been placed in glass vials at constant room temperature to weekly observe for syneresis. It turns out that organogels have lifetime of 3-6 weeks, while the organogels spiked with a hydrophilic surfactant possess lifetime of range 4 to 8 months, and most of the amphiphilic gels possess lifetime more than a year. The pure and mixed amphiphilic gel did not undergo syneresis on storage at room temperature for more than two years. While some of the co-gels exhibit syneresis after one year storage, most of them possess lifetime of about two years and more. Most of the amphiphilic gels show betterment in consistency over storage, while their properties remain nearly unchanged.

Gel flow properties and rheology: Gel flow properties, encompassing viscosity, yield point/value and low thixotropy, are important to fit in personal-care, cosmetic and pharmaceutical systems of commercial value, such as creams, pastes, ointments and gels. The viscosity of the disclosed organogels and amphiphilic gels are found to fall with externally applied shear rate, since the physical 3D gel-network breaks to a large part when the gels are subjected to shear. Removal of shear stress initiates rapid reformation of the 3D gel network, restoring most of the junction points of the clusters that were ruptured due to external shear. Rapid recovery of the gel-network to a large part, following the external application of shear that which is demonstrated

by the disclosed organogels and amphiphilic gels, is essential to ensure that the formulation will not flow off the site of application after administration. The yield point/value is an indication of the level of resistance to external forces before the system starts to flow, and thus an indication of the strength of the gel network. Yield point/value with low thixotropy provides for a clean, non-stringing ribbon/thread of the delivery vehicle composition (pastes, gels, ointments, creams, etc.) coming out the package (squeezeability, pumpability: important parameters for delivery systems for commercial toothpaste, gel, dermal creams/gel/ointment, etc.). Yield value/point is also required to suspend insoluble additives, such as abrasive particles and any insoluble additives, which are often incorporated in dentifrice compositions and skin-care/dermal compositions.

The shear rate of rubbing formulations onto skin is known to approach 10^5 s^{-1} . It is therefore expected that the viscosities of the disclosed gels at such a shear rate would allow easy application onto skin as their viscosities fall with increasing shear. The shear rate approaches to a much higher number during brushing the teeth with both manual and electric toothbrushes. Therefore, the disclosed gels with yield point and low thixotropy largely facilitate to suspend the debris loosened, and hence removal of them, during brushing the teeth.

Flow properties of the gels are influenced by parameters such as gel age, gelator concentration, nature of liquid solvent phase, etc.

The increase in viscosity with increasing gelator concentration reflects the fact that the denser gel-network is produced. The more robust 3D network traps and immobilizes the liquid continuous phase (solvent) to a greater degree, as a result of which, gel consistency, phase transition temperature and viscosity increase. A

- 50 -

sharp rise in viscosity is observed once the MGC is reached.

A significant difference is found between the viscosities of the disclosed gels containing different liquid phases. A major contribution to this stems from the different viscosities of the liquid phases (solvents). A viscous solvent, for example, Span 20, produces a gel with harder consistency, a high viscosity, as well as a yield point at lower gelator concentrations, whereas less viscous solvents, for example, vegetable oils, polysorbate 20, etc., produce softer gels with lower viscosities.

The gels, in which the liquid phases are composed of polysorbate 20 or polysorbate 80, have shown an increment in viscosity and consistency over the storage-time, due to formation of more junction points on storage.

Note on industrial stability-test: The disclosed gel formulations are "thermo-reversible", i.e. they melt upon heating over the gel-to-sol phase transition temperature to the sol phases that once again produce the gels on cooling below the sol-to-gel phase transition temperature without any appreciable change in the gel-properties. Therefore, the conventional procedure for industrial stability-check, which is associated with preserving the compositions at elevated temperature, such as 60°C, 90°C, for weeks to examine for any change in the composition, does not apply to the disclosed gel compositions, especially the ones that contain any suspended additives such as abrasives, insoluble thickeners, and the like. The stability test for any composition, which is based on the disclosed gels herein, should be done keeping at room temperature for the desired period of examination.

Example 1: Preparation of formulations

General process 1 for examples A1 to D10: The first and the second components were weighted and mixed, heated until the first component dissolved/dispersed in the latter, followed by cooling to room temperature by standing in room temperature. As the sol phase cooled to room temperature, it set to an opaque, smooth, semi-solid gel.

A. Organo-gels

Ex	Ingredients	
	Component-1 (x)%w	Component-2 (x)%w
1	Span 60 (15)	Corn oil (85)
2	Span 60 (15)	Isopropyle Myristate (40); Soybean oil (45)
3	Span 60 (14); Span 40 (6)	Sesame oil (5); Isopropyl Myristate (20); Olive oil (50); Ethyl Oleate (5)
4	Span 60 (12); Pluronic F-68 (4); Pluronic F-127 (3)	Soybean oil (30); Isopropyl Myristate (12); Sunflower oil (15); Cottonseed oil (5); Olive oil (19)
5	Span 60 (10); Pluronic F-77 (3); Tetronic 1107 (1); Brij-58 (2)	Olive oil (40); Ethyl Oleate (10); Ethyl Myristate (5); Soybean oil (7); Corn oil (5); Sunflower oil (5); Isopropyl Myristate (12)
6	Span 40 (10); Brij-58 (4); Pluronic F-127 (3)	Corn oil (15); Isopropyl Myristate (15); Olive oil (36); Castor oil (8); Sesame oil (4); Sunflower oil (5)

10

B. Pure Amphiphilic gel

Ex	Ingredients	
	Component-1 (x)%w	Component-2 (x)%w
1	Span 60 (18)	Tween 40 (82)
2	Span 60 (15)	Tween 20 (85)
3	Span 60 (15); Span 40 (5)	Tween 40 (80)
4	Span 60 (12); Brij-58 (3); Pluronic F-68 (2)	Span 20 (83)
5	Span 60 (15); Span 40 (5)	Span 80 (80)
6	Span 40 (16); Pluronic F-127 (3)	Tween 40 (81)

C. Mixed Amphiphilic gels

Ex	Ingredients	
	Component-1 (x)%w	Component-2 (x)%w
1	Span 60 (20)	Tween 20 (15); Tween 40 (65)
2	Span 60 (20)	Tween 20 (15); Span 20 (15); Tween 40 (50)
3	Span 60 (20)	Span 80 (5); Tween 20 (10); Tween 40 (25); Pluronic L-121 (20); Pluronic

- 52 -

		10R5 (20)
4	Span 60 (10); Span 40 (5); Pluronic F127 (4)	Pluronic 10R5 (30); Tween 20 (10); Pluronic L-64 (18); Tween 40 (23)
5	Pluronic F68 (5); Span 60 (12); Brij-58 (4)	Pluronic L-35 (25); Pluronic 17R4 (10); Span 80 (15); Tween 40 (29)
6	Span 40 (15); Pluronic F-107 (5)	Span 20 (10); Tween 20 (15); Tween 40 (30); Pluronic L-81 (10); Pluronic 10R5 (15)
7	Span 60 (16)	Span 80 (70); Pluronic 10R5 (5); Pluronic L-64 (5); Pluronic L-121 (4)
8	Span 60 (10); Span 40 (6)	Span 80 (60); Span 20 (5); Tween 80 (8); Pluronic 10R5 (11)

D. Co-gels

Ex	Ingredients	
	Component-1 (x)%w	Component-2 (x)%w
1	Span 60 (17)	Tween 20 (10); Tween 40 (25); Isopropyl Myristate (15); Olive oil (20); Pluronic L-121 (13)
2	Pluronic F68 (5); Span 60 (15); Brij-58 (2)	Isopropyl Myristate (20); Sunflower oil (10); Pluronic L-81 (10); Corn oil (10); Span 80 (25); Sesame oil (3)
3	Span 60 (20)	Tween 40 (20); Ethyl Oleate (10); Olive oil (30); Span 20 (5); Cottonseed oil (5); Pluronic L-64 (10)
4	Span 40 (8); Span 60 (12)	Tween 40 (25); Tween 20 (15); Olive oil (30); Isopropyl Myristate (10)
5	Span 40 (15); Span 60 (5)	Tween 80 (20); Span 20 (20); Pluronic 10R5 (15); Isopropyl Myristate (10); Olive oil (5); Sunflower oil (10)
6	Span 60 (17); Brij-58 (3); Pluronic F-107 (2)	Pluronic 10R5 (20); Olive oil (20); Ethyl Myristate (10); Span 80 (20); Tween 80 (8)
7	Span 40 (20)	Tween 40 (15); Tween 20 (15); Span 20 (5); Olive oil (20); Pluronic L-121 (10); Pluronic L-64 (15)
8	Span 40 (17); Pluronic F-107 (4); Pluronic F127 (4)	Tween 80 (20); Tween 40 (20); Sunflower oil (10); Isopropyl Myristate (15); Span 80 (10)
9	Span 60 (20)	Tween 80 (20); Olive oil (20); Tween 40 (10); Pluronic L-121 (10); Sunflower oil (10); Ethyl Myristate (5); Ethyl Oleate (5)
10	Span 60 (18); Pluronic F127 (2)	Tween 80 (10); Span 80 (5); Span 20 (5); Tween 40 (15); Pluronic L-121 (12); Olive oil (10); Sunflower oil (5); Isopropyl Myristate (8)

The gels are fibrous when the second component contains substantial amount of Tween 40 (>5%w).

Example 2: Preparation of transdermal compositions

The compositions E1 - G5 may be prepared according to general process 2 or 3, compositions H1 - I3
5 may be prepared according to general process 4 as described below.

General process 2: A. The first component (which is the non-aqueous gelling agent) and optionally a thickener agent, were dispersed into the second component
10 (which is the liquid dispersion medium that may contain humectants, flavouring agent, sweetening agent, coloring agent if required), then optionally the additives were added into the mixture. B. The obtained suspension / mixture / dispersion was heated to a constant temperature
15 5°C greater than the melting point of first component (gelling agent) with constantly stirring at a moderate propeller speed ranging between 100 rpm and 1200rpm (preferably 300rpm and 1000 rpm, most preferably between 600 and 800 rpm) for 10 minutes to 5 hours. C. The
20 obtained composition was allowed to cool down to room temperature while constantly stirring with lower propelling speed ranging between 100 rpm and 600rpm, preferably between 300 and 400rpm to obtain a gel. Any additives not compatible to high temperature were added at this stage
25 when during cooling the temperature reaches to about 40°C as a batch. D. The stirring was withdrawn to let the obtained gel settle down for 10 minutes to 10 hours.

General process 3: A. The first component and optionally a thickener agent, were dispersed into the
30 second component. B. The obtained suspension / mixture / dispersion was heated to a constant temperature 5°C greater than the melting point of first component (gelling agent) with constantly stirring at a moderate propeller speed ranging between 100 rpm and 1200rpm for 10
35 minutes to 5 hours. C. The obtained composition was allowed to cool down to room temperature while constantly stirring with lower propelling speed ranging between 100

rpm and 600rpm, to obtain a gel. D. The stirring was withdrawn to let the obtained gel settle down for 10 minutes to 10 hours. D. Additives were added during vacuum milling, first with low propeller speed ranging
 5 between 100 and 300rpm for 10 minutes to 1 hour as to incorporate the additives into the tubulosomes, and then with higher propeller speed ranging between 400 and 1200rpm for 10 minute to 5 hours.

General process 4: A. The first component and
 10 optionally a thickener agent, is dispersed into the second component. B. The obtained suspension / mixture / dispersion is heated at a constant temperature 5°C greater than the melting point of first component (gelling agent) with constantly stirring at a moderate
 15 propeller speed ranging between 100 rpm and 1200rm for 10 minutes to 5 hours. C. The obtained composition was allowed to cool down to room temperature while constantly stirring with lower propelling speed ranging between 100 rpm and 600rpm, to obtain a gel. D. The stirring was
 20 withdrawn to let the obtained gel settle down for 10 minutes to 10 hours. D. The additives were added during vacuum milling, first with low propeller speed ranging between 100 and 300rpm for 10 minutes to 1 hour as to incorporate the additives into the tubulosomes structure,
 25 and then with higher propeller speed ranging between 400 and 1200rpm for 10 minute to 5 hours.

Examples E

E1.

Ingredient	Conc
Span 60	15
Span 80	70
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic L-121	q.s
Methotrexate	0.25

30 E2, E3 and E4 contain Methotrexate in 0.1%, 0.5% and 1%, respectively.

E5.

Ingredient	Conc (w%)
Span 60	15

- 55 -

Tween 40	20
Span 80	50
Span 20	10
Isopropyl Myristate	q.s
Methotrexate	0.25

E6, E7 and E8 contain Methotrexate in 0.1%, 0.5% and 1%, respectively.

E9.

Ingredient	Conc. (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myristate	5
Pluronic 10R5	q.s
Methotrexate- γ -glycine-tris tripalmitate	0.25

5

E10, E11 and E12 contain Methotrexate- γ -glycine-tris tripalmitate in 0.1%, 0.5% and 1%, respectively.

E13.

Ingredient	Conc (w%)
Span 60	15
Tween 40	30
Span 80	40
Span 20	10
Isopropyl Myristate	q.s
Methotrexate- γ -glycine-tris tripalmitate	0.25

10

E14, E15 and E16 contain Methotrexate- γ -glycine-tris tripalmitate in 0.1%, 0.5% and 1%, respectively.

15

E17.

Ingredient	Conc (w%)
Span 60	15
Tween 40	30
Span 80	40
Span 20	10
Isopropyl Myristate	q.s
Methotrexate	0.20
Cyclosporin A	0.10
Infliximab	0.10

E18.

Ingredient	Conc (w%)
Span 60	15
Tween 40	30
Span 80	40
Span 20	10
Isopropyl Myristate	q.s

- 56 -

Methotrexate	0.20
Abatacept	0.10

E19.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Methotrexate	0.25
Anakinra	0.25

E20.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Methotrexate	0.25
Infliximab	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide	0.25

5

Examples E provide compositions suitable for treatment of Autoimmune disorders.

Examples F

10

F1.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Anakinra	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide	0.25

F2.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Etanercept	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-	0.25

- 57 -

uronamide	
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F3.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Infliximab	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide	0.25

F4.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Cyclophosphamide	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide	0.25

5

F5.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Leflunomide	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide	0.25

F6.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Sulfasalazine	0.25
N6 -(3-iodobenzyl)-adenosine- 5'-N-methyl-uronamide	0.25

Examples F provide compositions suitable for
10 treatment of Autoimmune disorders.

Examples G

- 58 -

G1.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Licofelone	0.25

G2.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Acetylsalicylic acid (Aspirin)	0.25

5

G3.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Phenylbutazone	0.25

G4.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
(8E)-8-[hydroxy-(pyridin-2-ylamino)methylidene]-9-methyl-10,10-dioxo-10 λ ⁶ -thia-9-azabicyclo[4.4.0]deca-1,3,5-trien-7-one	0.25

G5.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Ibuprofen	0.25

10

Examples G provide compositions suitable for treatment of anit-inflammatory disorders.

- 59 -

Examples H

H1.

Ingredient	Conc (w%)
Span 60	15
Span 80	30
Tween 80	32
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Lipase from <i>Candida rugosa</i>	4
Adenosine 3',5'-cyclophosphate	1.6
Paraxanthine	0.1
1,3-Dimethylxanthine	1
Extract of Andiroba	1
Forskolin	0.1

H2.

Ingredient	Conc (w%)
Span 60	15
Span 80	15
Tween 80	35
Span 20	5
Pluronic L-64	8
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Lipase from <i>Candida rugosa</i>	4
Adenosine 3',5'-cyclophosphate	1.6
Caffeine	0.1
1,3-Dimethylxanthine	1
Extract of Andiroba	1
Ephedrine	0.05

5

H3.

Ingredient	Conc (w%)
Span 60	15
Span 80	15
Tween 80	35
Span 20	5
Pluronic L-64	8
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Lipase from <i>Candida cylindracea</i>	4
Adenosine 3',5'-cyclophosphate	1.6
Aminophylline	0.1
1,3-Dimethylxanthine	1
Extract of Andiroba	1
Ephedrine	0.05

Examples H provide compositions suitable for transdermal fat catabolizing.

10

Examples I

I1.

Ingredient	Conc (w%)
------------	-----------

- 60 -

Span 60	15
Span 80	70
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic L-121	q.s
Lidocaine	0.75

I2.

Ingredient	Conc (w%)
Span 60	15
Span 80	35
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Lignocaine hydrochloride monohydrate	0.50

I3. [Can be used for the treatment to RA]

Ingredient	Conc (w%)
Span 60	15
Span 80	33
Tween 80	35
Pluronic L-64	5
Isopropyl Myrisate	5
Pluronic 10R5	q.s
Lignocaine hydrochloride monohydrate	0.50
Methyl linolenate	0.50
γ -Linolenic acid	0.1
cis-5,8,11,14,17-Eicosapentaenoic acid sodium salt	0.25

5 Examples I provide compositions suitable for
transdermal analgesics.

Example 3: Preparation of transdermal compo-
sitions: The compositions K1 - K11 may be prepared
10 according to general process 5, as described below.

Examples K

Ex K 1	
Ingredients	Conc (% w)
Span 60	17
Tween 40	25
Tween 20	15
Olive oil	20
Isopropile Myristate	5
Fumed Silica	5
PEG 400	5
Calcium Peroxide	0.1
Tetrasodium Pyrophosphate	2

- 61 -

Tetrapotassium Pyrophosphate	2
Xylitol	1.5
Zinc Carbonate	1
Sodium monofluorophosphates	0.12
Birch oil	0.18
Potassium Acesulfame	0.8
Flavor	0.3

Ex K 2	
Ingredients	Conc (% w)
Span 60	17
Pluronic F127	2
Tween 40	30
Tween 20	12
Sunflower oil	3.28
Olive oil	4
Pluronic L-64	2
Isopropyle Myristate	6
Silica	4
Brushite	2
PEG 400	10
Sodium Perborate tetrahydrate	3
Sodium Lauroyl Sarcosinate	1
Tetrasodium Pyrophosphate	2
Potassium Acesulfame	0.8
Flavor	0.4
Sodium monofluorophosphates	0.12
Potassium Hydroxide	0.1
Sodium Chloride	0.2
Zinc Oxide	0.1

Ex K 3	
Ingredients	Conc (% w)
Span 40	10
Span 60	10
Tween 80	15
Tween 40	25
Pluronic L-121	10
Pluronic 10R5	5
Olive oil	4
Isopropyl Myristate	4
Brushite	4
Silica	3

- 62 -

Sodium Percarbonate	1.5
Sodium Hydroxide	0.15
Sodium Chloride	0.3
Zinc oxide	0.1
Sodium dihydrogen pyrophosphate	1
Potassium dihydrogen pyrophosphate	1
Tetrasodium pyrophosphate	2
Sodium Fluoride	0.12
Sodium bicarbonate	1
Sodium Lauroyl Sarcosinate	1
Potassium Acesulfame	0.8
Flavor	0.4
Color	q.s

Ex K 4	
Ingredients	Conc (% w)
Span 60	15.5
Tween 40	30
Tween 80	10
Pluronic L-81	5
Pluronic L-121	5
Ethyl Myristate	2
Oilve oil	10
PEG 400	8
Fumed Silica	5
Sodium Chlorite	2.5
Terrasodium pyrophosphate	4
Sodium Chloride	0.3
Sodium Hydroxide	0.15
Sodium Lauroyl Sarcosinate	1.2
Potassium Acesulfame	0.8
Flavor	0.35
Zinc oxide	0.1
Titanium dioxide	0.1

Ex K 5	
Ingredients	Conc (% w)
Span 60	17
Tween 40	25
Tween 20	15
Pluronic L-64	3
Pluronic L-121	5

- 63 -

Isopropyl Myristate	5
Olive oil	3
PEG 400	10
Fumed Silica	5
Brushite	2
Sodium Chlorite	2.5
Terrasodium pyrophosphate	4
Sodium Chloride	0.3
Sodium Hydroxide	0.2
Sodium Lauroyl Sarcosinate	1.5
Potassium Acesulfame	0.8
Peppermint Oil	0.3
Sweet Birch oil	0.1
Zinc oxide	0.1
Titanium dioxide	0.1
Eucalyptol	0.1

Ex K 6	
Ingredients	Conc (% w)
Span 60	17
Span 80	5
Tween 80	20
Tween 40	25
Olive oil	5
Pluronic L-121	4
PEG 400	5
PEG 600	3
Fumed Silica	5
Brushite	2
PVP-Hydrogen Peroxide	2
Sodium Chloride	0.3
Cocamidopropyl betaine	2
Sodium Lauroyl Sarcosinate	0.5
Sodium dihydrogen phosphate	1
Potassium dihydrogen phosphate	0.8
Potassium Acesulfame	0.8
Flavor	0.35
EDTA	1
Zinc Citrate	0.25

Ex K 7	
Ingredients	Conc (% w)
Span 60	18

- 64 -

Tween 80	22
Tween 40	25
Olive oil	5
Pluronic L-121	4
Pluronic 10R5	3
PEG 400	7
Fumed Silica	5
Brushite	2
Carbamide Peroxide	2
Sodium Chloride	0.3
Cocamidopropyl betaine	2
Sodium Lauroyl Sarcosinate	0.5
Sodium dihydrogen phosphate	1
Potassium dihydrogen phosphate	0.8
Potassium Acesulfame	0.8
Flavor	0.35
EDTA	1
Zinc Citrate	0.25

Ex K 8	
Ingredients	Conc (% w)
Span 60	18
Tween 40	30
Tween 20	15
Isopropyl Myristate	5
Pluronic L-121	4
Silica	5
Brushite	3
PEG 400	8
Sodium Lauroyl Sarcosinate	1
Amylase	1
Dextranase	0.4
Cellulase	0.4
Papain	1
Bromelin	0.1
Prolase	0.2
Lipase	0.5
Q 10	0.5
DL- α -Tocopherol acetate	1
(+)-Magnesium L-ascorbate	0.4
Calcium D-pantothenate	0.2
Zinc citrate	0.3
Polyaminopropyl Biguanide	1.5

- 65 -

Xylitol	1.4
Terrasodium pyrophosphate	1
Potassium Acesulfame	0.7
Flavor	0.4

Ex K 9	
Ingredients	Conc (% w)
Span 60	18
Tween 40	30
Tween 80	20
Pluronic L-121	2
Silica	5
Brushite	3
PEG 400	8
Sodium Lauroyl Sarcosinate	1.2
Amylase	1
Dextranase	0.4
Cellulase	0.4
Papain	1
Bromelin	0.1
Prolase	0.2
Lipase	0.5
Q 10	0.5
DL- α -Tocopherol acetate	1
(+)-Magnesium L-ascorbate	0.4
Calcium D-pantothenate	0.2
Zinc citrate	0.3
Polyaminopropyl Biguanide	1.7
Xylitol	2
Thymol	0.1
Eucalyptol	0.1
Wintergreen oil	0.1
Terrasodium pyrophosphate	1
Potassium Acesulfame	0.7
Flavor	0.3
Sodium monofluorophosphates	0.12
Zinc Oxide	0.1
Titanium Dioxide	0.1
Aluminum Oxide	0.1
Color	q.s

Ex K 10	
Ingredients	Conc (% w)
Span 60	18

- 66 -

Tween 40	30
Tween 80	20
Pluronic L-121	2
Silica	5
Brushite	3
PEG 400	8
Sodium Lauroyl Sarcosinate	1.2
Phage M102	1
Phage E10	1
Phage F1	1
Amylase	1
Dextranase	0.4
Cellulase	0.4
Papain	1
Bromelin	0.1
Prolase	0.2
Lipase	0.5
Q 10	0.5
DL- α -Tocopherol acetate	1
(+)-Magnesium L-ascorbate	0.4
Calcium D-pantothenate	0.2
Zinc citrate	0.3
Polyaminopropyl Biguanide	1.4
Thymol	0.1
Eucalyptol	0.1
Terrasodium pyrophosphate	1
Potassium Acesulfame	0.7
Flavor	0.3
Zinc Oxide	0.1
Titanium Dioxide	0.1

Ex K 11	
Ingredients	Conc (% w)
Span 60	18
Tween 40	30
Tween 80	20
Pluronic L-64	2
Silica	5
Brushite	3
PEG 400	8
Sodium Lauroyl Sarcosinate	1.2
Phage M102	1
Phage E10	1

Phage F1	1
Amylase	1
Dextranase	0.4
Cellulase	0.4
Papain	1
Bromelin	0.1
Prolase	0.2
Lipase	0.5
Q 10	0.4
DL- α -Tocopherol acetate	1
(+)-Magnesium L-ascorbate	0.4
Calcium D-pantothenate	0.2
Zinc citrate	0.3
Polyaminopropyl Biguanide	1.4
Thymol	0.1
Eucalyptol	0.1
Terrasodium pyrophosphate	1
Potassium Acesulfame	0.68
Flavor	0.3
Zinc Oxide	0.1
Titanium Dioxide	0.1
Sodium monofluorophosphates	0.12

Examples K provide compositions suitable as dentifrice gel / cream.

table 1

Surfactant	Brand Name	HLB
2,4,7,9-Tetramethyl-5-decyne-4,7-diol		4.0
PEG-block-PPG-block-PEG, MN 1100		4.0
PEG-block-PPG-block-PEG, MN 2000		4.0
PEG-block-PPG-block-PEG, MN 2800		4.0
PEG-block-PPG-block-PEG, MN 4400		4.0
Ethylenediamine tetrakis(PO-b-EO) tetrol, MN 3600		4.0
Ethylenediamine tetrakis(EO-b-PO) tetrol, MN 7200		4.0
Ethylenediamine tetrakis(EO-b-PO) tetrol, MN 8000		4.0
Polyoxyethylene(2) isooctylphenyl ether	Igepal [®] CA-210	4.3
Sorbitan monooleate	Span [®] 80	4.3
PPG-block-PEG-block-PPG, MN 3300		4.5
Polyoxyethylene(2) nonylphenyl ether	Igepal CO-210	4.6
Sorbitan monostearate	Span [®] 60	4.7
Polyoxyethylene(2) oleyl ether	Brij [®] 92	4.9
Polyoxyethylene(2) stearyl ether	Brij [®] 72	4.9
Polyoxyethylene(2) cetyl ether	Brij [®] 52	5.3
Sorbitan monopalmitate	Span [®] 40	6.7
Merpol [®] A surfactant		6.7
2,4,7,9-Tetramethyl-5-decyne-4,7-diol ethoxylate		8.0
Triton [®] SP-135		8.0
Sorbitan monolaurate	Span [®] 20	8.6
PEG-block-PPG-block-PEG, MN 5800		9.5
PPG-block-PEG-block-PPG, MN 2700		9.5
Polyoxyethylene(4) lauryl ether	Brij [®] 30	9.7
Polyoxyethylene(5) isooctylphenyl ether	Igepal [®] CA-520	10.0
Polyoxyethylene(5) nonylphenyl ether	Igepal [®] CO-520	10.0
Polyoxyethylene sorbitol hexaoleate		10.2
Merpol [®] SE surfactant		10.5
Polyoxyethylene(20) sorbitan trioleate	Tween [®] 85	11.0
8-Methyl-1-nonanol propoxylate-block-ethoxylate		11.0
Polyoxyethylene sorbitan tetraoleate		11.4
Polyoxyethylene(8) isooctylphenyl ether	Triton [®] X-114	12.4
Polyoxyethylene(10) stearyl ether	Brij [®] 76	12.4
Polyoxyethylene(10) oleyl ether	Brij [®] 97	12.4
Merpol [®] OJ surfactant		12.5
Polyoxyethylene(10) cetyl ether	Brij [®] 56	12.9
Merpol [®] SH surfactant		12.9
Nonylphenol polyethylene glycol ether	Tergitol [®] NP-9	12.9
2,4,7,9-Tetramethyl-5-decyne-4,7-diol ethoxylate (5 EO/OH)		13.0
Triton [®] SP-190		13.0
Polyoxyethylene(9) nonylphenyl ether	Igepal [®] CO-630	13.0
Polyoxyethylene(10) isooctylphenyl ether	Triton [®] X-100	13.5
Polyoxyethylene(12) nonylphenyl ether	Igepal [®] CO-720	14.2
Polyoxyethylene(12) tridecyl ether		14.5
Polyoxyethylene(18) tridecyl ether		14.5
Polyoxyethylene(12) isooctylphenyl ether	Igepal [®] CA-720	14.6
Polyoxyethylene(20) sorbitan monooleate	Tween [®] 80	14.9
Polyoxyethylene(20) sorbitan monostearate	Tween [®] 60	15.0
PEG-block-PPG-block-PEG, MN 2900		15.0
PPG-block-PEG-block-PPG, MN 2000		15.0
Polyoxyethylene(20) stearyl ether	Brij [®] 78	15.3
Polyoxyethylene(20) oleyl ether	Brij [®] 98	15.3
Merpol [®] HCS surfactant		15.5
Polyoxyethylene(20) sorbitan monopalmitate	Tween [®] 40	15.6
Polyoxyethylene(20) cetyl ether	Brij [®] 58	15.7
Polyethylene-block-poly(ethylene glycol)Mn 2250		16.0
Polyoxyethylene(20) sorbitan monolaurate	Tween [®] 20	16.7

table 1 (cont.)

Polyoxyethylene(23) lauryl ether	Brij [®] 35	16.9
2,4,7,9-Tetramethyl-5-decyne-4,7-diol ethoxylate (15 EO/OH)		17.0
Polyoxyethylene(40) nonylphenyl ether	Igepal [®] CO-890	17.8
Polyoxyethylene(40) isooctylphenyl ether Triton [®] X-405	Triton [®] X-405	17.9
Polyoxyethylene(100) stearyl ether	Brij [®] 700	18.8
Polyoxyethylene(100) nonylphenyl ether	Igepal [®] CO-990	19.0
Polyoxyethylene(150) dinonylphenyl ether	Igepal [®] DM-970	19.0
PEG-block-PPG-block-PEG, MN 1900		20.5
PEG-block-PPG-block-PEG, MN 8400		24.0
Ethylenediamine tetrakis(PO-b-EO) tetrol, MN 15000		24.0
PEG-block-PPG-block-PEG, average Mn ca. 14,600		27.0
Sorbitan Tristearate	LUMISORB [™] STS K	2.1
Sorbitan Oleate	LUMISORB SMO K	4.3
Sorbitan Stearate	LUMISORB SMS KP	4.7
Sorbitan Laurate	LUMISORB SML K	8.6
Polysorbate 81	LUMISORB PSMO-5 K	10.0
Polysorbate 65	LUMISORB PSTS-20 K	10.5
Polysorbate 85	LUMISORB PSTT-20	11.0
Polysorbate 60	LUMISORB PSMS-20 K	14.9
Polysorbate 60, Liquid Kosher	LUMISORB PSMS-20 LK	14.9
Polysorbate 60, Low Color	LUMISORB PSMS-20 K LC	14.9
Polysorbate 80	LUMISORB PSMO-20 K	15.0
Polysorbate 20	LUMISORB PSML-20 K	16.7
PEG-80 Sorbitan Laurate	LUMISORB PSML-80	19.4
PEG-8 Dioleate	LUMULSE 42-O K	8.5
PEG-8 Oleate	LUMULSE 40-O K	11.8
PEG-8 Laurate	LUMULSE 40-L	12.8
PEG-12 Tallate	LUMULSE 60-T	13.6
PEG-20 Stearate	LUMULSE 100-S	15.6
PEG-40 Stearate	LUMULSE POE (40) MS KP	17.2
PEG-150 Distearate	LUMULSE 602-S K	18.4
PEG-100 Stearate	LUMULSE POE (100) MS	18.8
Glyceryl Ricinoleate	LUMULSE GMR K	2.6
Glyceryl Oleate	LUMULSE GMO K	2.8
Glyceryl Stearate	LUMULSE GMS K	4.0
Glyceryl Laurate	LUMULSE GML K	5.2
Glyceryl Stearate and PEG-100 Stearate	LUMULSE GMS-A	11.0
PEG-7 Glyceryl Cocoate	LUMULSE POE (7) GML	13.0
PEG-20 Glyceryl Stearate	LUMULSE POE (20) GMS K	13.5
Laureth-4	LUMULSE L-4	9.5
Laureth-12	LUMULSE L-12	14.5
Ceteareth-20	LUMULSE CS-20	15.2
Laureth-23	LUMULSE L-23	16.7
Glycereth-26	LUMULSE POE (26) Glycerine	18.4
PEG-5 Castor Oil	LUMULSE CO-5	4.0
PEG-25 Hydrogenated Castor Oil	LUMULSE HCO-25	10.8
PEG-25 Castor Oil	LUMULSE CO-25	10.8
PEG-40 Castor Oil	LUMULSE CO-40	13.0
PEG-40 Hydrogenated Castor Oil	LUMULSE HCO-40	14.0
PEG-50 Hydrogenated Castor Oil	LUMULSE HCO-50	14.1

Claims

1. A formulation comprising a first and a second component wherein
 - said formulation being non-aqueous and colloidal;
 - said first component is a liquid or solid, amphiphilic, non-ionic surfactant;
 - said second component is a liquid, water-free, organic dispersing medium;
 - said first component is (a) substantially insoluble at room temperature but (b) fully miscible when heated above its melting point in said second component;characterized in that said formulation contains vesicles (1) wherein
 - said vesicles are tubular shaped, multi-lamellar vesicles ("tubulosomes") comprising or consisting of stacked bi-layers of said surfactant molecules;
 - at least 90% of said surfactant is located (n/ n, determined by light scattering) within said vesicles.
2. A formulation according to claim 1, wherein said formulation comprises a network of said tubulosomes.
3. A formulation according to any of claims 1 - 2, wherein said second component is selected from the group consisting of liquid, non-ionic surfactants.
4. A formulation according to any of claims 1 - 2, wherein said second component is selected from the group consisting of vegetable oils, alcohols of vegetable oils, esters of vegetable oils, alkoxyates of vegetable oils, polyalkenes, acyclic and cyclic alkanes, acyclic and cyclic alkenes.
5. A formulation according to any of claims 1 - 4, wherein said first component is a solid, amphi-

philic, non-ionic surfactant; said formulation particularly being of the gel type.

6. A formulation according to any of claims 1 - 4, wherein said first component is a liquid, amphiphilic, non-ionic surfactant; said formulation particularly being of the emulsion type.
7. An oral care composition comprising a formulation according to any of claims 1 - 6.
8. A composition according to claim 7 additionally comprising bleaching agents, in particular peroxides and chlorites.
9. A composition according to claim 7 or 6 additionally comprising enzymes and / or bacteriophages.
10. A topical and/or transdermal composition comprising a formulation according to any of claims 1 - 6.
11. A composition according to claim 11 additionally comprising one or more pharmaceutically active ingredients, in particular one or more folate antagonists.
12. A composition according to claim 10 or 11 additionally comprising one or more pharmaceutically active ingredients selected from the group consisting of immunosuppressive, disease-modifying antirheumatic drugs (DMARDs), TNF- α blockers, Interleukin 1 blockers, monoclonal antibodies against B cells, T cell activation blockers, steroidal and non-steroidal Anti-inflammatory agents, non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, Sulphonanilides, Omega-3 fatty acids, analgesic agents, A₃ adenosine receptor (A₃AR) agonist and/or Lipase(s) in combination with an activator of lipolysis and a promoter of cAMP; in particular Methotrexate and its pharmaceutically accepted derivatives.

13. A method for manufacturing a formulation according to any of claims 1 - 6 comprising the steps of
- combining first and second component, preferably by vortexing.
 - 5 • heating the obtained mixture at least 5°C above the melting point of the first component
 - maintaining the temperature for a period from 10 min to 10 hrs,
 - slowly cooling down the obtained mixture.
- 10 14. A method for manufacturing a composition according to any of claims 7 - 12 comprising the steps of
- providing a formulation according to any of claims 1 - 6
 - 15 • adding additional components to obtain the desired composition.
15. Use of a formulation according to any of claims 1 - 6 in a topical product, in a transdermal product or in an oral care product.
16. A composition according to any of claims 7 - 12 as
20 pharmaceutical.
17. Use of a composition according to claims 10 - 12 for the reduction of unwanted fat located in the hypodermis.
18. Use of a composition according to claims 10 - 12
25 for the manufacture of a medicament for the treatment of obesity, adiposis.
19. Use of a composition according to claims 10 - 12 for cosmetic shaping of the body.

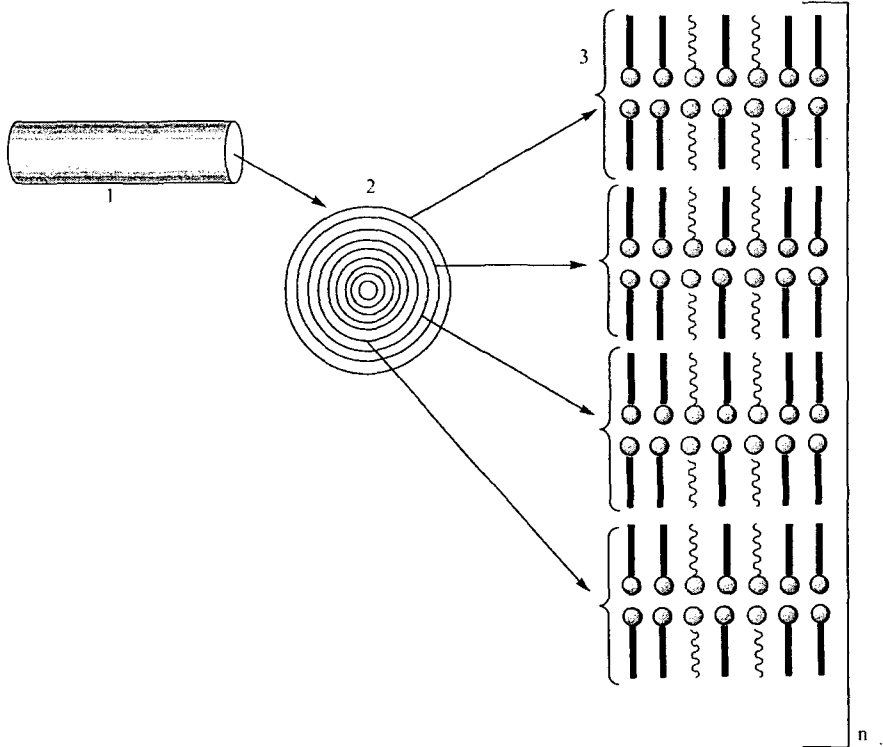


Fig 1

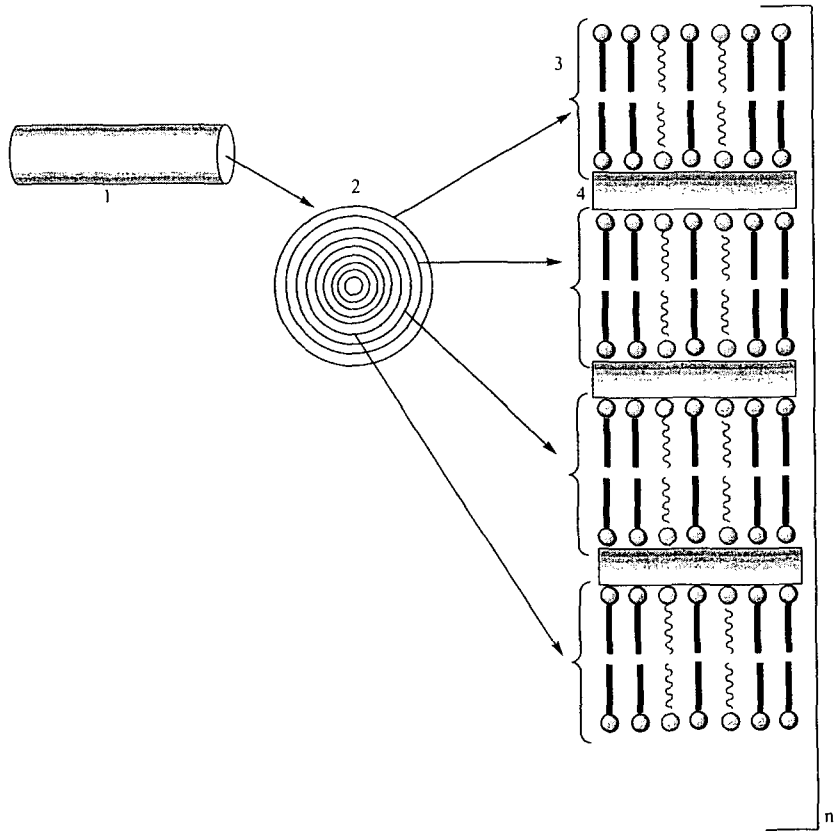


Fig 2

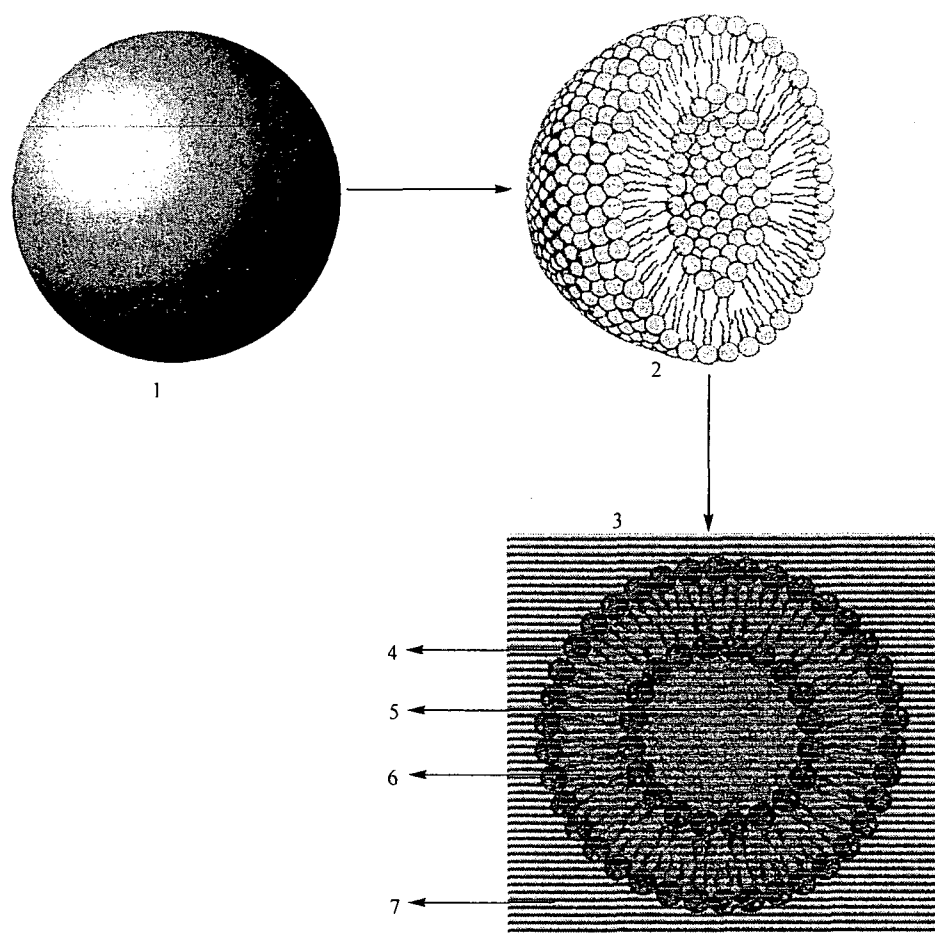


Fig. 3