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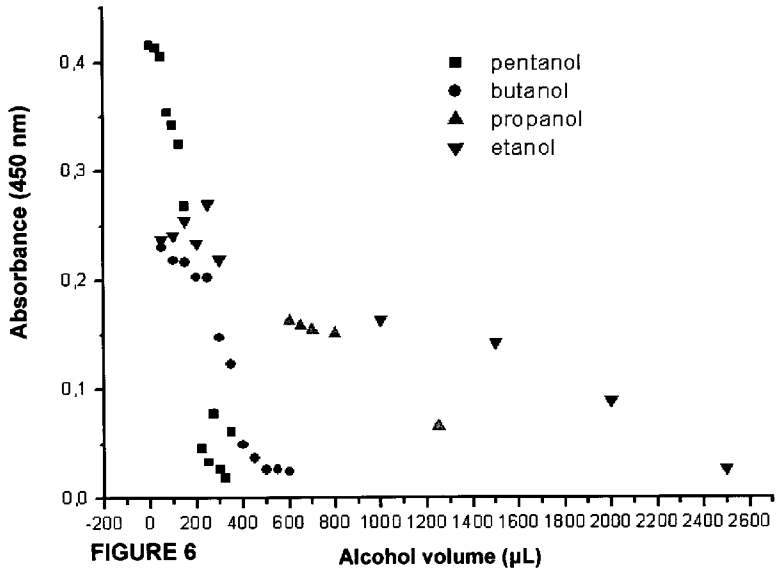

FIGURE 6

(57) Abstract: The present invention refers to a carrier system for weakly water soluble substances comprising (i) a lipid compound, (ii) a cosolvent and (iii) water, with said system being a liquid constituted of a lyotropic phase in thermodynamic equilibrium, in the form of phase L3 (sponge phase), obtained from stoichiometrically defined proportions. The invention also contemplates a process for obtaining the said carrier system for weakly water soluble substances, as well as its use as a carrier medium for weakly water soluble substances, such as pharmaceuticals, pesticides, herbicides, proteins, amino-acids, vitamins, antibiotics and similar substances for the preparation of compositions or for the coating of nanoparticles.

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CARRIER SYSTEM FOR WEAKLY WATER SOLUBLE SUBSTANCES, PROCESS FOR OBTAINING SAID SYSTEM AND ITS USES

Field of the invention

The present invention refers to a carrier system for weakly water soluble substances comprising (i) a lipid compound, (ii) a cosolvent and (iii) water, with the said system being a liquid constituted of a lyotropic phase in thermodynamic equilibrium, in the form of an L_3-phase (sponge phase), obtained from stoichiometrically defined proportions. The invention also contemplates a process for obtaining the said carrier system for weakly water soluble substances, as well as its use as a carrier medium for weakly water soluble substances, such as pharmaceuticals, pesticides, herbicides, proteins, amino-acids, vitamins, antibiotics and similar substances for the preparation of compositions or as a template for the preparation of high-porosity nanoparticles.

Background of the invention

The majority of lyotropic structures formed when amphiphilic molecules, such as soaps, detergents and lipids, are exposed to water is currently well categorised with their phase diagrams being well known. The lyotropic character of the liquid crystal phases is provided by solvent molecules. This is due to the fact that such phases are not evenly distributed, typically being more numerous in one part of the phase than in others.

This separation between amphiphilic and solvent gives rise to a great diversity of structures. Apart from the arrangement of the actual molecules within the amphiphilic aggregates, the lyotropic phases contain an arrangement of aggregates in structures of superior order. EKWALL (1975) (refer to Ekwall, P., "Advances in Liquid Crystals", Ed. G.W. Brown, Academic Press, New York, 1975) noted that, for several ternary systems (short chain/water ionic surfactant/aliphatic alcohol) the stability domain of the lamellar phase increases

in the direction of the water vertex in the phase diagram. In other words, following the addition of aliphatic alcohol, a characteristically micellar region of the phase diagram becomes an L_α-phase. The increase in the relative alcohol ratio results in three different phases: (i) the micellar L_1-phase, in a low $\phi_{alcohol}/\phi_{surfactant}$ ratio; (ii) the L_α-phase, at a higher ratio with the occurrence of the stability domain of the lamellar phase swollen with alcohol and (iii) the L_3-phase, characterised by being a narrow region. These phase transformations on a macroscopic scale most probably correspond to the relevant morphological transformations of the aggregated surfactants. The sequence corresponds to an increasingly smaller curvature for the alcohol/surfactant film and conforms to the principle according to which the addition of alcohol reduces the said curvature (the Gaussian folding module).

It is important to note that Ekwall was the pioneer, but at that time did not dispose of spectroscopic techniques capable of verifying the determined position of molecules, and, therefore, the system was only fully developed in 1987/1988 by Montpellier's group (see Ekwall, P. "Solutions of alkali soaps and water in fatty acids X. The basic structure of the molecules and the size of the particles of acid octanoates in the L_2-phase at water contents below 40%". Colloid & Polymer Science Volume 266 (8). pp. 729-733. August/1988).

The petroleum researchers Benton and Miller (refer to Benton, W.J. and Miller, C.A., Prog. Colloid Polymer Sci. 68, 71. (1983)) were the first to describe the appearance of a liquid crystal phase in the diluted region (< 10% of surfactant weight) of the surfactant/alcohol/water ternary mixtures used in the lubrication of oil wells. The authors worked with a series of anionic surfactants and medium size linear chain alcohols using polarised light in macroscopic and microscopic experiments. The presence of liquid crystals was confirmed by placing the sample in a test tube between the inter-crossing beams of two light polarisers. The liquid crystal phase appears with several birefringent textures.

Porte G., in a series of works carried out by his group in Montpellier (refer to Porte, G. *J. Phys. Cond. Mat.* 1992, 4, 8649), performed the characterisation of ternary mixtures of surfactant/ medium–linear-chain

alcohol/water using a system based on cetylpyridinium chloride and/or cetylpyridinium bromide, with this compound having a hydrophilic head and hydrophobic tail constituted of a hydrocarbonate chain. In summary, this group designed a phase diagram in the highly diluted region of the surfactant, which exhibits a radial behaviour, with the several successive phases depending mainly of the alcohol/surfactant stoichiometry and being independent of the water content. In the absence of alcohol, the detergent molecules in the diluted phase organise themselves as micelles, that grow in size and change form (giant micelles or cylindrical forms, depending on the counter-ion, chloride or bromide), with the cetylpyridinium chloride (CPCl) micelles remaining small and globular and the cetylpyridinium bromide (CPBr) micelles growing to form large flexible cylindrical forms. Swollen lamellas are formed by the progressive addition of water (termed the L_α-phase) and, following the addition of more alcohol, a phase comes up exhibiting optical isotropy and low viscosity. It is in this phase termed the L_3-phase that the Montpellier group concentrated their efforts.

The work of Saito and his collaborators is also very important (refer to Saito Y, Hashizaki K, Taguchi H, Ogawa N. "Solubilization of (+)-limonene by anionic/cationic mixed surfactant systems", DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY 29 (3): 345-348 2003). These researchers studied the combined effect of n-octyl sodium sulphate (SOS) and cetyltrimethylammonium bromide (CTAB) in the solubilisation of (+)-limonene in an aqueous solution using a "headspace" type gas chromatography technique. The results demonstrated that the mixture of SOS and CTAB resulted in positive synergistic effects for the solubilisation of (+)-limonene. These positive synergistic effects are explained from the perspective of the phase behaviour of this mixed surfactant system.

Another group of researchers studying the interaction of heparin with amphiphilic assemblies (refer to Ito Y., Okuyama T., Kashiwagi T., Imanishi Y. "Interaction of heparin with amphiphile assemblies and biocompatibility of the heparin complexes", JOURNAL OF BIOMATERIALS SCIENCE-POLYMER

EDITION 6 (8): 707-714 1994) ascertained that the addition of heparin to pre-formed vesicles of a cationic lipid compound having surfactant activity, namely dioctadecyldimethylammonium bromide (DODAB/DDOB), resulted in a rapid precipitation of the heparin/DODAB complex. On the other hand, the heparin stabilised the vesicle composed of dipalmitoil L-alpha-phosphatidylcholine (DPPC) that is a neutral lipid. However, DPPC was precipitated with heparin through the addition of a small quantity of stearylamine (SA) that is a cationic substance. The differential scanning calorimetric test of the heparin/amphiphilic mixtures revealed that the heparin/DODAB complex possesses a structure different from the original DODAB vesicle. The structure of the DPPC vesicle was not affected by the addition of heparin, while the structure of the heparin/DPPC-SA complex proved to be different from that of the DPPC-SA vesicle. The authors of this work concluded that the interaction of heparin with vesicles depends on the nature of the amphiphilics. They also verified that heparin was solubilised in the organic solvent when made up into complexes with vesicles of DODAB or of DPPC-SA. Furthermore, the authors reached the conclusion that although the membranes of polyurethaneurea mixed with complexes of heparin/DODAB or heparin/DPPC-SA are highly non-thrombogenic, they are relatively cytotoxic.

When studying the influence of cosolvents on the stability of catanionic vesicles (vesicles comprising surfactants with opposite charges), Yeh and collaborators (refer to Yeh S.J., Yang Y.M. and Chang C.H., "Cosolvent effects on the stability of catanionic vesicles formed from ion-pair amphiphiles", LANGMUIR 21 (14): 6179-6184 JUL 5 2005) produced catanionic vesicles in water, using the mechanical dispersal method, from four ion-pair amphiphiles (IPAs) derived from the pairing of alkyltrimethylammonium chlorides and sodium alkyl sulphates. Short chain alcohols (methanol, ethanol, 1-propanol and 1-butanol) were added to these vesicles as cosolvents in various concentrations, with these systems being systematically studied in relation to their effect on the stability of the resulting vesicles. Measurements by dynamic light scattering indicated that the vesicles formed from one of the IPAs (in

other words, dodecyltrimethylammonium dodecyl sulphate) may be effectively stabilised through the addition of appropriate quantities of 1-propanol and 1-butanol. Maximum life cycle times of over a year were observed and of 132 days for vesicles stable in solutions of 1-butanol at 5% and of 1-propanol at 15%, respectively. The authors concluded that this demonstrated the fact that the stabilisation of catanionic vesicles formed from IPAs is rendered possible through the addition of cosolvents. Furthermore, the authors also concluded that the stability of the catanionic vesicles is highly dependent on the concentration of the cosolvent and that, overall, the stability of the vesicle is increased with an increase in cosolvent concentration, attaining maximum stability at a specific concentration at which point the stability decreases with any further increase in concentration, with disintegration of the vesicles into their constituent molecules in solutions with very high concentrations of cosolvent.

Another group currently dedicated to researching pre-formed vesicle systems is coordinated by Luisi P. (refer to Thomas C.F., Luisi P.L. "Novel properties of DDAB: Matrix effect and interaction with oleate", JOURNAL OF PHYSICAL CHEMISTRY B 108 (31): 11285-11290 (2004)), with their most recent study relating to the interaction of a positively charged surfactant DDAB (didodecyldimethylammonium bromide) with pre-formed vesicles from POPC (1-palmitoil-2-oleoyl-sn-glycero-3-phosphocholine). They verified that the addition of 1.9 mM DDAB to pre-formed POPC vesicles in different concentrations results in the appearance of mixed vesicles due to the avid capture of DDAB by POPC, leading to the so-called matrix effect. This effect occurs when pre-formed POPC liposomes with a narrow size distribution range are present in an aqueous solution which gives rise to a rapid formation of mixed vesicles, with the final size distribution being extremely close to that of the pre-formed POPC liposomes. The final system of mixed vesicles remains stable in size and size distribution. This effect is regardless of the initial size of the POPC vesicles and requires relatively low concentrations of POPC compared to DDAB (up to 1:4). The authors also concluded that the mixture of

DDAB and oleate vesicles for molar fraction values of DDAB close to 0.4 lead to vesicular types having a narrow distribution centralised around 100 nm.

In studies of the crystallisation of membrane proteins, Wadsen, P. and collaborators (see Wadsen, P., Wöhri, A.B., Snijder, A., Katona, G., Gardiner, A.T., Cogdell, R.J., Neutze, R. and Engström, S. "Lipidic Sponge Phase Crystallization of Membrane Proteins. J. Mol. Biol. (2006) 364, 44-53), verified that the said crystallisation occurred advantageously in the sponge phase, rather than in the bicontinuous lipid cubic phases. Despite that these cubic phases may be used to host the growth of membrane protein crystals, they are rigid and difficult to handle and, furthermore, the conventional cubic phase interferes with the hydrophilic domains of the membrane proteins due to the limited size of the aqueous pores. The authors proposed the use of the sponge phase in the crystallisation of membrane proteins due to the fact that the said phase facilitates a considerable increase in the size allowed for the aqueous domains of the membrane proteins.

Vieira, D.B. and collaborators (refer to Vieira, D.B., Carmona-Ribeiro, A.M., "Synthetic Bilayer Fragments for Solubilization of Amphotericin B" (Note). Journal of Colloid and Interface Science **244,** 427– 431 (2001)) focussed on another application for surfactant aqueous emulsions. The authors studied the solubilisation of amphotericin B (AB) by means of synthetic bilayer fragments from dispersions of dioctadecyldimethylammonium bromide (DODAB) or of sodium di-hexadecylphosphate (DHP) in water, with the solubilisation of the pharmaceutical being monitored through the techniques of dynamic light scattering and optical spectroscopy. Starting from the premise that the low solubility of AB in water allows determination of the size distribution of the AB aggregates in water and subsequent comparatives of this distribution in the presence of DODAB or DHP bilayer nano-fragments, the authors verified that pharmaceutical large aggregates disappeared under incubation conditions with the bilayer nano-fragments. These authors also verified that the light absorption spectrum for AB in a weak solvent (i.e. water), in a good organic solvent (dimethyl sulphoxide:methanol 1:1), and in different lipid dispersions also demonstrated that solubilisation depends strictly on the

presence of bilayer fragments, with AB being weakly soluble in dispersions formed by completely closed vesicles of DODAB, DHP, phosphatidylcholine or asolectin. The chemical structure of AB and the increased hydrophobicity at the edges of the bilayer fragments led the authors to conclude that these hydrophobic regions interact with the polyenic component of the antibiotic leaving the hydroxylate group free to interact with the surrounding water. The authors also perceived the use of these synthetic bilayer fragments, which are cheap, for the creation of large areas of hydrophobic nano-surfaces well dispersed in water to control the release of AB and other water insoluble pharmaceuticals.

An important contribution to the studies relating to the solubilisation of amphotericin B was also provided through the work of Lincopan, N. and collaborators (see Lincopan, N., Mamizuka, E.M. and Carmona-Ribeiro A.M. "*In vivo* activity of a novel amphotericin B formulation with synthetic cationic bilayer fragments". Journal of Antimicrobial Chemotherapy (2003) 52, 412-418). The authors studied the solubilisation of amphotericin B (AMB) by means of bilayer fragments of dioctadecyldimethylammonium bromide (DODAB) by evaluating the role of such fragments through *in vivo* activity in an animal model (mice) using life extension and tissue charge against systemic candidiasis experiments. The experiment consisted of adding AMB (≤0.1 g/L) to a dispersion of powdered DODAB in water (10 g/L) previously prepared by sonication in the absence of organic solvents. The state of aggregation of the AMB was assessed by means of UV-visible range light absorption and dynamic light scattering technique to determine the size of the aggregate. The authors verified that the AMB was stabilised by the bilayer fragments of DODAB in its monomeric form and that the mixture of AMB with the dispersion of DODAB in pure water resulted in the disappearance of large aggregates of the water insoluble pharmaceutical. The life extension experiments allowed the authors to verify that both the bilayers of DODAB/AMB and of the traditional formulation of deoxycolate/AMB (DOC/AMB), had an identical effect when administered by the same route (intraperitoneal) and with the same dosage of 0.4 mg/kg/day during 10 days.

Other studies relating to organic molecules solubilisation in vesicules and the behaviour of the lamellar and non-lamellar lipid phases include: (1) Lohner K. "Effects of small organic-molecules on phospholipid phase-transitions". CHEMISTRY AND PHYSICS OF LIPIDS 57 (2-3): 341-362 MAR 1991; (2) Abe, M.; Yamauchi, H.; Ogino, K. In *Solubilization in Surfactant Aggregates*, Christian, S. D., Scamehorn, J. F., Eds., Marcel Dekker: New York, 1995; Chapter 10; (3) Nagarajan, R. *Curr. Opin. Colloid Interface Sci.* 1997, *2*, 282-293.[ChemPort]; (4) Jung M., Hubert D.H.W., van Veldhoven E., Frederik P.M., Blandamer M.J., Briggs B., Visser A.J.W.G., van Herk A.M., German A.L.; "Interaction of styrene with DODAB bilayer vesicles. Influence on vesicle morphology and bilayer properties".*Langmuir*; 16(3):968-979, February/2000.

Interesting work relating to spontaneous emulsification include: (1) Shahidzadeh N., Bonn D., Meunier J., et al. "Dynamics of spontaneous emulsification for fabrication of oil in water emulsions". *Langmuir* Dec.2000 16 (25): 9703-9708; (2) Sitnikova N.L., Sprik R., Wegdam G. e Eiser E. "Spontaneously Formed trans-Anethol/Water/Alcohol Emulsions: Mechanism of Formation and Stability". *Langmuir* 2005; 21(16) pp 7083 – 7089.

Other work related to miniemulsion can also be cited, such as: (1) Miller C.M., Venkatesan J., Silebi C.A., Sudol E.D., Elaasser M.S. "Characterization of Miniemulsion Droplet Size and Stability Using Capillary Hydrodynamic Fractionation". Journal of Colloid and Interface Science 1994 162 (1): 11-18; (2) Feitosa E., Barreleiro P.C.A., Olofsson G. "Phase transition in dioctadecyl-dimethylammonium bromide and chloride vesicles prepared by different methods", Chemistry and Physics of Lipids (2000) 105 (2): 201-213; (3) Stephanus A., Shantz D. F. "Cationic microemulsion-mediated synthesis of silicalite-1". Microporous and Mesoporous Materials 84 (2005) 236–246.

Another group of researchers dedicated its work to another weakly water soluble substance, taxol (see Wenk, M., Fahr, A., Reszka, R. e Seelig, J. (1996) "Paclitaxel Partitioning into Lipid Bilayers". Journal of Pharmaceutical Sciences, Vo. 85, No. 2). Wenk and collaborators have determined partition

coefficient of taxol in small unilamellar vesicles of lipid composed of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine and concluded that the bonding reaction is trigged by enthalpy, which can be explained by the existence of van-der-Waals type interactions between the hydrophobic pharmaceutical and the hydrophobic region of the lipid bilayer.

Other important contributions to the search for adequate carrier systems for weakly water soluble substances may be found in various patent documents. For example, patent US 6.251.416 describes a limpid uniphasic aqueous microemulsion of an agriculturally active pyretroid insecticide, where the said microemulsion is capable of releasing a great quantity of active substance and the concentrate of the microemulsion consisting of (weight ratio): (a) 0.015-4% of N-methylpirrolidone; (b) 0.005-2% of N- octylpyrrolidone; (c) 0.05-1.5% of a polymer surfactant in an ethoxylated/propoxylated (EO/PO) box; (d) 0.04-6% of ethoxylated castor oil or a tristyryl phenol ethoxylate, and (e) 0.0005-0.6% of a phosphate ester with a pH buffer.

Document US 6,494,941 describes microemulsions of a continuous aqueous or aqueous-organic phase and a discontinuous organic phase, with the latter containing at least: (a) a combination of tebuconazol and propiconazol active compounds, (b) an ether of phenol/styrene polyglycol and, when appropriate, (c) an organic solvent.

Document US 6,469,084 describes a process for the preparation of an aqueous composition that acquires the form of a gel at a given temperature. The process is characterised by the fact of placing a water soluble associative polymer constituted of a main hydrophilic chain and hydrophobic lateral groups into contact with at least one surfactant in a bilayer form when it is in solution under the same conditions of temperature and concentration. Preferentially, the compositions in gel or liquid form comprise vesicles, and more particularly liposomes. According to this invention, the process provides the means of considerably varying the viscosity of an aqueous composition containing an associative polymer by means of introducing a surfactant into the composition and selecting the conditions in which this surfactant is in a bilayer form.

Another important application of the liquid crystal phase is in particle coating. For example, patent US 5,531,925 describes particles, especially colloidal particles, comprising (A) an interior phase of (1) a lyotropic non-lamellar liquid crystal phase selected from the group consisting of a reverse cubic liquid crystal phase and a reverse hexagonal liquid crystal phase or (2) a homogenous L_3-phase or any combination of these, and (B) a surface phase (1) selected from the group consisting of a lamellar crystal phase and a lamellar liquid crystal phase, or (2) an L_3-phase or any combination of the same, with the said surface phase and the said interior phase being distinct. Furthermore, it is also mentioned that these particles are appropriated as particles or systems for the delivery of pharmaceuticals and in other medical and non-medical applications and that the structure of L_3 is constituted of multi-connected bilayers forming a bicontinuous structure of high connectivity, which may be contemplated as a disordered counterpart compared to the cubic phases.

Yet another application is provided in patent US 6,482,517 that describes a particle coated in a non-lamellar crystalline material including an internal matrix nucleus having at least one nano-structured liquid phase or a combination of the same for use in the delivery of active agents, such as medicines, nutrients, pesticides, etc. It is mentioned that the particles may be used to release one or more materials in an selected environment and that the L_3-phase is considered as a bicontinuous phase, being similar to the cubic phase, but not having the long-spectrum order that is characteristic of the cubic phase.

Document US 7,105,229 describes a particle coated in a non-lamellar, such as a non-lamellar crystalline material, non-lamellar amorphous material or non-lamellar semi-crystalline material including an internal matrix nucleus having at least one nano-structured liquid phase or at least one nano-structured liquid crystal phase or a combination of both, to be used in the delivery of active agents, such as medicines, nutrients, pesticides, etc. It is mentioned that the nano-structured matrix material may be: (a) a nano-structured L_1-phase material, (b) a nano-structured L_2-phase material, (c) a nano-structured micro-

emulsion or (d) a nano-structured L_3-phase material. The document does not mention the DODAB lipid as being a component of the L_3-phase.

Patent US 6,991,809 describes a particle comprising a first volume of hydrophobic domain rich material with adjustable dissolution and solubilisation characteristics and a second volume of a nano-structured non-lamellar crystalline material. It is mentioned that the nano-structured non-lamellar crystalline material is capable of remaining in equilibrium with a polar solvent or a water immiscible solvent or with both.

Liquid crystal phases also find applications in obtaining ceramic materials with enhanced qualities. For example, patent US 6,638,885 describes a mesoporous ceramic material with a pore size diameter in the range of approximately 10-100 nm produced in templates with a precursor ceramic as a lyotropic liquid crystal L_3-phase consisting of a random three-dimensional non-periodic network of a multiply connected continuous membrane. It mentions that a preferred process produces a inesoporous ceramic material that involves the production of a lyotropic liquid crystal L_3-phase template by the mixture of a surfactant, a co-surfactant and hydrochloric acid. This template is then coated with an inorganic ceramic precursor by adding tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS) to the L_3-phase which is followed by the conversion of the coated template to ceramic by the removal of any liquids. It is mentioned that the L_3-phase is a thermodynamically stable phase composed of the surfactant cetylpyridinium chloride (CpCl, mono-hydrated 1-hexadecylpyridinium chloride, $C_{16}H_{33}(N^+)C_5H_5(Cl^-).H_2O$); of the co-surfactant hexanol ($C_6H_{13}OH$, ca. 98% by GC), and hydrochloric acid (aqueous solution at 0.2 M). It is further mentioned that the L_3-phase possesses a viscosity comparable to water thus facilitating the addition of the inorganic precursors since this addition becomes a problem with more the viscous phases of the hexagonal, bicontinuous and lamellar type. It is also noted that the L_3 liquids are quite stable and may be stored for several weeks if the container is well sealed to prevent the loss of hexanol.

Patent US 6,423,770 describes a silicate material produced from the mixture of a templating mixture with pre-cured resin and one or more resin precursors, with the templating mixture comprising one or more surfactants, one or more alcohols and water. The surfactants are selected from the group consisting of cetyltrimethylammonium bromide (CTAB), Brij 30.TM. (tetraethylene glycol monododecyl ether) and cetylpyridinium chloride (CPC). Other surfactants with a similar molecular function or, in other words, an alkylic or alkylaril chain of approximately 10-20 carbon atoms having a non-polar or hydrophobic extremity and a polar or hydrophilic extremity containing a group such as a quaternary ammonium, oligomeric ethylene oxide unit, sulphonate, sulphate, phosphate or phosphonate may also be used. The alcohols are moderately polar such as 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol.

Document US 2004/0087447 describes a herbicide formulation comprising the incorporation of a herbicide in a micelle or vesicle and the absorption of the said micelle or vesicle containing the herbicide in a clay mineral. The formula is appropriated, more particularly, for herbicides with a negative charge at a pH above 6 and provides slow release and reduced draining of the herbicide to the deeper soil layers, thus decreasing the contamination of the soil and subterranean water. It is mentioned that the micelle are composed of a quaternary amine cation, for example, hexadecyltrimethylammonium (HDTMA) or octadecyltrimethylammonium (ODTMA); and the vesicles are composed of lipids with positive charges, for example, didodecyldimethylammonium bromide (DDAB) or dioctadecyldimethylammonium bromide (DDOB), wherein the micelle or vesicles containing the herbicide are in turn absorbed in a clay mineral having a negative charge. All examples of the preparation of the micelle or of the vesicles show that the compounds of quaternary amine cations or lipids having positive charges in buffer solutions are mixed with the herbicide for subsequent absorption by the clay mineral.

Despite the solutions presented above, in order to provide a vehicle for important substances that are poorly soluble or insoluble in water, such as

pharmaceuticals and other pharmacologically active substances, herbicides, insecticides, cosmetic substances, etc., there remains a need to improve the existing vehicles so as to achieve reduced toxicity and increased stability of the compositions or coatings that include the vehicles types of the present invention. These objectives should also be accompanied by a reduction in the concentration of the components presenting any toxicity and which, therefore, need to be quantitatively limited.

Summary of the Invention

Having ascertained that the stability and other desirable characteristics of carrier systems for weakly water soluble substances may be enhanced by establishing a relation between the lipid compound and the cosolvent for obtaining a stable lyotropic mixture being, preferentially, of low toxicity, that may be used as a vehicle for the active substance or as a template for depositing inorganic materials, that preferentially give origin to particulate surfaces, and more preferentially, nano-particles. Apart from their enhanced stability, the systems thus determined possess an improved capability for solubilising weakly water soluble compounds, such as pharmaceuticals, herbicides, fungicides and similar substances intending application through the compositions to which they are incorporated by delivery to a selected environment, such as an organism, the soil or the similar.

A first embodiment of the present invention refers to a carrier system for weakly water soluble substances comprising (i) a lipid; (ii) a cosolvent and (iii) water, with the quantity of (ii) in relation to (ii) being determined stoichiometrically for the formation of an L_3-phase. The lipid component may be natural or synthetic, provided it has a conformation that allows the thermodynamically stable accommodation of a weakly water soluble substance, being, preferentially, synthetic and selected from the group consisting of dioctadecyldimethylammonium bromide (DODAB) and dioctadeldimethylammoniun chloride (DODAC). The cosolvent component is

an organic compound with a polar group selected from the group consisting of hydroxyl, cetone, carboxyl, ester, aldehyde and amide.

In a preferred embodiment of the invention, the cosolvent is a hydroxylate compound, preferentially an alcohol with up to eight carbon atoms, more preferentially the alcohol is a straight chain mono-hydroxylate alcohol. In this preferred embodiment, the quantity of cosolvent is that sufficient for the formation of the L_3-phase, preferentially determined through the correlation between the stipulated lipid concentration in water capable of generating an L_3-phase, and the number of carbon atoms of the said alcohol by means of the equation y=295277*exp(-1,3806*x), where x indicates the number of carbon atoms of the said alcohol and y indicates the maximum quantity of the said cosolvent, expressed in micro litres, to provide a nematic-isotropic phase. Preferentially, the molar ratio between the lipid and the cosolvent varies between 1:12 and 0.0 01:1. The preferred alcohols are 1-ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, more preferentially, 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, and yet more preferentially, 1-pentanol.

A second embodiment of the invention provides a process for obtaining a carrier system for weakly water soluble substances consisting of a lipid/cosolvent/water system, with the said process being characterised by comprising the stages of: (a) dispersing the lipid component in water at a concentration sufficient to form the L_3-phase; (b) the careful addition of the cosolvent to the dispersion obtained in (a) in a quantity necessary for the formation of the L_3-phase; (c) heating the mixture obtained in (b) to temperature T_{L3} for the time sufficient for the appearance of a transparent stable lyotropic phase with an L_3-phase structure; and (d) cooling the mixture and letting it stand for sufficient time to attain equilibrium and the complete formation of the L_3-phase corresponding to the carrier system for weakly water soluble substances of the present invention. Preferentially, the concentration of the lipid component for obtaining the L_3-phase is of up to 10 mM, preferentially, of up to 5 mM. Preferably, the concentration of the cosolvent is

such that the molar ratio between the lipid and the cosolvent varies between 1:12 and 0.0 01:1. The temperature T_{L3} for heating the mixture for the formation of the L_3-phase depends on the lipid used or, in other words, depends on its T_m. Preferably, the temperature does not exceed 70° C, more preferentially, the heating temperature is 65° C and the lipid is DODAB or DODAC.

Alternatively, in the formation of the L_3-phase using the lipid/cosolvent/water mixture, when the quantity of cosolvent is in excess, it is eliminated by any mild conventional means such as, for example, dialysis, to allow the formation of the lyotropic phase (L_3- or sponge phase).

A third embodiment of the invention refers to the use of the carrier system for weakly water soluble substances of the invention as a vehicle for pharmaceutical compositions, herbicides, insecticide compositions and the similar.

A fourth embodiment of the invention refers to the use of the carrier system for weakly water soluble substances in the release of delivery of these substances in a selected environment, with such substances being selected from the group consisting of polymers, biological materials and mineral matter.

A fifth embodiment of the invention refers to the use of the carrier system for weakly water soluble substances of the invention in the covering of surfaces, preferentially with particles and more preferentially with nano-particles.

Brief description of the figures

Figure 1 shows, schematically, the L_3-phase structure that is characteristic of the structure of the carrier system of the present invention. (STREY, R.; JAHN, W.; PORTE, G.; BASSEREAU, P. Frezze fracture electron microscopy of dilute lamellar and anomalous (L3) phases. Languimuir, Washington, DC.v.6, p. 1635-1639.1990).

Figure 2 illustrates the definition of T_{L3} for the DODAB lipid.

Figure 3 illustrates the formation of the isotropic phase formed DODAB and n-pentanol in a region of greater concentration (milky phase). (1) = layer of cosolvent and, (2) = isotropic phase of surfactant and cosolvent, in a region of greater concentration.

Figure 4 illustrates the sequential modification of the structures for the DODAB/n-pentanol/water system through the monitoring of this modification using differential scanning: (a) spectrum of the dispersion of DODAB in hot water; (b) spectrum of the mixed micelle of DODAB and n-pentanol and (c) L_3-phase of the DODAB/n-pentanol/water system showing the bilayer signal.

Figure 5 illustrates, in accordance with the invention, the graph–form representation of the calculation of the quantity of cosolvent (alcohol) for obtaining the L_3-phase for the DODAB system (1.5 mM)/alcohol/water.

Figure 6 illustrates the formation region of the L_3-phase graphically, through absorbance measurement (measured at 450 nm), in accordance with the quantity of cosolvent (alcohol) for obtaining the L_3-phase for the DODAB system (1.5 mM)/alcohol/water.

Figure 7 shows the use of the carrier system for weakly water soluble substances in the solubilisation of amphotericin B.

Detailed description of the invention

Initially, some definitions closely related to the present invention are provided so as to facilitate its comprehension:

- "Lipid", in the context of the invention, means a double-chain natural or synthetic organic compound, structured with a hydrophilic head and a hydrophobic tail, with the hydrophobic tail having a three-dimensional arrangement constituted of chains that define an expandable space to allow the thermodynamically stable accommodation of a weakly water soluble substance.

- "Cosolvent" – Organic compounds having polar groups at not less than one of its extremities, which serve as "spacers" of the lipid chains.

- "L_3-Phase", in the context of the invention, means a bicontinuous liquid crystal phase having an orientation order (nematic), optical isotropy of low viscosity (transparent), frequently termed "sponge phase".

- "Swollen L_α-Phase", in the context of the invention, means the phase immediately previous to the appearance of phase L_3. The transition between the L_α and L_3 phases is induced by varying the temperature, salt concentration and the surfactant/cosurfactant ratio. This transition occurs in equilibrium between thermodinamically stable phases.

- "temperature T_{L3}" is the temperature between 5 to 20° C above temperature T_m (transition temperature of the lipid phase, from gel to liquid crystal) (see Figure 2, with lipid being DODAB).

– "thermodinamically stable", in the context of this invention, means a system at the lowest possible energy state.

It is common knowledge that an amphiphilic substance spontaneously molds itself and produces a large number of micellar structures when dissolved in water. These structures include globules, cylindrical or discoid bodies, as well as vesicles (non-micellar structures). These primary structures may organise themselves on a macroscopic scale in a manner that the entire system may become organised even in diluted solutions containing approximately 1% of surfactant. The morphology of the aggregates formed by the self-molding of the lipid molecules in solution and the evolution of this morphology with additives (cosolvents), such as medium chain alcohols, ketones, esters, and amides, is the physicochemical phenomenon that forms the basis of the present invention.

Depending on the concentration, the substances with surfactant activity in solution may result in systems with opposite characteristics. In the first case, the systems are microemulsions containing much water, much oil and a moderate quantity of surfactant mixture (surfactant + cosolvent). In such a situation, the hydrophilic and hydrophobic mediums have a symmetric role and are not submitted to local restrictions, with the exception of density restrictions.

Such systems are separated by a surfactant film that has its own mechanical properties (for example, spontaneous curvature) and elastic resistance to extra folding and, furthermore, incorporate the majority of surfactant and cosolvent molecules.

This situation is very different compared to oil free systems, or, in other words, binary (surfactant/water (or saline solution)) or ternary (surfactant/cosolvent/water (or saline solution)) systems. In these cases, the hydrophilic and hydrophobic mediums are no longer in symmetrical positions. In particular, the hydrophobic medium is submitted to strict geometrical restrictions and its local thickness cannot exceed twice the length l_{max} of all the hydrophobic chains (for example, paraffinic) of the surfactant molecules.

It has recently been observed that amphiphilic molecules aggregate to form flexible bilayers in very dilute solutions. In the case of swollen surfactant systems, there are two different phases that possess a surfactant bilayer as a basic unit. The first, namely the lamellar L_α-phase, is a birefringent phase with an one-dimensional arrangement of bilayers stacked in esmetic order, or, in other words, a liquid crystal in which the molecules are ordered in parallel layers. The second consists of bilayers interconnected in the three dimensions and is known as the sponge phase (L_3-phase). The present invention refers to obtaining this L_3-phase from a mixture of lipid, cosolvent and water, in stoichiometrically defined proportions. The lipid used in the present invention is an amphiphilic substance capable of forming a thermodynamically stable sponge phase and possesses a three-dimensional arrangement constituted of chains that define an expandable space by means of the cosolvent action, to allow the thermodynamically stable accommodation of a weakly water soluble substance. More preferentially, the lipid is a synthetic substance, such as, for example, dioctadecyldimethylammonium bromide (DODAB) or dioctadecyldimethylammonium chloride (DODAC), which are both synthetic double-chain lipids having surfactant activity that allow the progressive addition of short and medium chain linear alcohols. Typically, in accordance with the present invention, the sponge phase is formed spontaneously without

secondary aggregation in relation to time and remains in thermodynamic equilibrium.

The L_3-phase is important in the synthesis of new mesostructured inorganic materials that use lyotropic systems as templates, in the crystallisation of transmembrane proteins, in the transportation of pharmaceuticals and other bioactive molecules, in the coating of particles and especially nano-particles, amongst others.

The system of the present invention was developed through the observation that when organic compounds containing polar groups, such as, for example, alcohols with two or more carbon atoms, enter into contact with a dispersion containing closed lipid vesicles, such as, for example, DODAB or DODAC, a white interface zone is formed in a few minutes as a result of the spontaneous transition of the bilayer vesicles (closed, unilamellar, translucid) into miniemulsions, with the said white (milky) interface zone consisting of an isotropic phase formed by the lipid (for example, DODAB) and by the cosolvent (for example, n-pentanol) in a region of greater concentration (refer to Figure 3). With heating and the correct lipid:cosolvent proportion, the intended L_3-phase is formed. Figure 4 illustrates the sequential change of these structures.

The cosolvent molecules appear to have two fundamental roles, namely: (1) the organised insertion in the vesicle providing means for the expandability of the hydrophobic part of the lipid (for example, the two paraffinic long chains in the case of the DODAB molecule) and (2) filling up the inside of the two nanometric "drops" that compose the mixed micelles that occur in the region of greater concentration of the lipid (for example, DODAB). In other words, the closed vesicles, with a broad size distribution (in the range of 700-1200 nm) transform themselves spontaneously through the addition of a cosolvent, into stable miniemulsions, with a narrow size distribution (of approximately 250 nm), stabilised by a positive charge. Microcalorimetric scanning data reveals the disappearance of the typical DODAB vesicle bilayer. For example, the mixture of 1-pentanol (cosolvent) with pre-formed vesicles of 5mM DODAB

(lipid) form a white intermediary phase (refer to Figure 3) which, when diluted in an adequate proportion, give origin to a thermodynamically stable isotropic phase.

The DODAB compound (dioctadecyldimethylammonium bromide) is a synthetic double-chain lipid of a quaternary ammonium salt. Molecules of DODAB form vesicles when dispersed in water above the transition phase temperature T_m (gelto liquid crystal) (refer to Figure 2). Since the T_m of the aqueous dispersion of DODAB is between 44.8 and 45.5° C, it is believed the DODAB vesicles are in a gel state when at room temperature.

The cosolvents used in the present invention are organic compounds containing functional groups capable of interacting with the lipid to obtain the lyotropic phase, L_3-phase or sponge phase of the invention. Examples of such functional groups are: hydroxyl, for example, alcohols containing at least two carbon atoms, preferably, between two and eight carbon atoms; ketone, for example, ketones C_2-C_8; carboxyl, for example, carboxylic acids C_2-C_8; amide, for example, amides C_2-C_8; ester, for example, esters C_2-C_8 and aldehyde, for example, aldehydes C_2-C_8. Preferentially, the cosolvents used in the present invention are straight chain alcohols containing a hydroxyl at one extremity. More preferentially, the cosolvent of the ternary system of the present invention is selected from the group consisting of n-ethanol, n-propanol, n-butanol, n-pentanol, n-hexanol, n-heptanol ou n-octanol. Combined with the lipids, the cosolvents are capable of forming mixed micelles.

In the preferred embodiment of the present invention, the system comprises as the lipid, DODAB, as the cosolvent, a straight chain alcohol with 2 to 8 carbon atoms and water. The proportion of lipid:cosolvent for the formastion of the L_3-phase may be calculated by the equation $y=295277*\exp(-1.3806*x)$, where x indicates the number of carbon atoms of the said alcohol and y indicates the maximum quantity of the said cosolvent to provide a nematic-isotropic phase. Table 1 shows the compatibility of the values calculated and empirical for determining the maximum volume of alcohol for obtaining the L_3-phase with a DODAB/alcohol/water system for a constant

DODAB concentration of 1.5 mM. This accord may may also be seen graphically in Figures 5 and 6.

Table 1: Maximum quantity of alcohol added to the DODAB/water dispersion for obtaining the L_3-phase, related to the carbon atoms of the alcohol.

Number of carbon atoms	Maximum volume of alcohol in µl in the empirical mixture	Maximum volume of alcohol in µl calculated by the equation
2	2500	2434
3	1250	1254
4	600	646
5	350	333
6		172
7		88
8		46

It is important to note the difference between the carrier system for weakly water soluble substances of the present invention and the transport systems based on vesicles or liposomes for the vectorisation of pharmaceuticals. Vesicles or liposomes consist of closed bilayer lipids surrounding an aqueous nucleus and presenting themselves as folded membranes around three-dimensional structures, similar to micelle, but with two layers of molecules. Vesicles are formed by self-templating so as to protect the hydrophobic chains of water. One of the reasons that make the DODAB vesicle system of great interest is that it is an example of spontaneous vesiculation, or, in other words, the vesicles are formed by the simple addition of the lipid to water and heating above the transition phase temperature (T_m).

In the system of the present invention, the sponge phase is formed as a "fused" bilayer phase with each fusion occurring by means of narrowed bonds (refer to Figure 1). The transparency of the system (isotropy) occurs because these deformations are dynamic. An L_α-phase is formed before each L_3-phase. Thus, while the cosolvent is added, the sequence occurs: vesicles → progressively smaller vesicles → L_α-phase, and → finally, L_3-phase. This modification of the structures may be monitored by analysis of differential

scanning calorimetry (DSC), as illustrsted in Figure 4. It should be emphasised that if there is an excess of cosolvent, regardless of the amount, a multiphase appears but this does not serve the purpose of the present invention. However, with the elimination of this excess of cosolvent through dialysis, for example, the L_3-phase is formed again. This L_3-phase system is so important for achieving the solubilisation of weakly water soluble or insoluble substances that even sterically complicated molecules, such as amphotericin, are incorporated into the transporter system of the present invention. In other words, in adequate proportions, it is possible to provoke a profound structural change in the vesicular system of a lipid (for example, DODAB) through the addition of the cosolvent thus obtaining the intended L_3-phase or sponge phase.

The transporter system of the present invention differs radically from all known systems, such as that of Benton and Miller (1983) who worked with anionic surfactants (in a surfactant/alcohol/water system) with concentrations of approximately 10% in weight. In the system of the present invention, the concentration varies preferentially between 0.5 and 10 mM, which is the equivalent, in the case of the lipid being DODAB, to approximately 0.01 to 0.2% in weight. In other words, a concentration up to 100 times less, approximately. This difference is most important, especially when the carrier system for weakly water soluble substances is used for pharmaceutical compositions, in which the safety requirements with regard toxicity are extremely high.

The carrier systems for weakly water soluble substances may be obtained by a process comprising the stages of: (a) dispersing the lipid component in water at a concentration sufficient to form the L_3-phase; (b) the careful addition of the cosolvent to the dispersion obtained in (a) in a quantity necessary for the formation of the L_3-phase; (c) heating the mixture obtained in (b) to temperature T_{L3} for the time sufficient for the appearance of a transparent stable lyotropic phase with an L_3-phase structure; and (d) cooling the mixture and letting it stand for sufficient time to attain equilibrium and the complete

formation of the L_3-phase corresponding to the carrier system for weakly water soluble substances.

Preferentially, the concentration of the lipid component for obtaining the L_3-phase is of up to 10 mM, preferentially, of up to 5 mM. Preferably, the concentration of the cosolvent is such that the molar ratio between the lipid and the cosolvent varies between 1:12 and 0.001:1.

The temperature T_{L3} for heating the mixture for the formation of the L_3-phase depends on the lipid used or, in other words, depends on its T_m. Preferably, the temperature T_{L3} should be in the range between 5 and 20° C above T_m. In the case of the lipid DODAB, T_{L3} should be in the range between 65 and 70° C, more preferentially, the heating temperature is 65° C.

The carrier systems for weakly water soluble or insoluble substances of the present invention are useful as vehicles for compositions comprising one or more active principles. Such compositions may be pharmaceutical compositions, herbicide compositions, insecticide compositions, cosmetic compositions and the similar.

The system of the invention is particularly usable in the preparation of a vehicle for pharmaceutical compositions or compositions for agricultural use, such as herbicide compositions, insecticide compositions or nematocidal compositions and the similar.

The use of the system of the invention as a means of solubilising and transporting pharmaceuticals to a selected medium, for example, the body of a human or animal patient, referred to the transporter system for amphotericin B. As shown by Figure 7, the capability of solubilising and, thus, transporting amphotericin B with the transport system of the invention is clearly evident. The comparative seen in Figure 7 shows, through the spectrums of the UV absorption range, the profiles for amphotericin B (30 µl) in water, control (A); amphotericin B in pentanol, control (B); amphotericin B in its most appropriate solvent (sulphoxide dimethyl:methanol, for 20 µl (C) and 40 µl (D); amphotericin B in the system of the invention, and in one of its preferred forms

DODAB/n-pentanol/water, at successive additions of 20 µl, 40 µl, 60 µl and 80 µl of amphotericin B (E). Figure 7 shows the accord between the spectrums of amphotericin B (Figures 7C and 7D) in its best solvent and in the carrier system of the invention (Figure 7E).

It should be understood that the examples and embodiments described herein are merely for illustrative purposes and, in the light of the above, various modifications or alterations will become apparent to those versed in the techniques and shall be considered included within the spirit of this description and scope of the accompanying claims. All publications, patents and patent requests cited herein are incorporated for reference purposes in their entirety and for all purposes.

Example 1: Preparation of the System of the DODAB/alcohol/water invention

Weigh a sufficient quantity of DODAB in water at a concentration of 5 mM. Add the cosolvent carefully and heat to approximately 65° C ($T_{L3}>T_m$) for approximately 1 hour under constant agitation.

The mixture is then cooled to room temperature for sufficient time until equilibrium is attained and a transparent L_3–phase is formed.

Stable DODAB/alcohol/water systems may also be obtained at much lower concentrations than DODAB, such as, for example, 1.5 mM.

The system thus formed is stable and appropriate for use as a vehicle for compositions containing active substances weakly soluble in water. Alternatively, the system may be used as a template for depositing inorganic particles, for example, of particles, preferentially nano-particles.

Example 2: Use of the System of the DODAB/alcohol/water invention for the preparation of amphotericin B compositions

Prepare a DODAB/alcohol/water system at a DODAB concentration of 1.5mM in accordance with Example 1 above.

The L_3-phase obtained is used as a vehicle for amphotericin B through the incorporation of successively increasing quantities of amphotericin B by 20, 40, 60 and 80 µl. Figure 7 clearly shows that the system of the invention when used as a vehicle for amphotericin B is equal to the best solvent for this substance (dimethylsulphoxide:methanol 1:1). The spectrums for amphotericin B were obtained with an UV spectrophotometer (280-440 nm) – double-beam 1601 PC Shimadzu.

Example 3: Use of the System of the DODAB/alcohol/water invention in the preparation of compositions for agricultural use

In the same manner as described in Example 2, an active substance such as, for example, citronella, lemon grass extract, neem oil and the similar is incorporated to the DODAB/alcohol/water system with a DODAB concentration of up to 10mM.

In the same manner as described in Example 2, stable compositions are obtained (absence of flocculation or apparent coalescence), for a minimum period of two years, when incorporating an active substance with a broad application in agriculture, such as a natural insecticide, into the DODAB/alcohol/water system.

Example 4: Preparation of System of the invention DODAB/alcohol/water with dialysis

Weigh sufficient amount of DODAB to prepare dispersion of + 1,5 mM DOBAB in water. Add cosolvent carefully and heat to about 65 °C (TL3> Tm) for approximately 2 hours under constant stirring. Then, turn off the heat and continue with the agitation to achieve 30 °C. The system remains for at least 72 hours to stabilize the sponge phase. The absorbance is measured and being smaller than 0.05, the sample is transferred to a dialysis bag. Dialysis bags containing, for example, about 50 ml of L3 are placed in beaker containing 1 liter of water. The water outside the bag is exchanged several times (four at least).

The dialysis system thus formed is stable and suitable for use as a carrier for compositions containing active substances weakly soluble in water. Alternatively, the system can be used as a matrix for the deposit of inorganic particles, for example, of particles, preferably of nanoparticles.

Example 5: DOBAB Bromide Titering and Assessment of alcohol content of dialyzed phase from Example 4.

Bromide Titering: About 2.9 to 3.0 g of mercuric nitrate are dissolved in a few hundred milliliters of water with the addition of 20 ml 2 N HNO3. The solution is completed with water to 1000 ml. Indicator: 100 mg of diphenylcarbazone are dissolved in 100 ml of 95% alcohol and stored in the dark, preferably in the refrigerator. Standard chloride: Sodium chloride is dried at 120 °C and 584.5 mg are dissolved in water and completed up to 1000 ml. The solution contains 10 milliequivalents per liter of chloride. It is used for the standardization of each new batch of mercuric nitrate solution.

Procedure: a 0.2 ml sample is placed in a 25 ml Erlenmeyer into which is added 4 drops of indicator. The titrant agent, mercuric nitrate, is placed in a microburette. The clear and colorless solution becomes an intense blue-violet with the addition of the first drop of mercuric nitrate solution in excess. The dialyzed system L3 contains 90% of unavailable bromide ions for titration. In other words, the bromide ions choose to compose the structure L3dialyzed, instead of forming a complex salt with mercury ions. Thus, the titration of alcohol after the dialysis is only possible with the structure break down. The bromide is available in 0.1 ml volume, and after the break (with ethanol) its volume goes to 0.6 ml. One can break the structure of L3dialyzed by three ways: with cooling (successive cycles of freezing / defreezing), addition of large amounts of salt or addition of ethanol in excess.

That is, the dialyzed sponge phase of example 4 must be damaged to make bromide available for titration.

Alcohol content: The concentration of alcohol within the bag is very small after the dialysis of example 4. For ethanol, measurements of

refractometry were made, and the result is that about of <0.1 % ethanol remains at the phase (compared with 15% in the sponge phase, i.e., the phase dialyzed retains <1 % of the initial value). It is important to note that refractometry measures can be made without damaging the phase. The pentanol was determined by headspace chromatography, FID detector.

Phase after Dialysis	
Compounds	DODAB, water, pentanol
Phase preparation	Δ >65 <70 °C; 72 h of rest; longstanding dialysis.
Phase Appearance	Viscosity similar to that of water; Transparency (optical isotropy)
Stability	Stable
Bromide titer	10 % titerable
Turbidity	Transparent (optical isotropy)
Morphology	Bilayers (seen by EPR)
Lipid Retention after dialysis	Complete
Incorporation of nonpolar molecules	Possible, essays with n-octanol

CLAIMS

1. A carrier system for weakly water soluble substances wherein said system comprises: (i) a lipid; (ii) a cosolvent and (iii) water, whereas the quantity of (ii) to (i) is stoichiometrically determined for the formation of an L_3-phase.
2. The carrier system according to claim 1 wherein the ratio amount of lipids to cosolvent varies in a range from 1:12 to 0.001:1.
3. The carrier system according to claim 1 wherein the lipid concentration is of up to 10 mM.
4. The carrier system according to claim 1 wherein the lipid concentration varies in a range from 1.5 to 5.0 mM.
5. The carrier system according to claim 1 wherein the lipid concentration varies in a range from 5 to 10 mM.
6. The carrier system according to claim 1 wherein said lipid is selected from the group of natural and synthetic lipids.
7. The carrier system according to claim 6 wherein said lipid is a synthetic lipid.
8. The carrier system according to claim 7 wherein said synthetic lipid is selected from the group consisting of dioctadecyldimethylammonium bromide and dioctadecyldimethylammonium chloride.
9. The carrier system according to claim 1 wherein said cosolvent is an organic compound having at least one polar group selected from the group consisting of hydroxyl, aldehyde, carboxyl, ketone, ester and amide.
10. The carrier system according to claim 9 wherein the organic compound is a compound having a hydroxyl group.
11. The carrier system according to claim 10 wherein the compound having a hydroxyl compound is a straight chain alcohol having at least 2 carbon atoms.

12. The carrier system according to claim 11 wherein the straight chain alcohol is selected from the group consisting of 1-ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol.

13. The carrier system according to claim 12 wherein the straight chain alcohol is 1-pentanol.

14. Process for obtaining a carrier system for weakly water soluble substances consisting of a lipid/cosolvent/water system, comprising the following stages:

(a) dispersing the lipid component in water at a concentration sufficient for the formation of the L_3-phase;

(b) carefully adding the cosolvent to the dispersion obtained in (a) in a quantity necessary for the formation of the L_3-phase;

(c) heating the mixture obtained in (b) to temperature T_{L3} for the time sufficient for the appearance of a transparent stable lyotropic phase with an L_3-phase structure; and

(d) cooling the mixture and letting it stand for sufficient time to attain equilibrium and the complete formation of the L_3-phase corresponding to the carrier system for weakly water soluble substances.

15. Process according to claim 14 wherein the sufficient concentration of lipid for the formation of the L_3-phase does not exceed 10 mM.

16. Process according to claim 14 wherein the amount of lipid to cosolvent varies from 1:12 to 0.001:1.

17. Process according to claim 14 wherein the lipid is a synthetic lipid selected from the group consisting of dioctadecyldimethylammonium bromide and dioctadecyldimethylammonium chloride.

18. Process according to claim 14 wherein the cosolvent is an organic compound with at least one polar group selected from the group consisting of hydroxyl, aldehyde, carboxyl, cetone, ester and amide.

19. Process according to claim 18 wherein said organic compound is a straight chain alcohol selected from the group consisting of 1-etanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol.

20. Process according to claim 14 wherein the temperature T_{L3} varies from 5 to 20° C above T_m of the lipid used.

21. Process according to claim 20 wherein said temperature T_{L3} is a temperature not exceeding 70° C when the lipid used is dioctadecyldimethylammonium bromide or dioctadecyldimethylammonium chloride.

22. Process according to claim 14 wherein the rest time in step (d) takes at least 72 hours.

23. Process according to claims 14 and 22 comprising an additional dialysis step.

24. Use of the system defined in claims 1 to 13 characterized as being a vehicle of a composition comprising an active ingredient.

25. Use according to claim 24 wherein said composition is for application in agriculture.

26. Use according to claim 24 wherein the active ingredient is selected from the group consisting of pharmaceutical, herbicide, insecticide, protein, vitamin and antibiotic.

27. Use according to claim 24 wherein the insecticide is selected from the group consisting of neem and citronella oil.

28. Use of the system defined in claims 1 to 13 characterized as being a template for the deposit of inorganic particles.

29. Use according to claim 26 wherein said particles are nanoparticles.

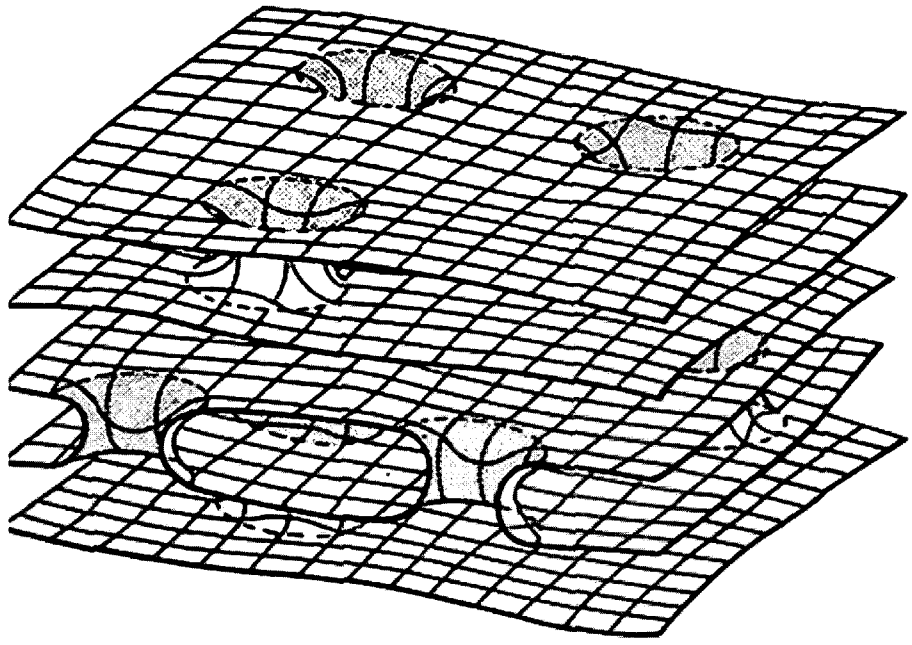

FIGURE 1

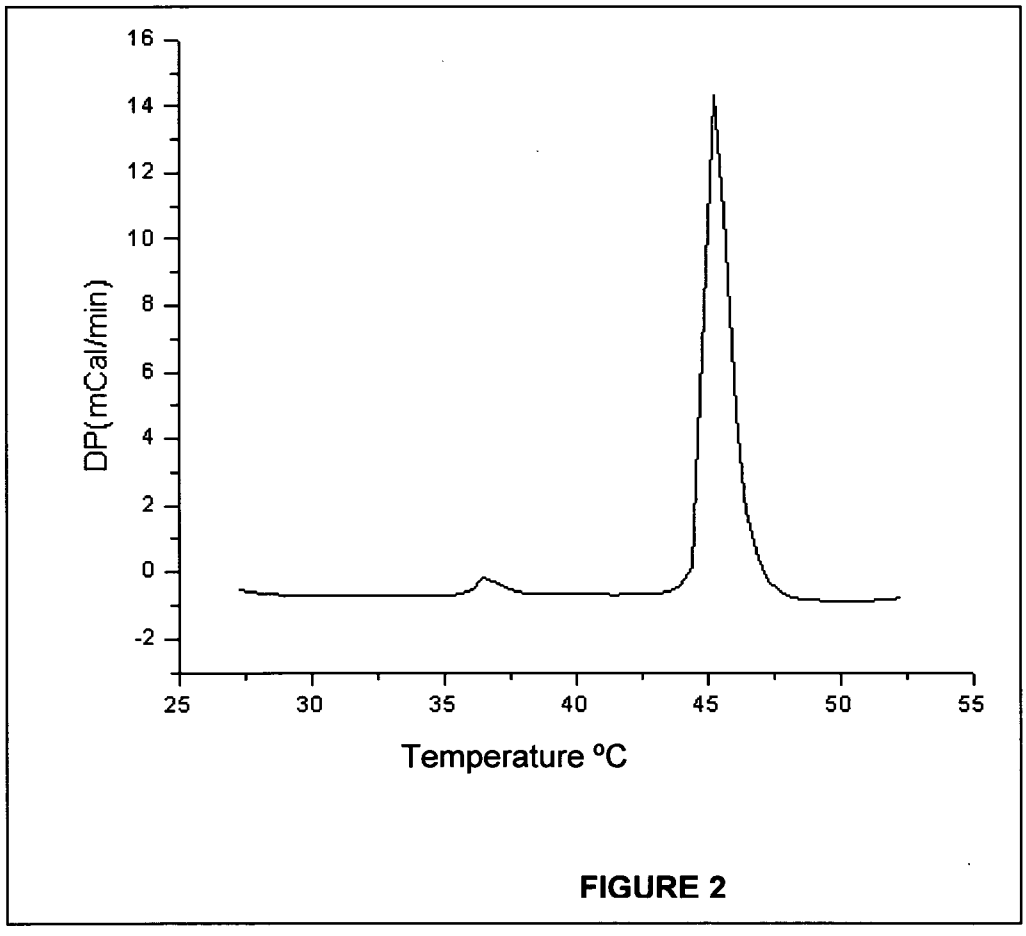

FIGURE 2

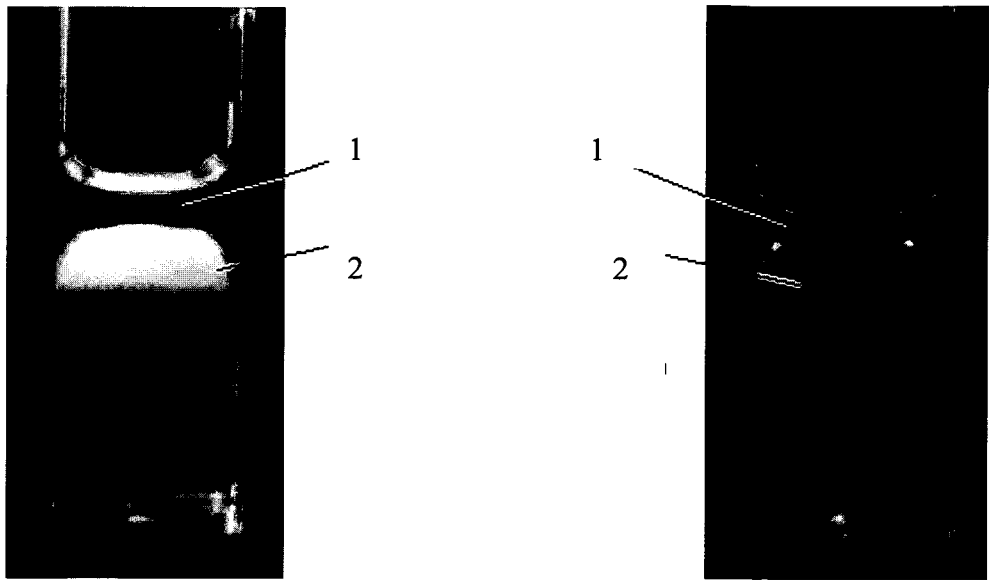

FIGURE 3

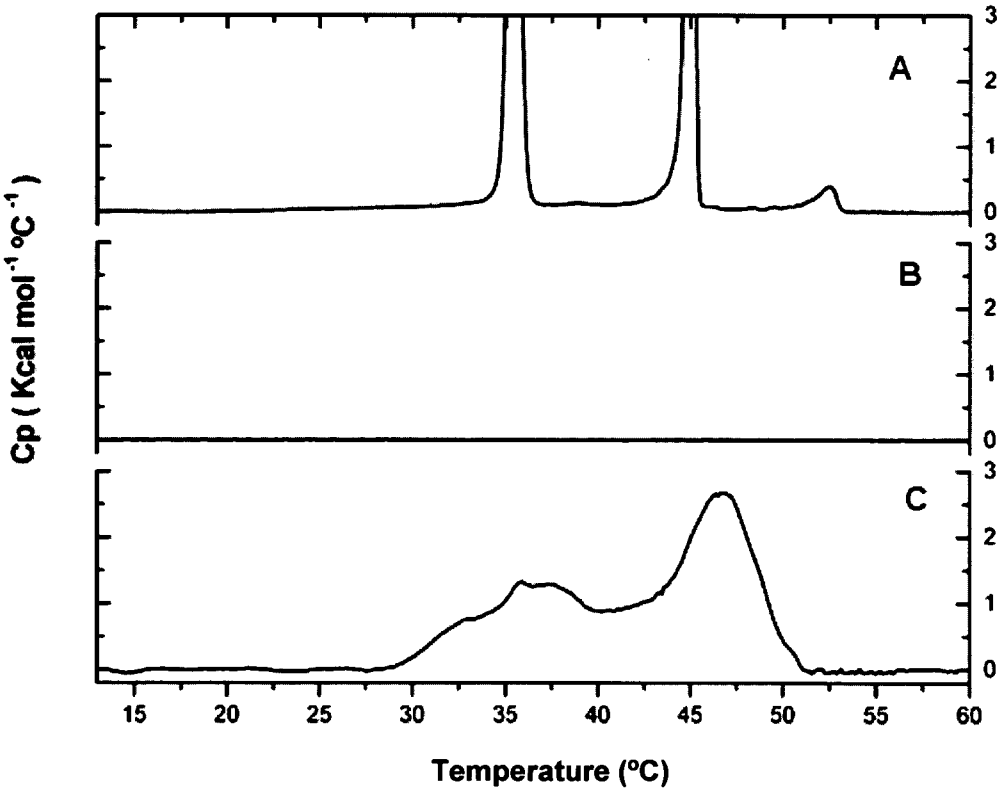

FIGURE 4

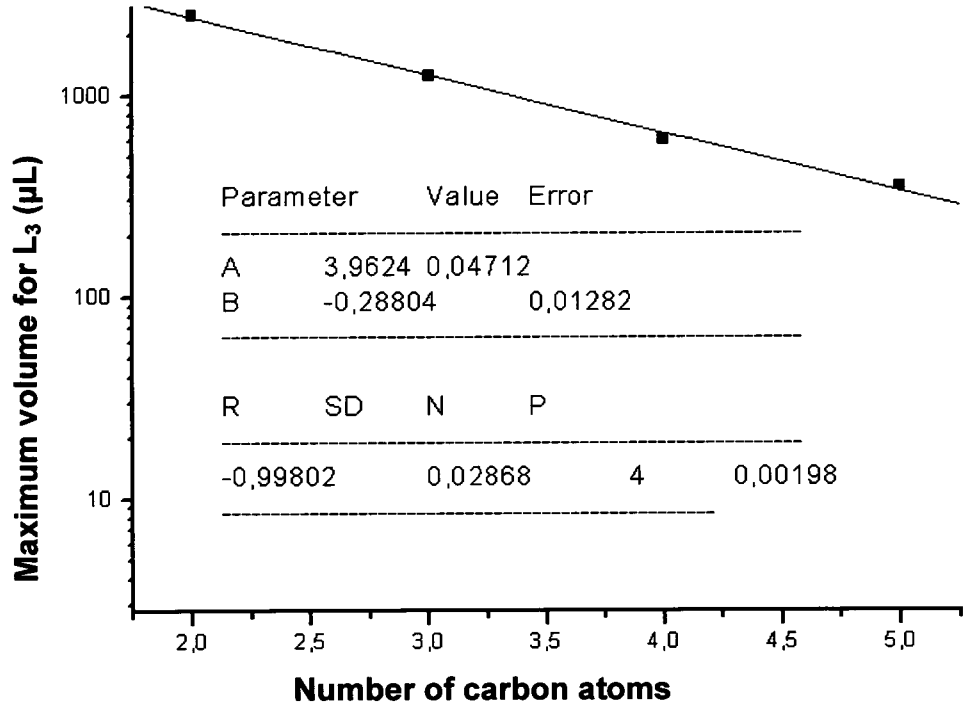

FIGURE 5

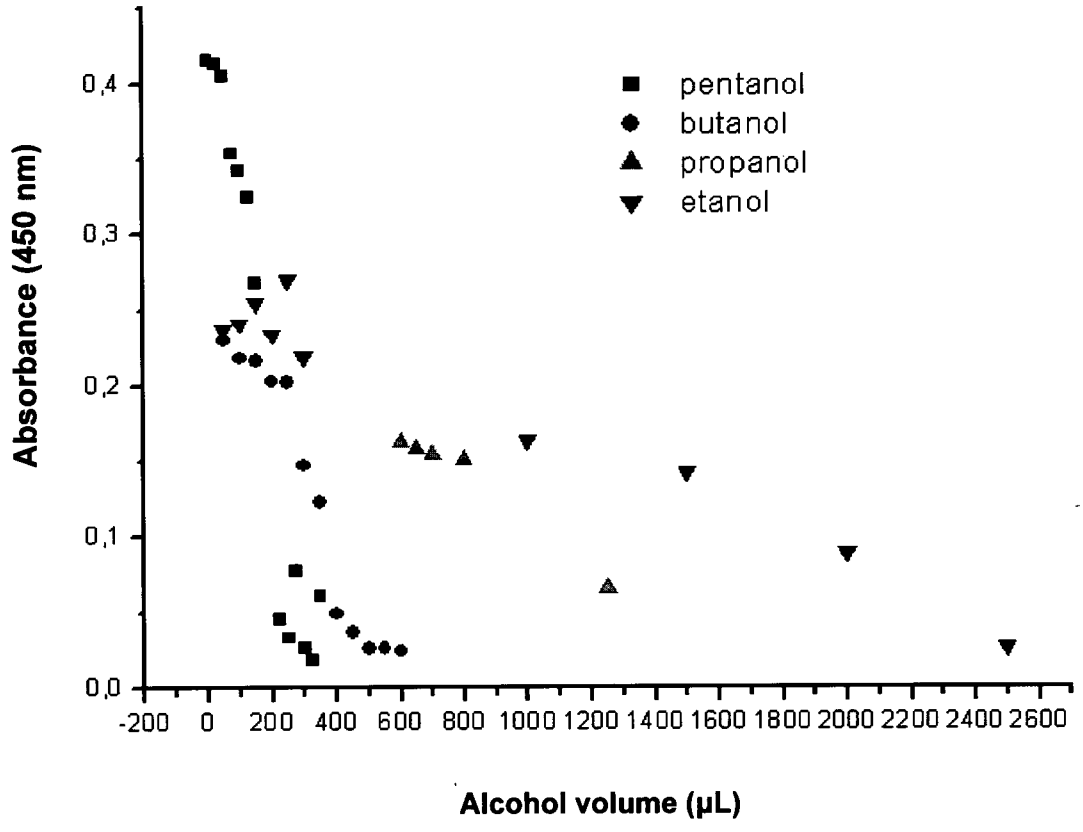

FIGURE 6

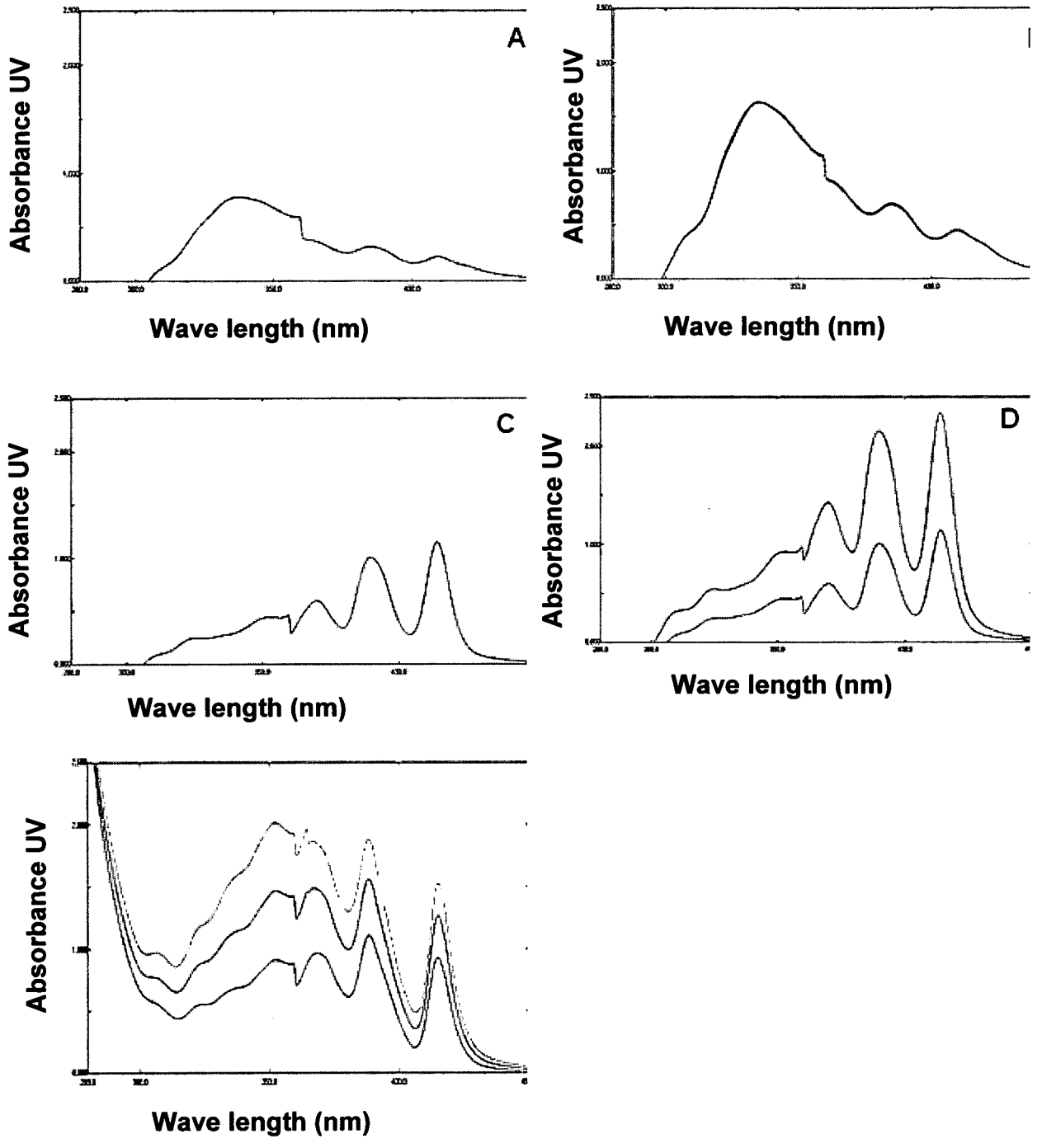
A
Absorbance UV
Wave length (nm)
Absorbance UV
Wave length (nm)
C
Absorbance UV
Wave length (nm)
D
Absorbance UV
Wave length (nm)
Absorbance UV
Wave length (nm)

FIGURE 7