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NOTICE OF ENTITLEMENT

We, **S.A. A.T.T.A. Applications et Transferts de Technologies Advancees**, the applicant/Nominated Person in respect of Application No. 22778/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors by assignment.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TENTH day of MARCH 1994

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1642889)

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PREPARATIONS COMPRISING A FLUOROCARBON AND A LIPOPHILIC/FLUOROPHILIC ORGANIC COMPOUND, AND THEIR USES

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(56) Prior Art Documents
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WO 91/00110

(57) Claim

1. A composition in the form of a dispersion, emulsion or gel, comprising:

an oily phase comprising at least one fluorocarbon compound;

an aqueous phase; and

a surfactant; characterised in that the composition further includes 0.01 - 50% w/v of a lipophilic/fluorophilic compound having a fluorinated region and a hydrocarbon region, or a mixture of such compounds; said lipophilic/fluorophilic compound(s) being adapted to improve the affinity of the surfactant for the oily phase, whereby said dispersion, emulsion or gel is significantly stabilised relative to a dispersion, emulsion or gel lacking said lipophilic/fluorophilic compound.

25. A method for stabilizing the particle size of fluorocarbon emulsions, comprising the step of adding a particle stabilizing amount of a fluorophilic/lipophilic compound of the formula

.../2

$$R_F{}^1W\text{-}R_H{}^1 \qquad (I)$$

wherein $R_F{}^1$, W, and R_{H1} are as defined in Claim 4, to either the oily phase component or the aqueous phase component of a fluorocarbon emulsion prior to emulsification.

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(54) Title: PREPARATIONS COMPRISING A FLUOROCARBON AND A LIPOPHILIC/FLUOROPHILIC ORGANIC COMPOUND, AND THEIR USES

(57) Abstract

Fluorocarbon emulsions comprising a stabilizing, particle size controlling fluorophilic/hydrophilic compound which can have the formula R_F^1-W-R_H^1 (I), wherein R_F^1 is a linear, branched or cyclic C_{2-14} fluorocarbon group; R_H^1 is a linear, branched or cyclic C_{2-18} saturated or unsaturated hydrocarbon group; and W is absent or is a bivalent species chosen from the group consisting of -O-, -S-, or various fluorinated structures. Use of the fluorophilic/lipophilic compound in the dispersions of the invention provides stable particle size and efficient emulsification. The dispersions of the invention can comprise biologically useful additive and can be used for various purposes, as oxygen carriers, contrast agents, or diagnostic agents.

PREPARATIONS COMPRISING A FLUOROCARBON AND A LIPOPHILIC/FLUOROPHILIC ORGANIC COMPOUND, AND THEIR USES

The present invention relates to formulations comprising highly fluorinated or perfluorinated compounds, referred to generally as fluorocarbons. It relates particularly to fluorocarbon emulsion formulations that form emulsions having superior emulsion stability and controlled particle sizes.

Background of the Invention

Fluorocarbon compounds and their formulations have numerous applications in human and veterinary medicine as therapeutic and diagnostic agents. Fluorocarbons have many potential applications in the biomedical field, as blood substitutes, or more generally, as carriers in applications wherein oxygen must be supplied to organs and tissues, for example, in the treatment of cardio- and cerebrovascular disease, angioplasty, in organ preservation and in cancer therapy. Fluorocarbon formulations are also useful in diagnostic procedures, for example as contrast agents, and in the field of veterinary therapy (Riess, J. G., Hemocompatible Materials and Devices: Prospectives Towards the 21st Century, Technomics Publ. Co, Lancaster, Pa, USA, Chap 14 (1991); Vox Sanguinis., Vol. 61:225-239 (1991). One commercial biomedical fluorocarbon emulsion, Fluosol®, (Green Cross Corp., Osaka, Japan), is presently used, for example, as an oxygen carrier to oxygenate the myocardium during percutaneous transluminal coronary angioplasty (R. Naito, K. Yokoyama, Technical Information, Series n° 5 and 7, 1981).

The dispersed phase of fluorocarbon emulsions must have a stable particle size to be suitable for biomedical use. One of the drawbacks of the Fluosol emulsion is its low stability; the particle size of fluorocarbon emulsions such as Fluosol® can be maintained only if they are transported and stored in the frozen state. The frozen emulsions are then defrosted and mixed with two annex solutions before use. These storage

requirements seriously limit the field of application of Fluosol. Although more stable fluorocarbon emulsions are being developed (Oxygent® and Imagent®, Alliance Pharmaceutical Corp., San Diego, California), it is desirable to have fluorocarbon emulsions that are stable enough to store for long periods without refrigeration. Such storage stability would extend the use of fluorocarbons beyond medical facilities in order to meet, for example, the requirements of the army and civil defense. It is also desirable to control particle sizes to adapt the emulsion characteristics to specific applications.

Fluorocarbons are oily substances that are immiscible with water, and therefore fluorocarbon-in-water emulsions, such as Fluosol® and Oxygent®, are presently prepared using lecithins and/or poloxamers of the Pluronic F-68® type as surfactants to disperse the fluorocarbon and stabilize the emulsion. Surfactants are commonly amphiphilic compounds having a hydrophobic end region and a hydrophilic end region. Lecithins have a hydrophobic end region comprising a hydrocarbon groups which have a low affinity for fluorocarbons. It is desirable to improve the affinity of the surfactant film for the fluorocarbon phase and to reduce the interfacial tension between the fluorocarbon and aqueous phases. (Riess, J.G., Comptes Rendus du 2ème Congrès Mondial des Agents de Surface (Paris, May 1988), ASPA 4:256-263 (1988)).

Several strategies can be employed to overcome this disadvantage of the emulsifying surfactants described. One approach is to develop more effective surfactants, for example, those having a hydrophobic end which is fluorophilic, for use in the preparation of classic emulsions. Efforts in this direction have led to new fluorinated surfactants such as those described in the documents EP-A- 0 255 443, EP-A-A 0 311 473 and WO 90/15807.

Another strategy is to prepare microemulsions, i.e., preparations of compounds which organize themselves spontaneously into dispersed systems (H.L. Rosano and W.E.

Gerbacia, U.S. Patent No. 3,778,381, December 11, 1973; and G. Mathis, J.J. Delpuech, FR-A-2 515 198, 3.29.1983). In an example of a microemulsion described by Cecutti et al., Eur. J. Med. Chem., 24, 485-492 (1989), the dispersed phase is itself totally constituted of mixed hydrocarbon/fluorocarbon molecules. However, this strategy is not generally applicable to fluorocarbons, particularly those of the examples described in the present invention. Moreover, it is still totally uncertain whether the intravenous administration of microemulsions is safe. To our knowledge, no example of such administration exists in human medicine, whereas the classical emulsions, such as the lipidic emulsions for parenteral nutrition are abundantly used.

It would be advantageous to be able to emulsify any fluorocarbon chosen solely on the basis of its own advantageous properties and its efficacy, without regard to the problem of emulsification. For example, it would be advantageous to be able to prepare stable emulsions of perfluorooctyl bromide (PFOB, Perflubron®, Alliance Pharmaceutical Corp., La Jolla, California) on account of its radiopacity, and of its potential as a contrast agent in diagnostics. It would also be advantageous to set the particle size in the emulsion at a value chosen *a priori*.

Summary of the Invention

The invention provides a composition in the form of a dispersion, emulsion or gel, comprising:

an oily phase comprising at least one fluorocarbon compound;

an aqueous phase; and

a surfactant; characterised in that the composition further includes 0.01 - 50% w/v of a lipophilic/fluorophilic compound having a fluorinated region and a hydrocarbon region, or a mixture of such compounds; said lipophilic/fluorophilic compound(s) being adapted to improve the affinity of the surfactant for the oily phase, whereby said dispersion,

emulsion or gel is significantly stabilised relative to a dispersion, emulsion or gel lacking said lipophilic/fluorophilic compound. The invention further provides methods of manufacturing the preparations, and their uses. The preparations of the invention preferably comprise an amphiphilic organic fluorophilic-lipophilic compound which comprises at least one hydrocarbon radical and at least one highly fluorinated hydrocarbon radical. It may comprise at least one linear aliphatic chain and at least one fluorinated linear aliphatic chain. It may be of the formula R_F^1-W-R_H^1 wherein R_F^1 is a fluorinated hydrocarbon radical (or group) and R_H^1 is a hydrocarbon radical (or group) as defined herein and W is a single bond or is -O-, -S-, or a hydrocarbon group or a hydrocarbon group having fluorinated regions as defined herein.

The lipophilic/fluorophilic compound of the invention can be a branched chain structure comprising hydrocarbon groups and fluorinated hydrocarbon groups, as for example, formulas (II) and (III). The fluorinated hydrocarbon groups of the compound can be further substituted by Br and Cl in addition to F. In a preferred embodiment of the invention, the lipophilic/fluorophilic compound is of the formula

$$CF_3(CF_2)_{t1}-(CH_2)_{t2}-CH=CH-(CH_2)_y-CH_3$$

wherein t_1 = 2 to 11, t_2 = 0 or 1 to 6 and y = 1 to 15.

The lipophilic/fluorophilic compound is advantageously constituted of one or more essentially hydrocarbon fragments of the formula (II) described below and one or more highly fluorinated fragments, typical examples of such compounds being the molecules $CF_3(CF_2)_t(CH_2)_yCH_3$ or

$$CF_3(CF_2)_{t1}-(CH_2)_{t2}-CH=CH-(CH_2)_y-CH_3$$

The preparations of the invention further comprise a surfactant selected from a lecithin, a lecithin analog, or the perfluoroalkylated surfactants. The proportions of the components of the preparations are preferably from about 10 to 130% weight/volume of a fluorocarbon-containing phase; from 0.05 to 10% weight/volume of a surfactant; and from about 0.1 to 50% weight/volume of the fluorophilic/lipophilic compound in a suitable aqueous phase.

The emulsions can further comprise any additive suitable to enhance the purpose of the formulation, such as mineral salts, buffers, pharmaceuticals, nutrients, or diagnostic agents. The fluorocarbon can be any suitable fluorocarbon compound, but preferably those molecular species disclosed herein.

The preparations of the invention are prepared by adding an appropriate quantity of the fluorophilic/lipophilic compound to the fluorocarbon or to the aqueous phase prior to emulsification to achieve the desired final concentration of the compound in the emulsion. The addition of the fluorophilic/lipophilic compound acts to bring the emulsion particles to a desired size more rapidly, and to stabilize the

emulsion against changes in particle size on storage. The stabilizing effect is relatively independent of storage temperature.

The preparations can have various forms: dispersions, emulsions or gels, and can be used for various purposes, as oxygen carriers, drug carriers or as contrast agents.

Brief Description of the Drawings

Figure 1 represents the change in the average diameters (in μm) of particles of perfluorooctyl bromide (PFOB; perflubron®) emulsions conforming to the invention and comprising the fluorophilic/lipophilic compound $C_6F_{13}CH=CHC_8H_{17}$: F6H8E, and of particles of a reference emulsion, prepared without F6H8E, as a function of time (in days) during aging, at 25°C or 40°C.

Figure 2 represents the change in the average diameters (in μm) of particles of Perflubron® emulsions of the invention comprising the fluorophilic/lipophilic compound $C_8F_{17}CH=CHC_8H_{17}$: F8H8E, and of particles of a reference emulsion, prepared without F8H8E, as a function of time (in days) during aging at 40°C.

Figure 3 represents the change in the average diameters (in μm) of particles of perfluorooctyl bromide emulsions of the invention comprising the fluorophilic/lipophilic compound F8H10, and of particles of a reference emulsion, as a function of time (in days) during aging at 40°C.

Figure 4 represents the change in the average diameters (in μm) of particles of perfluorooctyl bromide (perflubron) emulsions of the invention comprising the fluorophilic/lipophilic compound $C_8F_{17}CH=CHC_8H_{17}$(F8H8E), and particles of a reference emulsion prepared without F8H8E, as a function of time (in days) during aging at 40°C.

Figure 5 represents the change in the average diameter (in μm) of particles of perfluorooctyl bromide (perflubron™) emulsions of the invention comprising the fluorophilic/lipophilic compound $C_6F_{13}C_{10}H_{21}$ (F6H10), and of

particles of a reference emulsion prepared without F8H10, as a function of time (in days) during aging at 40°C.

Figure 6 represents the change in the actual diameters (in μm) of particles of perfluorooctyl bromide (perflubron™) emulsions of the invention comprising the fluorophilic/lipophilic compound $C_8F_{17}CH=CHC_8H_{17}$ (F8H8E) in 0.7% w/v amount, and of particles of a reference emulsion prepared without F8H8E, as a function of time (days) during aging at 40°C.

Figure 7 represents the change in the average diameters (in μm) of particles of 1,2-bis-(F-butyl)ethene (F-44E) emulsions of the invention comprising the fluorophilic/lipophilic compound $C_8F_{17}CH=CHC_8H_{17}$ (F8H8E), and of particles of a reference emulsion prepared without F8H8E, as a function of time (in days) during aging at 40°C.

Figure 8 represents the change in the average diameters (in μm) of particles of perflubron® emulsions of the invention comprising the fluorophilic/lipophilic compound $C_6F_{13}C_{12}H_{25}$ (F6H12), and of particles of a reference emulsion prepared without F6H12, as a function of time (in days) during aging at 40°C.

Figure 9 demonstrates the effect of F8H8E (Dowel structure, $C_8F_{17}CH=CHC_8H_{17}$), on PFOB emulsion particle size and particle size stability, as a function of the number of passes, and the influence of adding F8H8E on the percentage of particles (a) smaller than 0.12 μm and (b) larger than 0.6 μm.

☆ : Change in mean particle diameter d <u>without</u> F8H8E;

★: change in mean particle diameter d <u>with</u> F8H8E;

▵: percent of particles <0.12 μm diameter <u>with</u> F8H8E;

□: percent of particles <0.12 μm diameter <u>without</u> F8H8E;

▲: particles > 0.6 μm <u>without</u> F8H8E;

■: percent of particles > 0.6 μm <u>with</u> F8H8E.

Detailed Description of the Invention

The present invention is directed to forming substantially stable dispersed preparations, whether in the form of dispersions, emulsions or gels, through the use of additives that improve the stability of emulsions wherein the hydrophobic or oily phase of the preparation contains a highly fluorinated compound or a perfluorocarbon compound, prepared using classical surfactants. The additives also provide a tight control of particle size.

Definitions:

Fluorocarbon is an analogue of a hydrocarbon which is highly fluorinated, having at least half of the hydrogen atoms replaced by fluorine atoms, or perfluorinated, having all of the hydrogen atoms replaced by fluorine atoms.

Hydrocarbon radical, hereinafter R_H, is a linear, branched or cyclic, saturated, monounsaturated or polyunsaturated hydrocarbon group, wherein the unsaturated bonds are ethylenic or acetylenic. In these groups, one or more atoms of the carbon chain can be replaced by other bivalent species, such as O or S.

Fluorinated hydrocarbon radical, hereinafter R_F, is a linear, branched, or cyclic hydrocarbon group which is highly fluorinated, having at least half of the hydrogen atoms replaced by fluorine atoms, or perfluorinated, having all of the hydrogen atoms replaced by fluorine atoms. Some of the fluorine atoms can be replaced by Cl and Br; one or more atoms of the carbon chain can be replaced by other bivalent species, such as O or S.

Fluorophilic/lipophilic compound is an amphiphilic molecule having a fluorinated hydrocarbon radical, as defined above, linked to a substantially hydrocarbon radical, as defined above, of the conventional composition of carbon and hydrogen.

Preparations according to the invention accordingly comprise (1) an oily or hydrophobic phase comprising at least one highly fluorinated compound or perfluorocarbon;

(2) a continuous phase; (3) at least one conventional surfactant; and (4) an amphiphilic organic compound having a fluorophilic region comprising a fluorinated hydrocarbon radical and a lipophilic region, comprising a hydrocarbon radical.

According to a preferred embodiment of the invention, the dispersed preparation is of the oil-in-water type wherein the hydrophobic phase containing the fluorocarbon or highly fluorinated compound is dispersed in a continuous aqueous phase.

According to one embodiment of the invention, the organic fluorophilic-lipophilic compound is of the formula:

$$R_F^1\text{-}W\text{-}R_H^1 \qquad (I)$$

wherein

R_F^1 is a linear, branched or cyclic C_{2-14} fluorocarbon group;

R_H^1 is a linear, branched or cyclic C_{1-18} saturated or unsaturated hydrocarbon group; and

W is absent or is a bivalent species chosen from the group consisting of -O-, -S-, or is of the formula:

$$-X^1(CH_2)_p\text{-}\underset{\displaystyle R^2}{\overset{\displaystyle X^2}{CH}}\text{-}(CH_2)_q\text{-}X^3\text{-}R_F^2$$

or

$$-X^1(CH_2)_p\text{-}\underset{\displaystyle R^2}{\overset{\displaystyle X^2}{CH}}\text{-}(CH_2)_q\text{-}X^3\text{-}R_H^2$$

wherein

X^1, X^2 and X^3 are absent or are independently selected from the group consisting of -O-, or -S-;

R_F^2 is a fluorocarbon independently selected from the group defined for R_F^1;

R_H^2 is a hydrocarbon independently selected from the group defined for R_H^1; and

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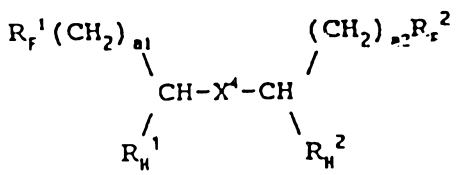
R^2 is a fluorocarbon or a hydrocarbon independently selected from the group defined for R_F^1 or R_H^1; and

p and q are independently 1-10;

provided that R_F^1 and R_F^2 comprise at least 4 F atoms, and correspond to a hydrocarbon analogue wherein F atoms replace from 50% to 100% of the hydrogen atoms.

In yet other embodiments, the carbon chain of the R_H^1 or R_H^2 region of the fluorophilic-lipophilic compound can contain a substituent selected from the group consisting of -O- and -S-, wherein R^1 is a linear or branched C_{1-12} alkyl group.

According to another embodiment of the invention, the organic fluorophilic/lipophilic compound is of the formula:



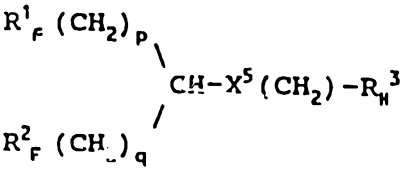
(II)

wherein

X^4 is -O-, -S- or -S-S-; and

a1 and a2 are independently from 0 to 11.

According to yet another embodiment of the invention, the organic fluorophilic/lipophilic compound is of the formula:



(III)

wherein

X^5 is -O-, -S-, or -S-S-;

p and q are independently from 1 to 10;

R_F^1 and R_F^2 are independently selected from a group of perfluoroalkylated radicals having from 2 to 10 carbon atoms, and R_H^3 is selected from the group of hydrocarbon radicals having from 2 to 16 carbon atoms.

AUSTRALIA PATENT OFFICE

The preparations of the invention, whether in the form of a dispersion, an emulsion or a gel, comprise a substantially aqueous phase which is not miscible with the oily phase, as well as at least one natural or synthetic surfactant, in particular a hydrophilic-lipophilic surfactant such as those generally used for the preparation of dispersions, emulsions

AUSTRALIA PATENT OFFICE

or gels. Examples of such surfactants are lecithins, perfluoralkylated surfactants, and their mixtures.

The fluorocarbon dispersions to which the compositions of the invention are directed are distinct from the conventional oil-in-water emulsions in their physical complexity. Oil particles are held dispersed in conventional emulsions and dispersions by virtue of a surfactant molecule, which is a molecule having an amphipathic structure comprising a lipophilic region, such as a hydrocarbon structure which has affinity for fatty substances which are also mainly hydrocarbons, and also comprising a hydrophilic or polar region, which has affinity for the polar water molecules of the aqueous phase. Without a surfactant, the water immiscible oil phase would separate rapidly from the aqueous phase in the presence of water. The surfactant acts to lower the interfacial tension between the aqueous phase and the lipid phase and to build an interfacial film around each droplet of the dispersed phase, which stabilizes the emulsion.

Fluorocarbons are heavy water immiscible liquids which are like oily substances except that they are neither hydrophilic nor lipophilic. Thus the interfacial tension between fluorocarbon liquids and an aqueous phase cannot be effectively reduced by conventional surfactants. However, an amphiphilic system that is analogous to a conventional lipophilic/hydrophilic surfactant, but having fluorophilic/hydrophilic regions is preferable. This system is structured, according to the present invention by using, in combination, paired molecules comprising a conventional surfactant and a fluorophilic/lipophilic molecule, which act together in association to reduce the interfacial tension and stabilize the dispersion.

In this case, the addition of compound R_f'-W-R_H' which bears both a lipophilic hydrogenated part (R_H') and a fluorophilic fluorinated part (R_f') facilitates the adhesion of the aqueous phase to the oily, fluorocarbon-based phase of the dispersion, emulsion or gel, by interaction of this

compound with the lipophilic part of the hydrophilic-lipophilic surfactant.

In such preparations, indeed, the conventional hydrophilic-lipophilic surfactant on the one hand, and the R_F^1-W-R_H^1 compound on the other hand, constitute two distinct types of molecules whose contributions are complementary and assure to the conventional surfactant a good aqueous/lipidic membrane phase interaction, and the latter (R_F^1W-R_H^1 compound) a good lipidic membrane/fluorocarbon interaction.

This can be illustrated schematically in terms of synergistic surfactant effects as follows:

Surfactant Effect	Water	Fluorocarbon
(1)	hydrophilic <--> lipophilic	
(2)		lipophilic <--> fluorophilic

Contribution (1) is furnished by the hydrophilic-lipophilic surfactant and contribution (2) by the lipophilic-fluorophilic compound, for example of formula RF^1-W-R_H^1, in conformity with the invention.

The R_F^1-W-R_H^1 compounds are generally very unreactive and nontoxic, and thus suitable for biomedical applications. Their use in the formulations of the invention eliminates the need to use other surfactants whose biocompatibility must be tested. The desired effect can also be obtained by using small quantities of R_F^1-W-R_H^1.

According to the invention, the fluorophilic chain of compound R_F^1-W-R_H^1 which corresponds to R_F^1, and in some cases to R_F^2, is a straight or branched fluorinated hydrocarbon radical, of 2 to 14 carbon atoms, which may bear oxygen atoms and/or other substituents for example, Cl or Br.

Examples of fluorinated radicals that can be used are:

$CF_3(CF_2)_t$- wherein t = 1 to 11;

$(CF_3)_2CF(CF_2)_v$- wherein v = 0 to 8;

$CF_3(CF_2CF(CF_3))_w$- wherein w = 1 to 4;

$C_2F_5(CF_2CF(CF_3))_w$- wherein w = 1 to 4;

$(CF_3)_2(CFCF_2CF(CF_3))_w$- wherein w = 1 to 3; and

$$R_f^3 \diagdown CFO(CF_2CF_2)_x- \diagup R_f^4$$

wherein x = 1 to 6; and

R_f^3 and R_f^4 are independently chosen from the group consisting of CF_3-, C_2F_5-, $n\text{-}C_3F_7-$, $n\text{-}C_4F_9$, and $CF_3CF_2CF(CF_3)-$; or

R_f and R_f together form a bivalent radical chosen from the group consisting of:

$-CF_2(CF_2)_2CF_2-$

$-CF_2(CF_2)_3CF_2-$; and

$-CF_3CF_2O-(CF_2CF_2O)_y-CF_2-$

wherein y = 0 to 3; and

$CF_3(CF_2)_2O-(CF(CF_3))(CF_2O)_y-CF(CF_3)-$

wherein y = 0 to 2.

Among the fluorinated radicals corresponding to the above formulas, the radical of formula $CF_3(CF_2)_t$, in which t is a whole number from 1 to 11, and preferably from 3 to 9, are particularly useful.

According to the invention, the lipophilic part of compound $R_f^1\text{-}W\text{-}R_H^1$, represented by R_H^1 and possibly R_H^2 is a linear, branched or cyclic, saturated or unsaturated, hydrocarbon radical, of from 1 to 18 carbon atoms, which may bear in its chain 1 or several groups.

Examples of radicals from among which R_H^1 and R_H^2 can be chosen are:

(a) $CH_3-(CH_2)_{y1}-$ wherein y_1 = 1 to 17;

(b) $CH_3(CH_2)_{y2}(CH=CH)_q(CH_2)_{y3}-$

$CH_3(CH_2)_{y2}-CON(R_H^1)-(CH_2)_{y3}-$

$CH_3(CH_2)_{y2}-S-(CH_2)_{y3}-$

and $CH_3(CH_2)_{y2}-N(R_H^1)-(CH_2)_{y3}-$

wherein y_2 and y_3 are independently 1 to 16,

q=0 or 1, and R_H^1 is as defined above;

(c) $CH_3(CH_2-CH_2-O)_{y4}-CH_2-$ wherein y4 = 1 to 8; and

(d) $CH_3(CH(CH_3)CH_2O)_{y5}-CH-CH_3$ wherein y5 = 1 to 5.

According to a particularly preferred embodiment of the invention, in compound R_F^1-W-R_H^1:

R_H^1 is R^4-CH=CH-$(CH_2)_p$- wherein R^4 is a linear alkylated radical of 2 to 12 carbon atoms, and p is equal to 0 or is a whole number from 1 to 8, and

W is a single bond.

Examples of compounds R_F^1-W-R_H^1 that can be used in this embodiment of the invention are:

$$CF_3(CF_2)_{t1}-(CH_2)_{t2}-CH=CH-(CH_2)_{y6}-CH_3$$

in which t_1 is a whole number from 2 to 11, t_2 is a whole number from 0 to 6 and y_6 is a whole number from 1 to 15.

These compounds can be prepared by classical procedures, for example, by addition of a perfluoroalkylated iodide of formula CF_3-$(CH_2)_{t1}(CH_2)_{t2}I$ to an olefin of formula CH_3-$(CH_2)_{y6}$-CH=CH_2, followed by dehydroiodation (J. Org. Chem. 27:2261 (1962) and J. Org. Chem. 37:24-29 (1972)).

Examples of compounds corresponding to the above formula are those in which t_1=3,5,7,9 or 11 (preferably 3,5 or 7) t_2=0, and y_6= 3,5,7 or 9 (preferably 5,7 or 9).

These compounds are of much interest, as they are of low toxicity. Intraperitoneal injection of such compounds into mice at a dose of 25 mL/kg body weight showed no toxicity. Intravascular injection of such compounds in the form of an emulsion (F6H10E/EYP 25/6% w/v) into rats is well tolerated by the animals (no death resulted among 33 animals given a 15ml/kg body weight dose). The half retention time in liver for F6H10E is about 24 days (to be compared with 65 days for perfluorotripropylamine).

According to a preferred embodiment of the invention, the R_H^1 moiety of compound R_F^1-W-R_H^1, is a linear alkylated radical of 4 to 12 carbon atoms, and

W is a single bond.

Examples of compounds R_F^1-W-R_H^1 that are useful in this second embodiment of the invention are the semi-fluorinated n-alkanes which can be prepared by the procedures described by Rabolt et al. in Macromolecules, 17(12), 2786-2794 (1984) or by Twieg et al. in Polym. Prep., 25, 154-5 (1984).

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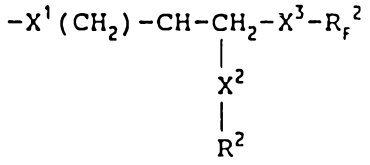
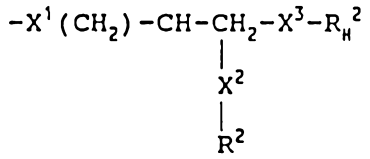
According to other embodiments of the invention, the R_H^1 moiety of the compound R_F^1-W-R_H^1 is an alkylated, linear radical of C4 to C12; and R_F^1-W- or

W is a group of one of the following formulas:



or



in which X^1, X^2, X^3, R_H^2, R_F^2, and R^2 are defined as above.

In these different embodiments of the invention, R_F^1 is preferably a perfluorinated linear radical of formula $CF_3(CF_2)_t$, and t is a whole number from 1 to 11.

Compounds R_F^1-W-R_H^1 which correspond to these different embodiments of the invention can be prepared by classical procedures. In the preparations of the invention, the fluorocarbons constituting the oily phase can be linear or cyclic compounds, with molecular weights preferably from 400 to 700, and they can be chosen, for example, from among perfluorodecalin, 1,2-bis(F-alkyl)ethenes, 1,2-bis(F-butyl)ethenes, 1-F-isopropyl,2-F-hexylethenes and 1,2-bis(F-hexyl)ethenes, perfluoromethyldecalins, perfluorodimethyldecalins, perfluoromethyl-, and dimethyladamantanes, perfluoromethyl-dimethyl- and trimethylbicyclo (3,3,1) nonanes and their homologs, perfluoroperhydrophenanthrene, ethers of formulae: $(CF_3)_2CFO(CF_2CF_2)_2OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_3OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_2F$, $(CF_3)_2CFO(CF_2CF_2)_3F$, $F[CF(CF_3)CF_2O]_2CHFCF_3$, $[CF_3CF_2CF_2(CF_2)u]_2O$ with u= 1, 3 or 5, amines $N(C_3F_7)_3$, $N(C_4F_9)_3$, $N(C_5F_{11})_3$, perfluoro-N-methylperhydroquinolines and perfluoro-N-methylperhydroisoquinolines, perfluoroalkyl hydrides such as

$C_6F_{13}H$, $C_8F_{17}H$, $C_8F_{16}H_2$ and the halogenated derivatives $C_6F_{13}Br$, $C_8F_{17}Br$ (perflubron), $C_6F_{13}CBr_2CH_2Br$, 1-bromo 4-perfluoroisopropyl cyclohexane, $C_8F_{16}Br_2$, $CF_3O(CF_2CF_2O)_uCF_2CH_2OH$ with u=2 or 3. These compounds can be used alone or in mixtures.

In preparations in the form of dispersions, emulsions or gels, the surfactants used generally comprise a hydrophilic part and a hydrophobic part, and can consist of fluorinated or non-fluorinated surfactants. Preferably, classical surfactants are used, such as those usually employed in preparations for biomedical use, for example, phospholipids and poloxamers such as copolymers of polyoxyethylene-polyoxypropylene type, such as Pluronic F-68®, and their mixtures.

When the preparation of the invention is in the form of a dispersion, an emulsion or a gel and comprises an aqueous phase and at least one surfactant, its composition is generally in the following ranges:

from 10 to 130% in weight/volume of oily phase;
from 0.1 to 10% in weight/volume of surfactant(s); and
from 0.01 to 50% in weight/volume of lipophilic-fluorophilic organic compound(s), the rest being constituted by the aqueous phase.

In a preferred embodiment, the composition contains from 0.01% to 10% of a lipophilic/fluorophilic organic compound or a mixture of such compounds.

The preparations in the form of emulsions can be made by the classical procedures generally used to prepare emulsions. For example, such preparations can be made by dispersing the surfactant(s) and the R_f'-W-R_H' compounds in an aqueous phase which may contain other additives, then adding the oily phase to this dispersion and emulsifying the whole mixture by classical techniques. Appropriate techniques are described, for example, in EP-A- 0 231 070 and EP-A- 307 087. Compound R_f'-W-R_H' can also be added to the oily phase before mixing the two phases.

The compounds of the invention achieve emulsion particle size stability when added to 90/4% w/v PFOB/EYP emulsion. These compounds retain particle size at 13μm after sterilization, and maintain this particle size for 3 months at 40°C (Figures 2, 3, and Table II). By comparison, the reference emulsion containing only PFOB/EYP grows from 15μm after sterilization to 0.32μm after 3 months at 40°C. The same phenomenon of stabilization is observed when the compounds of the present invention are added to F-44E/EYP 90/4% w/v emulsions; the particle size stays at 0.14μm after sterilization, and after 3 months at 40°C. By comparison, the particle size diameter in the reference emulsion increases from 0.15μm to 0.32μm (Figures 7, 8, Table III).

The compounds of the invention also achieve emulsion particle size control and stability. The adjustment of particle size is obtained by adjusting, for a given amount of fluorocarbon, the amount of the compounds of the lipophilic/fluorophilic "dowel" compounds of the invention with respect to the amount of surfactant. The effective dowel/surfactant ratio is independent of both the nature or species of the fluorocarbon molecule and the concentration of the fluorocarbon in the emulsion. The effective dowel/surfactant ratio has been found to be in the molar ratio of between about 1/10 and 10/1, with a preferred molar ratio of 1/1. This broad range of effective dowel/surfactant molar ratios was determined in studies using several different fluorocarbon species, for example, F-decalin, perfluorooctyl bromide (Perflubron®), and F44-E, in emulsions having fluorocarbon concentrations of from about 20% w/v to 100% w/v, and containing an amount of EYP surfactant varying from about 1 to 8% w/v. This comprises a 10^{-3} to 10^{-4} M concentration of the EYP surfactant, and equivalent mole concentrations of other surfactants were found to be similarly effective. The molar ratio of dowel/EYP shown to be effective in these studies was equal to 1/5, 1/3, 1/1, and 2/1.

In studies using effective concentrations of surfactant and lipophilic/fluorophilic compounds of the invention, the particle size can vary between 0.22-0.25μm and 41μm after preparation; this particle size is retained after 3 months at 40°C (Figures 5,6, Table II).

The compounds of the invention facilitate the formation of the emulsion and lead to emulsions with fine particle size after a reduced number of passes or a reduced amount of energy. When the compound F8H8E of the invention is added to perfluorooctyl bromide/lecithin emulsion, 30% of fine particles are obtained after 10 passes. By comparison, the reference emulsion without the compounds of the invention requires 20 passes to obtain the same percentage of fine particles (Figure 9).

The preparations of the invention, whatever their form (dispersions, emulsions or gels), can also comprise other additives, for example those generally used in emulsions, such as mineral salts, buffers, osmotic agents, oncotic agents, nutritive agents, or other ingredients that help to improve the characteristics, the stability, the efficacy and the tolerance of the emulsions.

The preparations of the invention can be used in the pharmaceutical field as medicaments in the form of emulsions or dispersions administrable, for example, orally or through the trachea, or by injection into the blood stream or into other cavities or organs of the body.

The preparations of the invention can also be used in pharmacy, cosmetics, in the veterinary or phytosanitary fields, in biology and medicine, in particular as oxygen carriers that can be employed, among other uses, as blood substitutes, or more generally for the administration of oxygen. Certain preparations of the invention can also be used as contrast agents to facilitate diagnosis, particularly by radiography, sonography or nuclear magnetic resonance imagery. The preparations, gels, emulsions or other dispersions of the invention can be used as media for treating

cerebral and cardiac ischemia, for peri-operative hemodilution, for the preservation of organs, tissues, embryos, semen, as media to be used in cardiovascular therapy and surgery, for example as cardioplegic or reperfusion solutions, or in coronary angioplasty, media serving as an adjuvant in radiotherapy and chemotherapy of cancer, or as drug vehicle.

Other characteristics and advantages of the invention will be better seen in the following examples and in Figures 1-9. The present invention is described in detail using the following examples; however, these preferred embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

In these examples, the lipophilic-fluorophilic $R_f^1-W-R_H^1$ compound is of the formula:

$CF_3(CF_2)_t-(CH=CH)_y-(CH_2)_yCH_3$, or $CF_3(CF_2)_t-(CH_2)_yCH_3$

and is designated hereinafter generally as $F_{t+1}H_{y+1}E_v$, or $F_{t+1}H_{y+1}$, respectively, and specifically as:

F6H8E when t=5 and y=7, v=1;

F8H8E when t=7 and y=7, v=1;

F6H6E when t=5 and y=5, v=1;

F6H10 when t=5 and y=9, v=0.

EXAMPLES 1, 2 AND 3 : STABILIZATION OF AN EMULSION OF PERFLUOROOCTYL BROMIDE/LECITHIN 90/4% IN WEIGHT PER VOLUME (w/v) USING A COMPOUND R_fWR_H.

Reference emulsion A:
Emulsions of Perflubron®/lecithin (90/4 % w/v)

32 g of egg-yolk lecithin and a mixture of salts whose composition is shown in detail in Table I was dispersed with Ultra Turrax under nitrogen (24000 t/min, 10 min) in 393 mL of injectable water. Perfluorooctyl bromide (PFOB, Perflubron®) (375 mL) was added slowly to this dispersion under nitrogen. The mixture was dispersed for 10 mn at 30-40°C.

The coarse emulsion obtained was passed under nitrogen through a microfluidizer (M110F). After 10 passes under a

pressure of 12000 psi in the chambers cooled to 35°C, the emulsion was recovered, filled in flasks then sterilized at 121°C for 15 mn. The ageing was monitored at 5,25 and 40°C (Table II and Figure 1) and the average size of the particles measured by photosedimentation.

Table I : Composition of reference emulsion A (for 100 mL).

PFOB	90 g
Lecithin	4 g
NaCl	0,3 g
EDTACaNa2	0,02 g
$NaHPO_4$-Na_2PO_4	35 mM
α-Tocopherol	0,002 g
H_2O for injection	qsp 100 ml

Example 1 : Stabilization of an emulsion of perfluorooctyl bromide/lecithin by addition of $C_6F_{13}CH=CHC_8F_{17}$ (F6H8E)

32 g of egg-yolk lecithin and a mixture of salts of the above composition (Table I) was dispersed under nitrogen using an Ultra Turrax T50 (24000 t/min, 10 min) in 379 mL of injectable water at 30-40°C. F6H8E (14.3 mL) was slowly added to this dispersion, which was stirred for 2 min. Perfluorooctyl bromide (375 mL) was then slowly added. The whole was emulsified for 10 min at 24000 t/min at 30-40°C. The coarse emulsion obtained was run under nitrogen through the microfluidizer and after 10 passes (12000 psi, 35°C) the emulsion was filled in vials, sterilized and stored at 5,25 and 40°C (Table II and Figure 1).

The composition of this emulsion was the same as above but for the presence of F6H8E (2.34 g)

Example 2 : Stabilization of the emulsion of perfluorooctyl bromide/lecithin by addition of $C_8F_{17}CH=CHC_8H_{17}$ (F8H8E)

The protocol described in example 1 was used with 377 mL of water, 16.3 mL of F8H8E and 375 mL of perfluorooctyl bromide. After microfluidization the emulsion was sterilized and stored at 40°C (Table II and Figure 2).

Example 3 : Stabilization of an emulsion of perfluorooctyl bromide/lecithin by addition of $C_8F_{17}C_{10}H_{21}$ (F8H10)

The protocol described in example 1 and 2 was used with 377 mL of water, 22.4 g of F8H10 and 375 mL of perfluorooctyl bromide. After microfluidization the emulsion was sterilized and stored at 40°C (Table II and Figure 3).

EXAMPLES 4 AND 5 : STABILIZATION OF AN EMULSION OF PERFLUOROOCTYL BROMIDE/LECITHIN 90/2% IN WEIGHT PER VOLUME (w/v) USING A COMPOUND R_FWR_H.

Reference emulsion B : Emulsions of perfluorooctyl bromide /lecithin (90/2 % w/v)

The same protocol described in example of Reference A was used but for 16 g of egg-yolk lecithin.
The aging was monitored at 40°C (Table II and Figure 4).

Example 4 : Stabilization of an emulsion of perfluorooctyl bromide/lecithin by addition of $C_8F_{17}CH=CHC_8F_{17}$ (F8H8E)

The protocol described in example 1 was used with 385 mL of water, 8.38 mL of F8H8E, 16 g of lecithin and 375 mL of perfluorooctyl bromide. After microfluidization, the emulsion was sterilized and stored at 40°C (Table II and Figure 4).

Example 5 : Stabilization of the emulsion of perfluorooctyl bromide/lecithin by addition of $C_6F_{13}C_{10}H_{21}$ (F6H10)

The protocol described in example 1 was used with 392 mL of water, 7,53 mL of F6H10, 32 g of lecithin and 375 mL of perfluorooctyl bromide. After microfluidization the emulsion was sterilized and stored at 40°C (Table II and Figure 5).

EXAMPLE 6 : STABILIZATION OF AN EMULSION OF PERFLUOROOCTYL BROMIDE (PFOB)/LECITHIN 90/1% IN WEIGHT PER VOLUME (w/v) USING A COMPOUND R_FWR_H.

Reference emulsion C : Emulsions of perfluorooctyl bromide/lecithin (90/1% w/v)

The same protocol described in example of reference A was used but for 8 g of egg-yolk lecithin.

The aging was monitored at 40°C (Table II and Figure 6) and the average size of the particles was measured by photosedimentation.

Example 6 : Stabilization of an emulsion of perfluorooctyl bromide/lecithin/water by addition of $C_8F_{17}CH=CHC_8F_{17}$ (F8H8E)

The protocol described in example 1 was used with 382 mL of water, 4,19 mL of F8H8E, 8 g of lecithin and 375 mL of perfluorooctyl bromide. After microfluidization the emulsion was sterilized and stored at 40°C (Table II and Figure 6).

It is seen that the addition of small quantities of compounds of the type R_F-W-R_H to the formula of concentrated fluorocarbon emulsions results in strong stabilization. The size of the fluorocarbon droplets increases significantly more slowly (compare in particular the average diameters of the droplets after 12 days and 3 months) in the emulsions containing these mixed hydrocarbon/fluorocarbon compounds than in the reference emulsions which contain none. These results are also illustrated in figures 1, 2, 3, 4 and 5. It is also noteworthly from example 4, 5 and 6 that the average particle size can be adjusted, and remains constant over a significant

Table II : Comparison of stability over time, at 40°C, of perfluorooctyl bromide/lecithin 90/4% w/v of various formulations containing R_FWR_H and without (as measured by mean diameter, d, of emulsion particles in μm).

Formulation of emulsions PFOB/lecithin/R_FWR_H % w/v	at preparation	after sterilization	after 12 days at 40°C	after 3 months at 40°C
Ref A: 90/4/0	0.14	0.15	0.17	0.32
Example 1: 90/4/2.34 (F6H8E)	0.12	0.13	0.15	0.15
Example 2: 90/4/2.85 (F8H8E)	0.10	0.13	0.13	0.13
Example 3: 90/4/2.8 (F8H10)	0.11	0.13	0.14	0.14
Ref B: 90/2/0	0.13	0.24	0.29	0.36
Example 4: 90/2/1.4 (F8H8E)	0.20	0.25	0.28	0.28
Example 5: 90/2/1.4 (F6H10)	0.17	0.22	0.25	0.25
Ref C: 90/1/0	0.20	0.40	0.42	0.47
Example 6: 90/1/0.7 (F8H8E)	0.20	0.40	0.41	0.40

period of time, by adjusting the amount of EYP + mixed hydrocarbon/fluorocarbon compound present in the formulation.

EXAMPLES 7 and 8 : STABILIZATION OF AN EMULSION OF 1,2-BIS(F-BUTYL)ETHENE/LECITHIN 90/4% IN WEIGHT PER VOLUME (w/v) USING A COMPOUND R_fWR_H.

Reference D : Emulsions of 1,2-bis(F-butyl)ethene (F-44E)/lecithin/(90/4% w/v)

4 g of egg-yolk lecithin and a mixture of salts whose composition was shown below are dispersed with Ultra Turrax under nitrogen (24000 t/min, 10 min) in 41.16 mL of injectable water. 1,2-Perfluorobutylethene (F-44E) (54 mL) was added slowly to this dispersion under nitrogen. The mixture is dispersed for 10 mn at 30-40°C.

The coarse emulsion obtained is transferred under nitrogen into a microfluidizer (M110F). After 12 passes under a pressure of 12000 psi in the chambers cooled to 35°C, the emulsion was recovered, placed in flasks, then sterilized at 121°C for 15 min. The aging was monitored at 40°C (Table III and Figure 7) and the average size of the particles is measured by photosedimentation.

Composition of the reference emulsion (for 100 mL).

Composition	Grams
F-44E	90
Lecithin	4
$NaHPO_4$-Na_2PO_4	54mM - 15.3mM
H_2O for injection	41.2

Example 7 : Stabilization of an emulsion of 1,2-bis(F-butyl)ethene (F-44E)/lecithin by addition of $C_8F_{17}CH=CHC_8H_{17}$ (F8H8E)

4 g of egg-yolk lecithin and a mixture of salts of the above composition were dispersed in 39.94 mL of injectable water at 30-40°C. F8H8E (2.05 mL) was slowly added to this dispersion, which is stirred for 2 min (8000t/min). 1,2-bis(F-butyl)ethene (F-44E) (54 mL) was then slowly added to the F8H8E/lecithin mixture under nitrogen. The whole was

emulsified for 10 min at 24000 t/min at 30-40°C. The coarse emulsion was transferred under nitrogen into the microfluidizer and after 12 passes (12000 psi, 35°C) the emulsion was sterilized and stored at 40°C (Table III and Figure 7).

Example 8 : Stabilization of an emulsion of 1,2-bis(F-butyl)ethene (F-44E)/lecithin/water by addition of $C_6F_{13}C_{12}H_{25}$ (F6H12)

The protocol described in example 7 was used with 39.9 mL of water 2 mL of F6H12, 4 g of lecithin and 54 mL of perfluorooctyl bromide. After microfluidization the emulsion was sterilized and stored at 5, 25 and 40°C (Table III and Figure 8).

It is seen that the addition of small quantities of compounds R_f-W-R_H to the formula of concentrated fluorocarbon emulsions results in strong stabilization, because the size of the fluorocarbon droplets increases significantly more slowly (compare in particular the average diameters of the droplets after 12 days and 3 or 4 months) in the emulsions containing these mixed compounds than in the reference emulsion which contains none.

EXAMPLE 9 : FACILITATION OF EMULSIFICATION OF PERFLUOROOCTYL BROMIDE BY ADDITION OF $C_8F_{17}CH=CHC_8F_{17}$ (F8H8E)

Reference Emulsion E: Emulsion of Perfluorooctyl bromide (90/4/ % w/v)

Table III : Comparison of stability over time, at 40°C, of 1,2-bis(F-butyl)ethene (F-44E)/lecithin 90/4% w/v containing R_fWR_H and without.

Formulation of emulsions F-44/lecithine/R_fWR_H % w/v	at preparation	after sterilization	after 12 days at 40°C	after 3 months at 40°C
Ref D: 90/4/0	0.14	0.15	0.17	0.32
Example 7: 90/4/2.34 (F6H8E)	0.13	0.14	0.13	0.14
Example 8: 90/4/2.85 (F8H8E)	0.14	0.15	0.16	

The protocol described in Example 1 was used. The average particle size was measured during microfluidization after 1, 2, 3, 4, 5, 7 and 10 passes. The percentage of fine particles (d < 0,12 μm) and of coarse particle (d > 0,6 μm) was evaluated.

Results are reported in Figure 9.

Example 9 : Effect of the addition of $C_8F_{17}CH=CHC_8F_{17}$ (F8H8E) on the emulsification of perfluorooctyl bromide.

The same protocol as for reference emulsion E was used but for the addition of (F8H8E) as described in example 2.

Results are shown in Figure 9.

It is seen that upon the addition of small amounts of the mixed fluorocarbon-hydrocarbon amphiphilic compounds small emulsion droplets (smaller than 0.12μm) are formed more rapidly. The number of droplets larger than 0.6μm is reduced faster and lower average particle size is attained faster.

The invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All modifications which come within the meaning and range of the lawful equivalency of the claims are to be embraced within their scope.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

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Claims:

1. A composition in the form of a dispersion, emulsion or gel, comprising:

an oily phase comprising at least one fluorocarbon compound;

an aqueous phase; and

a surfactant; characterised in that the composition further includes 0.01 - 50% w/v of a lipophilic/fluorophilic compound having a fluorinated region and a hydrocarbon region, or a mixture of such compounds; said lipophilic/fluorophilic compound(s) being adapted to improve the affinity of the surfactant for the oily phase, whereby said dispersion, emulsion or gel is significantly stabilised relative to a dispersion, emulsion or gel lacking said lipophilic/fluorophilic compound.

2. A composition according to Claim 1, wherein said lipophilic/fluorophilic compound comprises at least one hydrocarbon radical and at least one highly fluorinated hydrocarbon radical.

3. A composition according to Claim 1, wherein said lipophilic/fluorophilic compound comprises at least one linear aliphatic chain and at least one fluorinated linear aliphatic chain.

4. A composition according to Claim 1, wherein the lipophilic-fluorophilic compound is of the formula:

$$R_F^1\text{-}W\text{-}R_H^1 \qquad (I)$$

wherein

R_F^1 is a linear, branched or cyclic C_{2-14} fluorocarbon group;

R_H^1 is a linear, branched or cyclic C_{1-18} saturated or unsaturated hydrocarbon group; and

W is a single bond or is a bivalent species chosen from the group consisting of -O-, -S-, or is of the formula:

$$-X^1(CH_2)_p-\underset{\substack{|\\ X^2\\ |\\ R^2}}{CH}-(CH_2)_q-X^3-R_F^2$$

or

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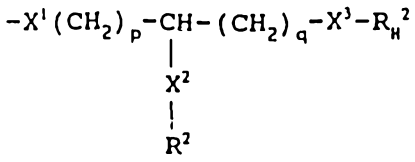


wherein

X^1, X^2 and X^3 are absent or are independently selected from the group consisting of -O- or -S-;

R_f^2 is a fluorocarbon independently selected from the group defined for R_f^1;

R_H^2 is a hydrocarbon independently selected from the group defined for R_H^1;

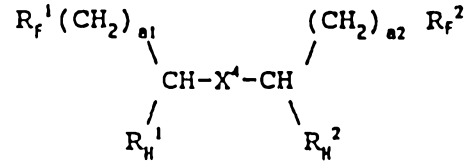
R^2 is a fluorocarbon or a hydrocarbon independently selected from the group defined for R_f^1 or R_H^1; and

p and q are independently 1-10;

provided that R_f^1 and R_f^2 comprise at least 4 F atoms, and correspond to a hydrocarbon analogue wherein F atoms replace from 50% to 100% of the hydrogen atoms.

5. A composition according to Claim 4, wherein a substituent chosen from the group consisting of -O- or -S- is present in the carbon chain of R_H^1 or R_H^2.

6. A composition according to Claim 1, wherein the fluorophilic-lipophilic compound is of the formula:



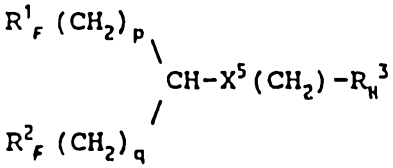
(II)

wherein

X4 is -O-, -S- or -S-S-; and

a1 and a2 are independently from 0 to 11.

7. A composition according to Claim 1 wherein said lipophilic/fluorophilic compound is of the formula



(III)

wherein

X^5 is -O-, -S-, or -S-S-;

p and q are independently from 1 to 10;

R_f^1 and R_f^2 are independently selected from a group of perfluoroalkylated radicals having from 2 to 10 carbon atoms, and R_H^3 is selected from the group of hydrocarbon radicals having from 2 to 16 carbon atoms.

8. A composition according to any one of Claims 4 to 7 wherein R_f^1 or R_f^2 is further substituted by Cl or Br.

9. A composition according to any one of Claims 4 to 7 wherein R_f^1 and R_f^2 are independently selected from the group consisting of:

$CF_3(CF_2)_t$- wherein t = 1 to 11;

$(CF_3)_2CF(CF_2)_v$- wherein v = 0 to 8;

CF_3-$(CF_2CF(CF_3))_w$- wherein w = 1 to 4;

C_2F_5-$(CF_2CF(CF_3))_w$- wherein w = 1 to 4;

$(CF_3)_2(CF$-$CF_2CF(CF_3))_w$- wherein w = 1 to 3; or

$$\begin{array}{l} R_f^3 \\ \diagdown \\ \quad CFO(CF_2CF_2)_x- \\ \diagup \\ R_f^4 \end{array}$$

wherein x = 1 to 6; and

R_f^3 and R_f^4 are independently chosen from the group consisting of CF_3-, C_2F_5-, n-C_3F_7- and $CF_3CF_2CF(CF_3)$-; or

R_f^3 and R_f^4 together form a bivalent radical chosen from the group consisting of:

$-CF_2(CF_2)_2CF_2-$

$-CF_2(CF_2)_3CF_2-$; and

CF_3CF_2O-$(CF_2CF_2O)_y$-CF_2-

wherein y = 0 to 3; and

$CF_3(CF_2)_2O$-$(CF(CF_3))(CF_2O)_y$-$CF(CF_3)$-

wherein y = 0 to 2.

10. A composition according to Claim 2, wherein said highly fluorinated hydrocarbon group is $CF_3(CF_2)_t$- and wherein t = 1 to 11.

11. A composition according to any one of Claims 2- 4, wherein R_H^1 and R_H^2 are independently selected from the group consisting of:

(a) $CH_3-(CH_2)_{y^1}-$ wherein y_1 = 1 to 17;

(b) $CH_3(CH_2)_{y^2}(CH=CH)q(CH_2)_{y^3}-$
$CH_3(CH_2)_{y^2}-CON(R_H^1)-(CH_2)_{y^3}-$
$CH_3(CH_2)_{y^2}-S-(CH_2)_{y^3}-$
and $CH_3(CH_2)_{y^2}-N(R_H^1)-(CH_2)_{y^3}-$
wherein $_{y2}$ and $_{y3}$ are independently 1 to 16, q=0 or 1, and R_H^1 is as defined in Claim 4;

(c) $CH_3(CH_2-CH_2-O)_{y4}-CH_2-$ wherein $_{y4}$ = 1 to 8; and

(d) $CH_3(CH(CH_3)CH_2O)_{y5}-CH-CH_3$ wherein $_{y5}$ = 1 to 5.

12. A composition according to Claim 2 or 7, wherein: R_H^1 is $R^4-CH=CH-(CH_2)_p-$, wherein R^4 is a C_{2-12} alkyl group, and p = 0 or 1 to 8, and W is a single bond.

13. A composition according to Claim 9, wherein said fluorophilic/lipophilic compound is of the formula:

$$CF_3(CF_2)_{t^1}-CH_2)_{t^2}-CH=CH-(CH_2)_{y6}-CH_3$$

wherein t_1 = 2 to 11, t_2 = 0 or 1 to 6 and y_6 = 1 to 15.

14. A composition according to Claim 10, wherein t_2 = 0; t_1 = 3, 5, 7, 9, or 11, and y_6 = 5, 7 or 9.

15. A composition according to Claim 2 or 7, wherein: R_H^1 is a straight chain C_{4-14} alkyl group, and W is absent.

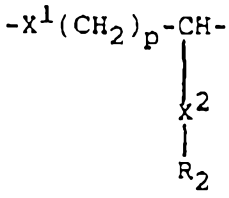
16. A composition according to Claim 5 or 10, wherein: R_H^1 is a straight chain C_{4-12} alkyl group, and W is O or S.

17. A composition according to Claim 2 or 7, wherein: R_H^1 is a straight chain C_{4-12} alkyl group, and W is a group of formula:

$$-X^1(CH_2)_p-\underset{\displaystyle X^2}{\underset{|}{CH}}-(CH_2)_q-X^3-R_F^2$$
$$\quad\quad\quad

18. A composition according to either of Claims 4 to 11, wherein:

R_H^1 is a straight chain C_{4-12} alkyl group, and R^1_B-W- or W is a group of formula:



wherein X^1, X^2, X^3 and R_H^2 are as defined in Claim 1.

19. A composition according to any one of Claims 1, 2, 4, or 7, further comprising a physiologically effective additive selected from the group consisting of mineral salts, buffering agents, osmotic agents, oncotic agents, pharmaceutical products, nutritive products, and diagnostic agents.

20. A composition according to any one of Claims 1, 2, 4, or 7, wherein said fluorocarbon is chosen from the group consisting of perfluorodecalin, perfluorooctyl bromide, 1,2-bis-(F-alkyl)-ethenes, the perfluoromethyldecalins, the perfluorodimethyldecalins, the perfluoromethyl- and dimethyladamantanes, the perfluoromethyl-, dimethyl- and trimethylbicyclo (3,3,1) nonanes and their homologs, the perfluoroperhydrophenanthrenes, the ethers of formulas: $(CF_3)_2CFO(CF_2CF_2)_2OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_3OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_2F$, $(CF_3)_2CFO(CF_2CF_2)_3F$, $F(CF(CF_3)CF_2O)_2CHFCF_3$, $(CF_3CF_2CF_2(CF_2)_u)_2O$ with u=1, 3 or 5, amines $N(C_3F_7)_3$, $N(C_4F_9)_3$, $N(C_5F_{11})_3$, perfluoro-N-methylperhydroquinolines and perfluoro-N-methylperhydroisoquinolines, perfluoroalkyl hydrides, and the halogenated derivatives $C_6F_{13}Br$, $C_8F_{17}Br$, $C_6F_{13}CBr_2CH_2Br$, 1-bromo 4-perfluoroisopropyl cyclohexane, $C_8F_{16}Br_2$, $CF_3CF_2CF_2-C(CF_3)_2-CH_2CH_2CH_2-CF(CF_3)_2$, or $CF_3O(CF_2CF_2O)_uCF_2-CH_2OH$ with u=2 or 3.

21. A composition according to Claim 18, wherein said fluorocarbon is an 1,2-bis-(F-alkyl)ethene selected from the group consisting of bis(F-butyl)-1,2-ethenes, F-isopropyl-1-F-hexyl-2-ethenes and the bis(F-hexyl)-1,2-ethenes.

22. A composition according to Claim 18, wherein said fluorocarbon is a perfluoroalkyl hydride selected from the group consisting of $C_6F_{13}H$, $C_8F_{17}H$, and $C_8F_{16}H_2$.

23. A composition according to any one of Claims 1, 2, 4, or 7, wherein said surfactant is selected from the group consisting of the lecithins, their analogs and the perfluoroalkylated surfactants.

24. A composition according to any one of Claims 1, 2, 4, or 7, comprising:

an oily dispersed fluorocarbon-containing phase in a concentration of from 10 to 130% weight/volume;

a surfactant in a concentration of from 0.05 to 10% weight/volume;

a fluorophilic-lipophilic compound in a concentration of from 0.1 to 50% weight/volume;

in a continuous aqueous phase.

25. A method for stabilizing the particle size of fluorocarbon emulsions, comprising the step of adding a particle stabilizing amount of a fluorophilic/lipophilic compound of the formula

$$R_F{}^1W\text{-}R_H{}^1 \qquad (I)$$

wherein $R_F{}^1$, W, and R_{H1} are as defined in Claim 4, to either the oily phase component or the aqueous phase component of a fluorocarbon emulsion prior to emulsification.

26. The method of Claim 25, wherein said fluorophilic/lipophilic compound is added in an amount sufficient to attain a final concentration in the emulsion of from 0.1 to 50% weight/volume.

27. A method for adjusting the particle size in fluorocarbon emulsions, comprising the steps of:

providing an emulsion formulation comprising a fluorocarbon, a surfactant, and an aqueous phase; and

adding to said formulation a fluorophilic/hydrophilic compound of the formula

$$R_F{}^1\text{-}W\text{-}R_H{}^1 \qquad (I)$$

wherein R_F^1, W, and R_H^1 are as defined in Claim 4, so that the molar ratio of said fluorophilic/hydrophilic compound to said surfactant is from 1:10 to about 10:1, to form a mixture; and

emulsifying said mixture to form a fluorocarbon emulsion wherein substantially all of the emulsion particles have particle diameters below 0.6µm.

28. A composition substantially as hereinbefore described with reference to any one of the examples and/or drawings.

29. A method for stabilizing particle size of fluorocarbon emulsions substantially as hereinbefore described with reference to any one of the examples and/or drawings.

30. A method for adjusting particle size in fluorocarbon emulsions substantially as hereinbefore described with reference to any one of the examples and/or drawings.

Dated this 3rd day of April, 1996
Alliance Pharmaceutical Corp.
by DAVIES COLLISON CAVE
Patent Attorneys for the applicants.

AUSTRALIAN PATENT OFFICE

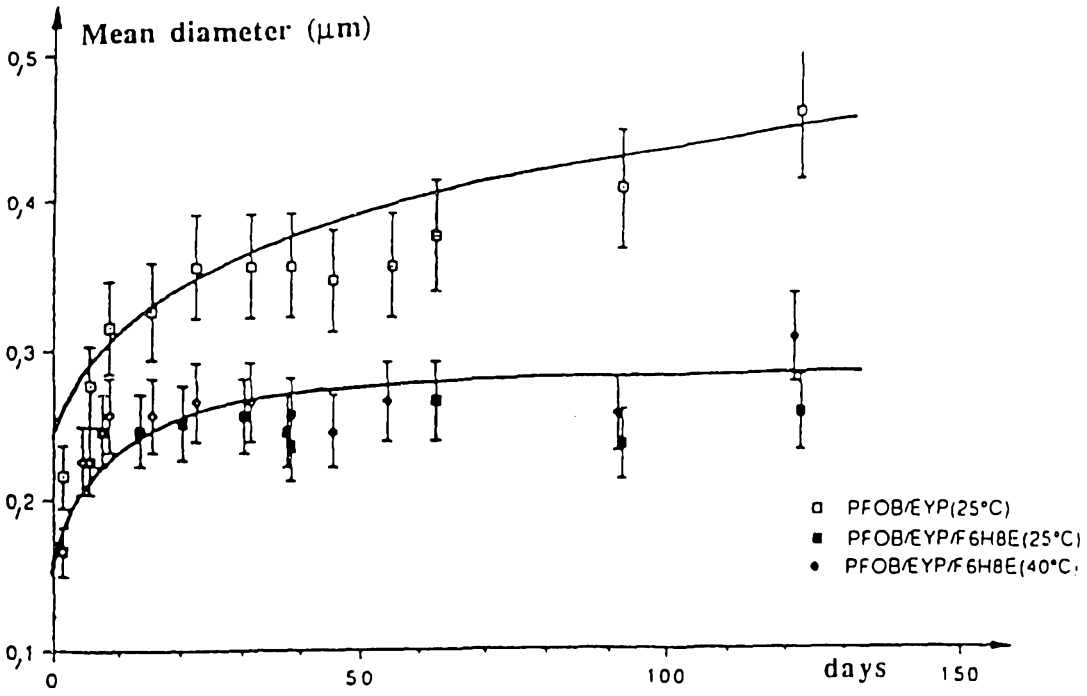


FIG. 1

Figure 2

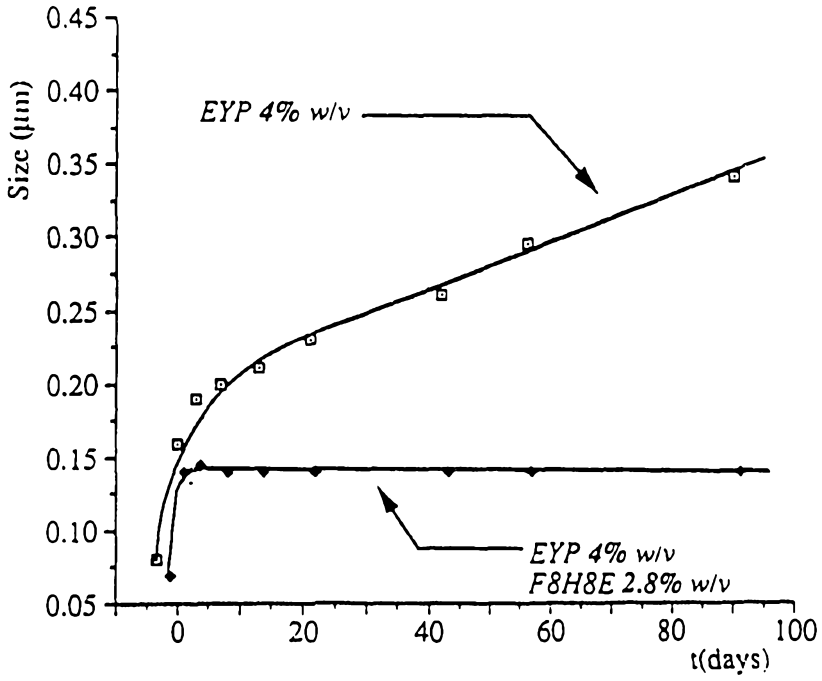


Figure 3

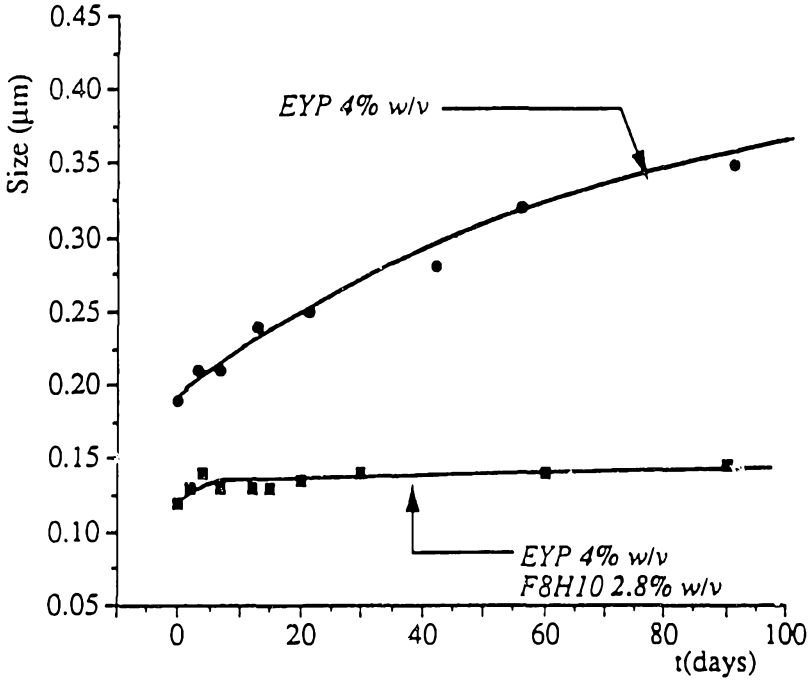


Figure 4

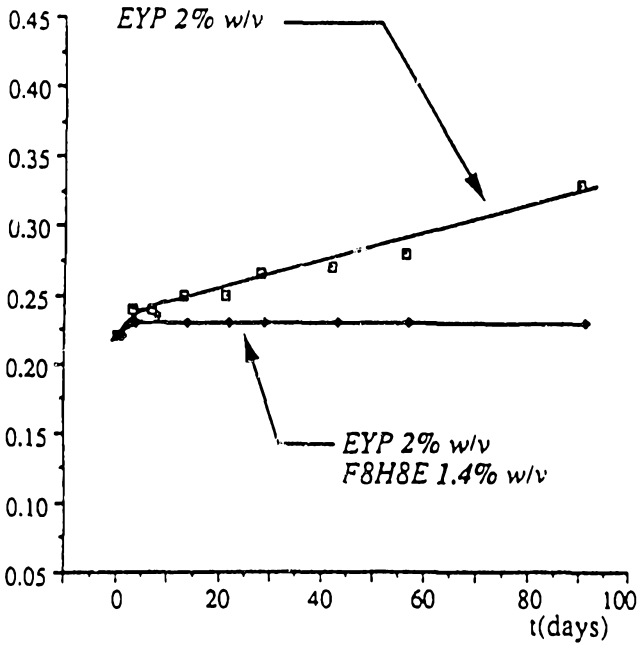


Figure 5

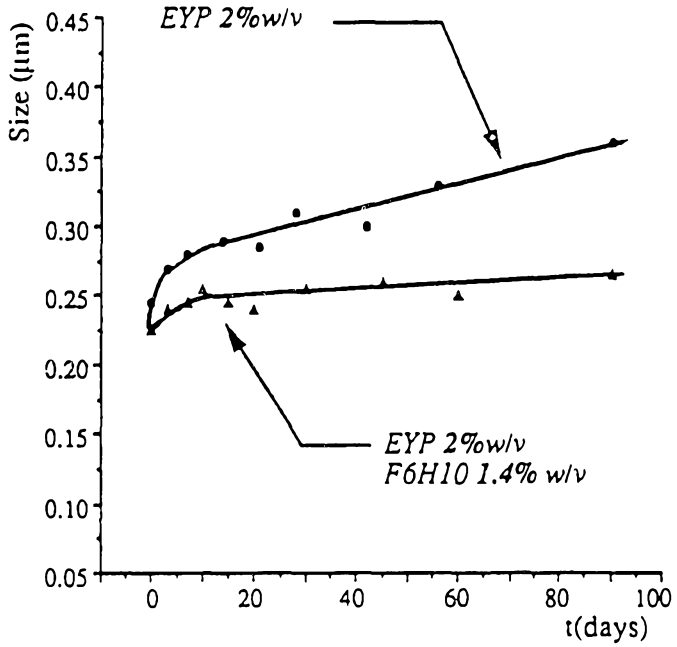


Figure 6

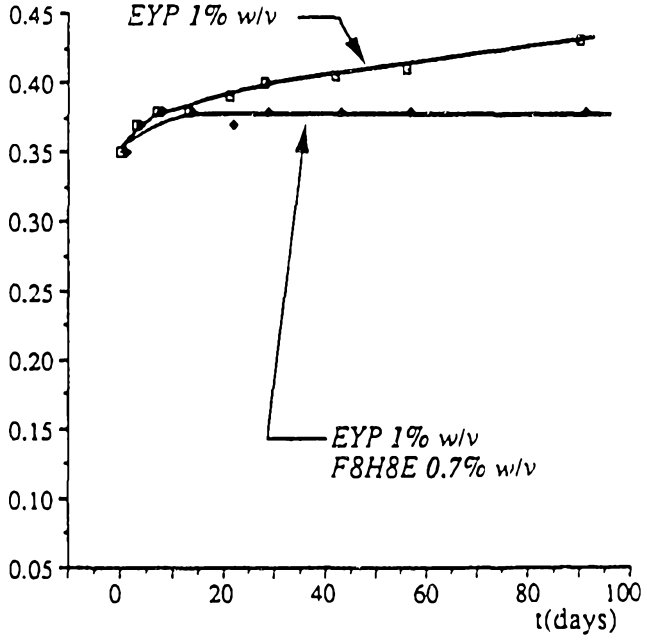


Figure 7

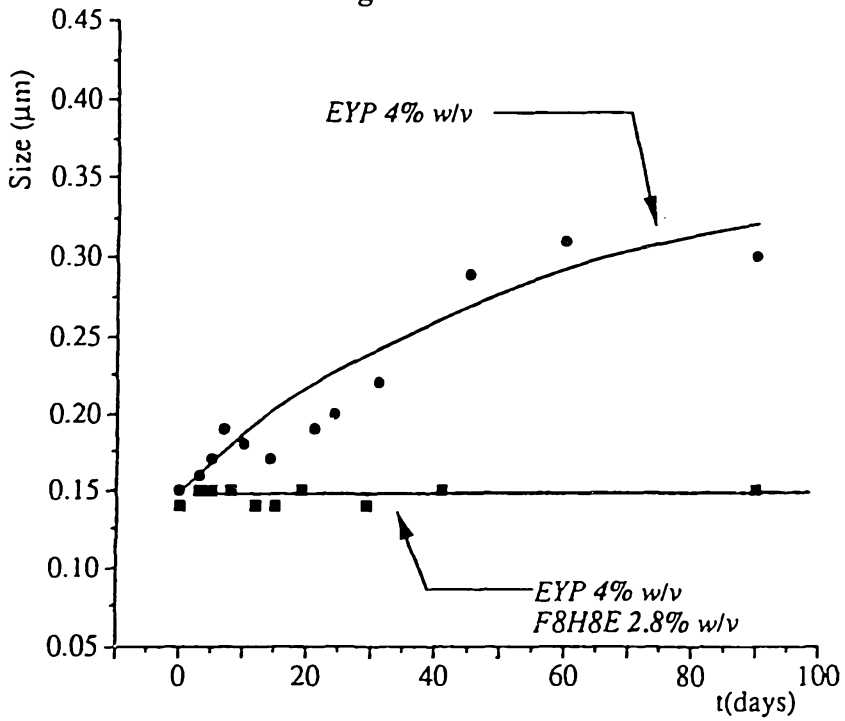


Figure 8

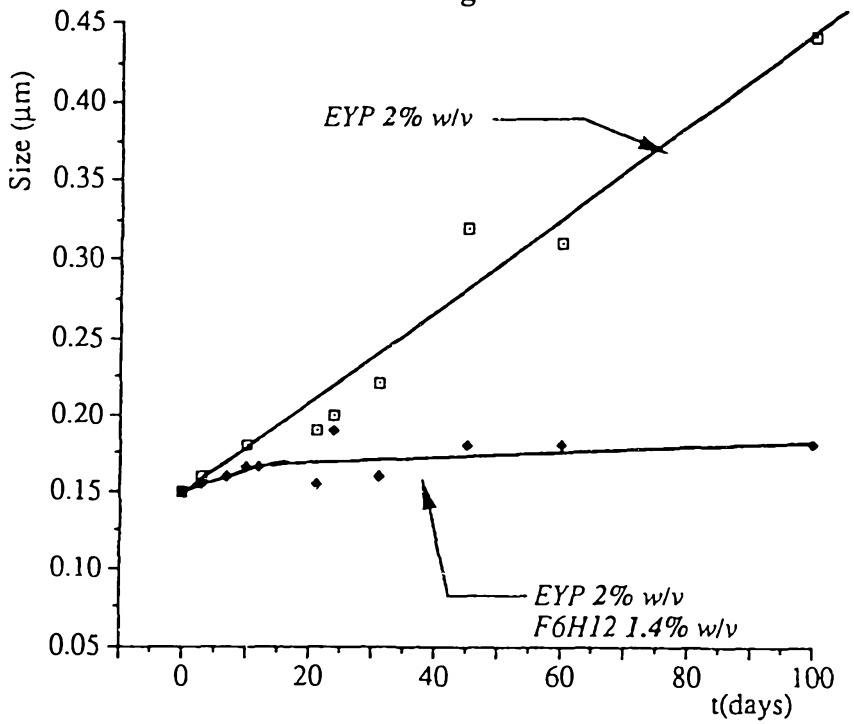
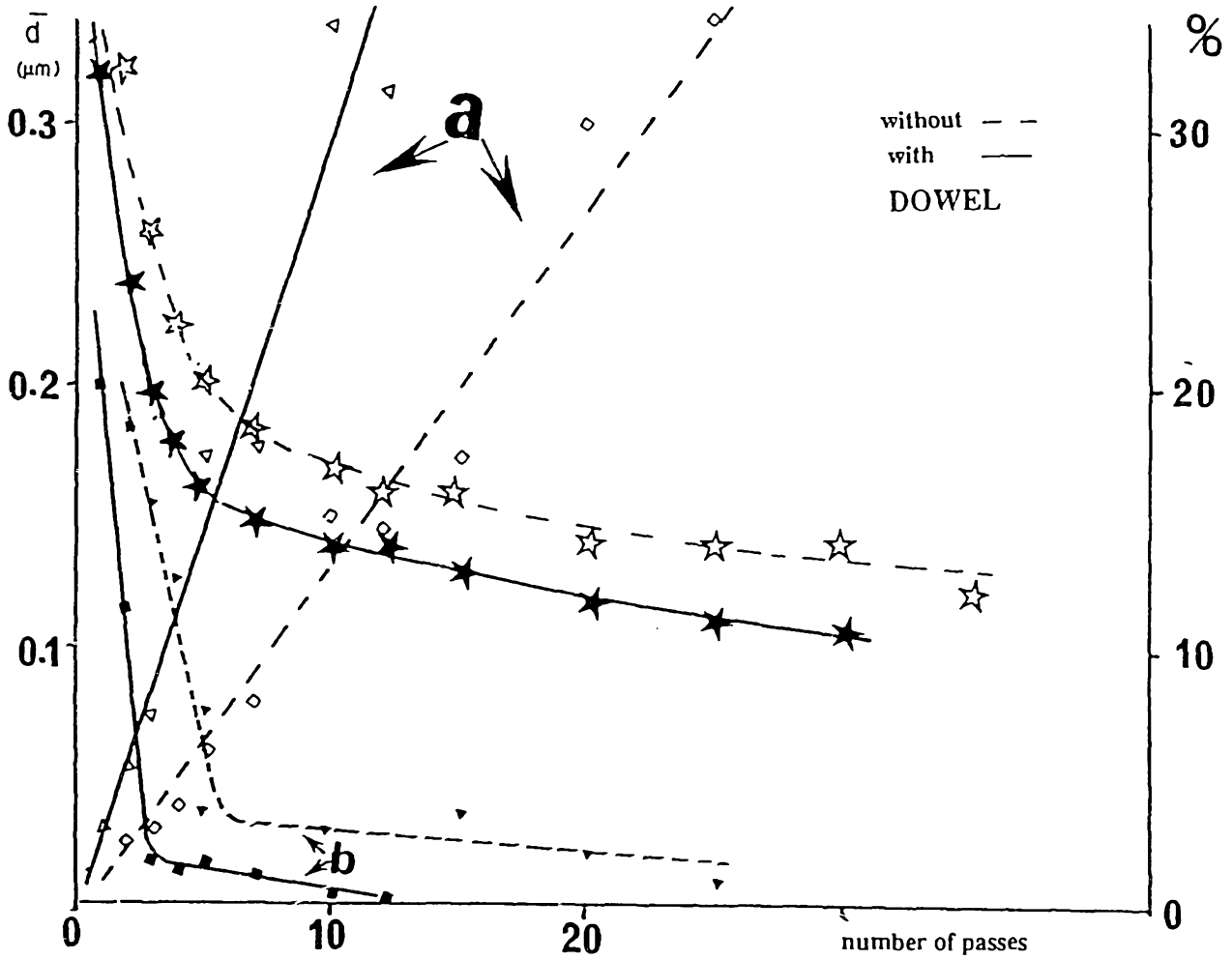


Figure 9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INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01597

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00; A61K9/107

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,9 100 110 (D.LONG) 10 January 1991 see claims 1,4,10,13-15,19,21 see page 9, line 11 - line 17 see page 9, line 29 - page 10, line 35 see page 11, line 8 - line 12 see page 11, line 20 - line 24 see page 12, line 7 - line 8 see page 13, line 15 - line 25 see page 17, line 20 - line 24	1-4,10, 12-15, 19-21, 23-27
X	EP,A,0 196 776 (I.S.C. CHEMICALS LTD.) 8 October 1986 see claims 1-3,5-7 see page 4, line 3 - page 5, line 22	1,20,24

° Special categories of cited documents :[10]

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 OCTOBER 1992	09. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201597 SA 62292

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP-A-0196776	08-10-86	GB-A,B 2171330	28-08-86
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