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POTENTIAL BLOOD SUBSTITUTES SYNTHESIS AND MICROEMULSIFICATION
OF MIXED HYDROGENATED AND FLUORINATED OILS

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ABSTRACT

A synthetic method for preparation of mixed hydrogenated and fluorinated oils of general formula $R_F-CH_2-CH=CH-R_H$ in which the fluorinated and hydrogenated parts could be altered at will is described. For the first time, fluorinated oils which have a high capacity for oxygen have been microemulsified using a hydrogenated surfactant (ionic or non-ionic), opening new perspectives for the production of blood substitutes.

INTRODUCTION

Perfluorinated compounds have been widely used as blood substitutes for a variety of reasons : lack of availability of matched blood (large demand, geographical isolation, refusal to accept transfusion (Jehovah's Witnesses) or in organ banks, etc..).

Various fluorinated derivatives have been developed that have both a high capacity for absorbing oxygen, and are rapidly eliminated from the organism. The best known are perfluoro-decahydronaphtaline (F-decaline) and perfluorotripropylamine (F.T.P.A.). However, when injected intravenously in the pure state, these

substances lead to the formation of emboli. They must, therefore, be administered as emulsions of the oil in water type (Fluosol-DA) using emulsifying agents such as Pluronic F-68 (polyoxyethylene/polyoxypropylene polymer, MW = 8350) or egg yolk phospholipids. Fluosol-DA has been employed in human studies, and appears to be a good blood substitute, although it has to be kept refrigerated, as its long term stability is low.

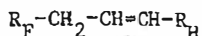
One way around this problem would be to use a microemulsion of the oil in water (O/W) type. Microemulsions have the double advantage of spontaneous formation and good long term stability⁽¹⁾.

However, in order to form a microemulsion from a perfluorinated oil such as F-decaline, fluorinated surfactants are required. This due to the segregation between the fluorinated and hydrogenated chains, which has been described by Mukerjee⁽²⁾. This is true for both aqueous^(3,5) and non-aqueous media⁽⁶⁾. Various examples of surfactants of general formula R_FCOONa ^(3,4) or $R_F(OCH_2CH_2)_nOH$ ⁽⁵⁾ have been described for the preparation of microemulsions from fluorinated oils. These molecules are eliminated slowly from the organism and liberate toxic fluoride ions, and so they cannot be employed as blood substitutes. At the present time, only hydrogenated (non-ionic or amphoteric) surfactants types are biocompatible.

We report here a synthetic method for preparation of mixed hydrogenated and fluorinated oils in which the fluorinated and hydrogenated parts could be altered at will. For the first time, these fluorinated oils which have a high capacity for oxygen have been microemulsified using a hydrogenated surfactant (ionic or non-ionic) opening new perspectives for the production of blood substitutes.

RESULTS AND DISCUSSION

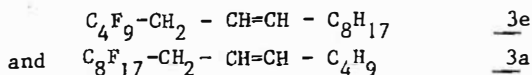
We opted for the following type of molecule :



A Wittig reaction for fluoroalkylation carried out in a solid-liquid

and we have, therefore, included it in the followins studies for comparison (Table 2).

We chose molecules of different degrees of fluorination and different chain lengths :



The results presented in Table 2 show that :

- i) The partially fluorinated oils have a good capacity for absorbing oxygen, similar to that of blood, although less than that of F-decaline. The degree of fluorination seemed to have little effect on oxygen solubility.
- ii) The surface tensions of these compounds were lower than that of F-decaline, especially for the more highly fluorinated compound 3a. It is likely that these oils are sufficiently volatile to be

TABLE 2

Comparison of mixed hydrogenated/fluorinated oils with F-decaline

	Blood	F-decaline	3e	3a
Solubility of O ₂ 37°C, ml/100ml	20.6 ^x	40.3 ^x	25 ^{xx}	25 ^{xx}
surface tension 37°C mN/m		19.7 ^{xxx}	18.8 ^{xxx}	15.5 ^{xxx}

^x literature value (9)

^{xx} measured using a Clark electrode. The electrode is immersed in KCl solution, separated from the test substance by a membrane that is permeable only to oxygen. The oxygen concentration at equilibrium is recorded.

^{xxx} measured using an automatically equilibrating surface tensiometer (Prolabo).

rapidly eliminated from the organism. However, we did not carry out a toxicity study as they are insoluble in DMSO, which is the solvent used for intraperitoneal injections. Toxicity studies using microemulsions prepared from these oils are planned.

Preparation of microemulsions from oils of type $R_FCH_2CH=CHR_H$ using hydrogenated surfactants

i) - Using cetyltrimethylammonium bromide

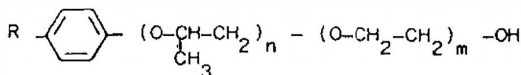
The first attempts to prepare microemulsions from these partially fluorinated oils used cetyltrimethylammonium bromide (C.T.A.B.) as surfactant and 1-butanol as cosurfactant. These agents are known for their ability to form microemulsions from hydrogenated oils (both oil-in-water O/W, and water-in-oil W/O types) (1).

We used a C.T.A.B./butanol ratio of 1/2 which is widely used for hydrogenated oils. The results were encouraging as we obtained two microemulsion regions A and B in the phase diagram of $C_8F_{17}-CH_2-CH=CH-C_4H_9$ (Figure 1).

All measurements were carried out at 37°C. The two zones A and B come closer together as the R_F chain length is reduced, and as the R_H chain length is increased. For $C_4F_9-CH_2CH=CH-C_8H_{17}$ (Figures 2,3,4 and 5) zones A and B coalesce and the phase diagram resembles that of a totally hydrogenated oil.

All the microemulsions were stable over a period of several months.

This showed that microemulsions could be formed from the mixed fluorinated and hydrogenated oils using hydrogenated surfactants. However, we were keen to use non-toxic and hence non-ionic compounds. We therefore replaced C.T.A.B. with non-ionic surfactants such as :



whose synthesis has been reported in a previous publication (10).

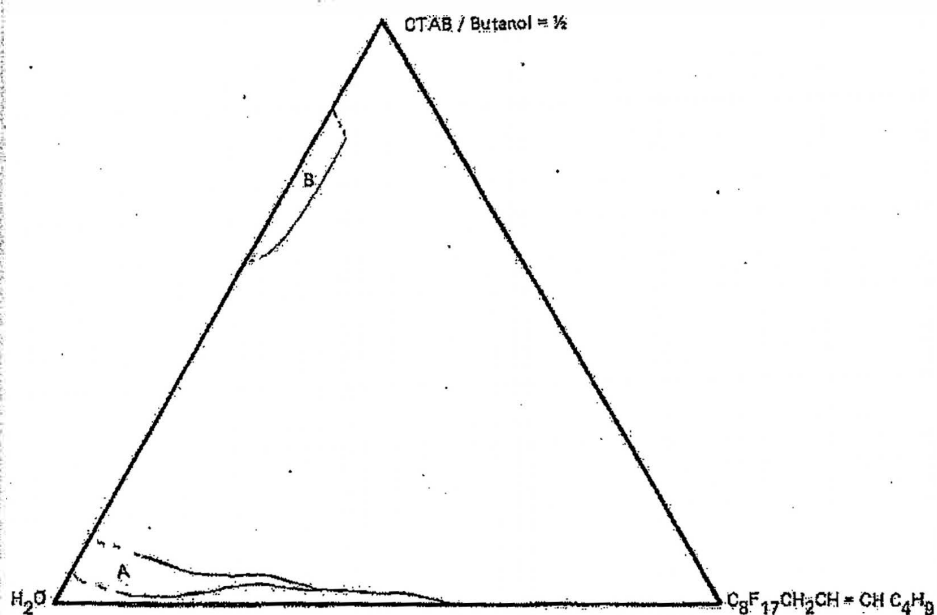


Figure 1. Phase diagram for system
 H_2O , $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}=\text{CHC}_4\text{H}_9$, CTAB/butanol 1/2

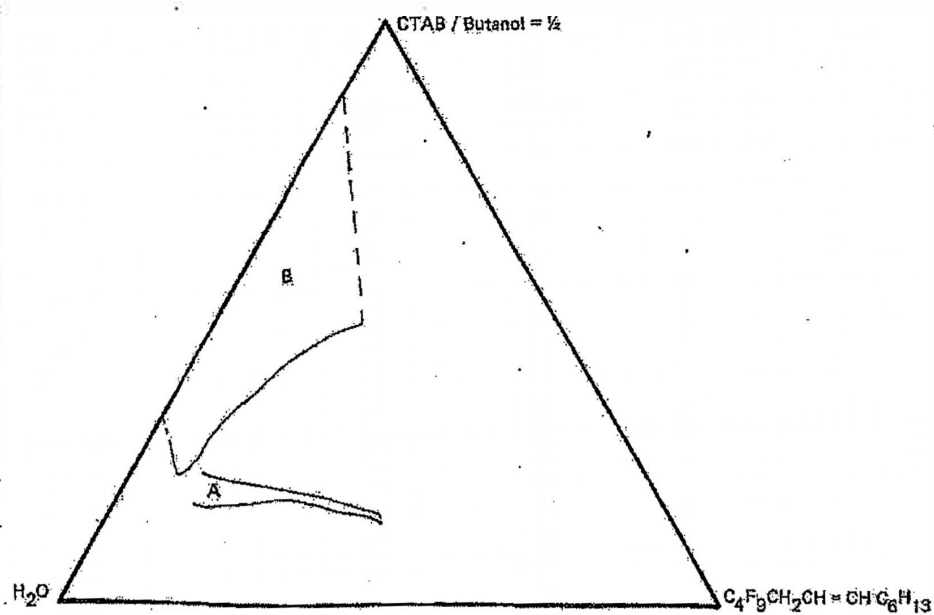


Figure 2. Phase diagram for system
 H_2O , $\text{C}_4\text{F}_9\text{CH}_2\text{CH}=\text{CHC}_6\text{H}_{13}$, CTAB/butanol 1/2

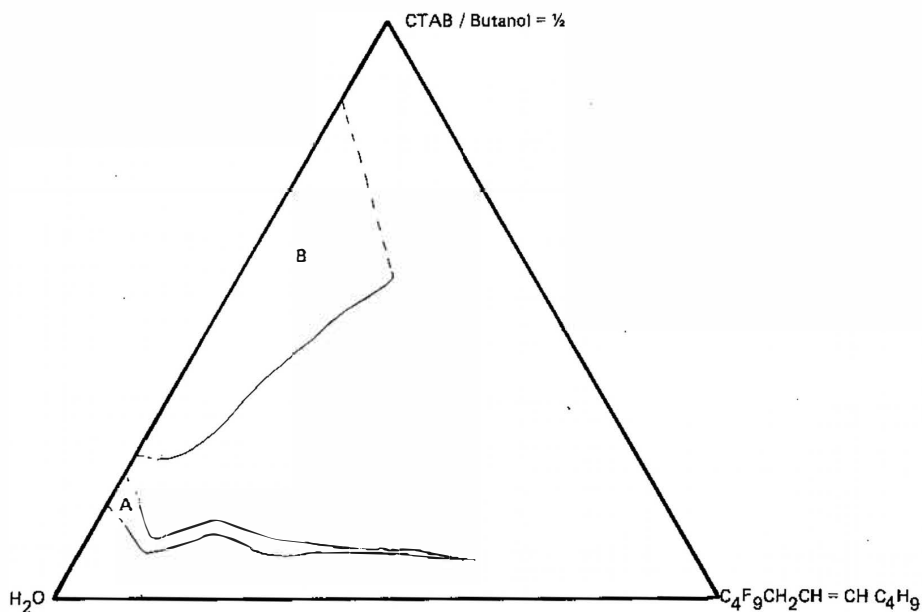


Figure 3. Phase diagram for system
 H_2O , $\text{C}_4\text{F}_9\text{CH}_2\text{CH}=\text{CHC}_4\text{H}_9$, CTAB/butanol = 1/2

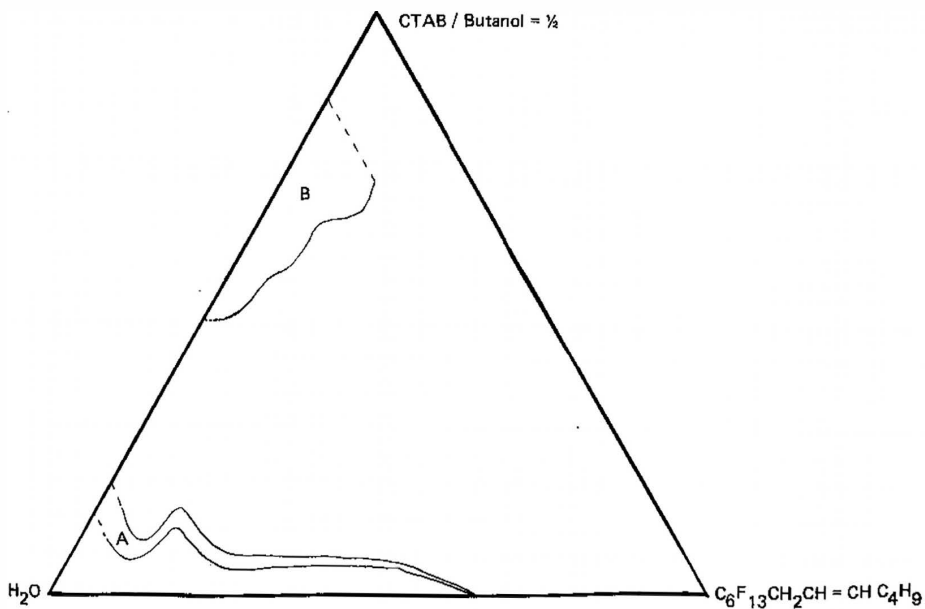


Figure 4. Phase diagram for system
 H_2O , $\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}=\text{CHC}_4\text{H}_9$, CTAB/butanol = 1/2

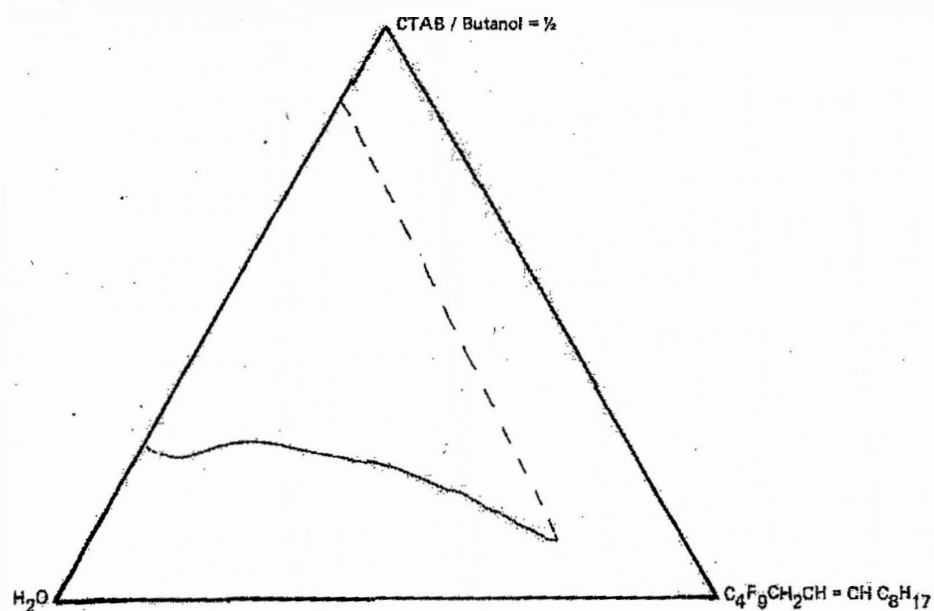


Figure 5. Phase diagram for system
 H_2O , $\text{C}_4\text{F}_9\text{CH}_2\text{CH}=\text{CHC}_8\text{H}_{17}$, CTAB/butanol = 1/2

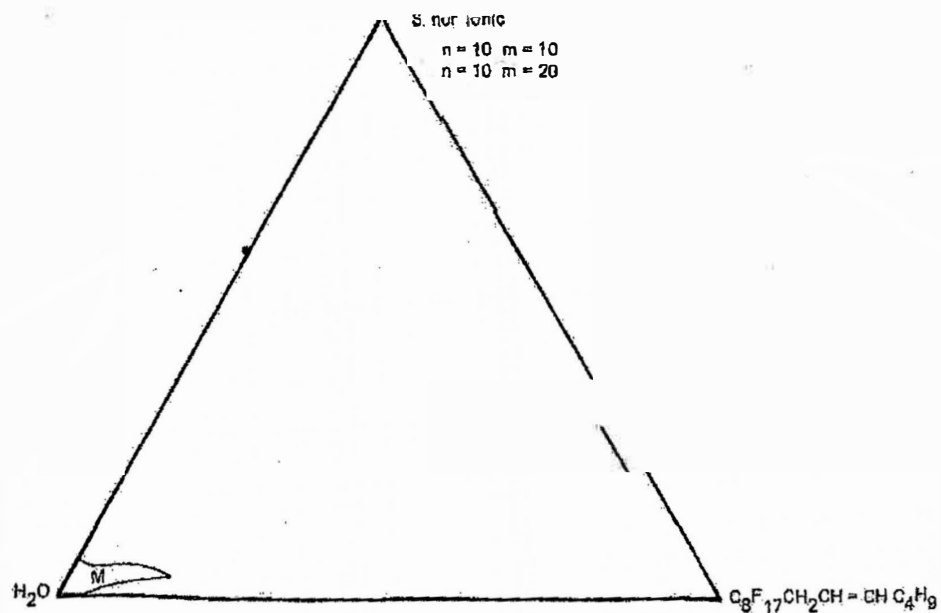
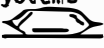
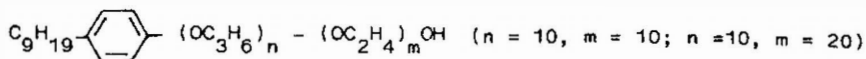


Figure 6. Phase diagrams for systems
 H_2O , $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}=\text{CHC}_4\text{H}_9$, C_9H_{19}  $(\text{OC}_3\text{H}_7)_n - (\text{OC}_2\text{H}_4)_m\text{OH}$
 $(n = 10, m = 10; n = 10, m = 20)$

ii) - Using two non-ionic surfactants



Several trials using the oil $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}=\text{CHC}_4\text{H}_9$ (Figure 6) were carried out. We obtained a small microemulsion zone in the water-rich region without using any cosurfactant. The area of this zone was similar for both surfactants. It is interesting that the microemulsion zone is situated in the water-rich region, where there is very little surfactant (O/W type). It would, therefore, be suitable for use as a blood substitute which has to be diluted in aqueous media.

CONCLUSION

We were able to produce microemulsions from partially fluorinated oils using both hydrogenated ionic and non-ionic surfactants. Since oxygen was found to have a high solubility in these oils, they would be suitable for use as blood substitutes. Mixed fluorinated and hydrogenated oils could be developed with high capacity for oxygen. Microemulsions could be prepared from them using non-ionic high molecular weight surfactants of the Pluronic type, which are currently used in biomedical applications.

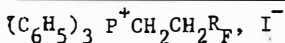
EXPERIMENTAL

A. Synthesis of mixed fluorinated and hydrogenated oils

Proton NMR spectra were recorded on a Varian T 60 apparatus at 60 MHz, and ^{19}F spectra at 90 MHz on a Perkin Elmer R 32. Chemical displacements (δ) are expressed in ppm with respect to TMS as internal standard for ^1H and CF_3COOH for ^{19}F .

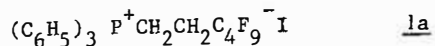
Elemental analyses were carried out by the CNRS microanalysis in Lyon (France). The purity of the synthesized products was $98 \pm 0.3\%$.

A.1. - Preparation of partially fluorinated phosphonium salts 1



General method

0.1 mole of fluoroalkyl iodide $R_FCH_2CH_2I$ (Atochem) and 0.1 mole of triphenyl phosphine were heated and shaken without solvent at 95°C overnight for $R_F = C_4H_9$ and for 6 h for $R_F = C_6F_{13}$, C_8F_{17} . The solid residue obtained was left to cool, washed in toluene and then ether. The white solid remaining was dried under vacuum at 45°C.



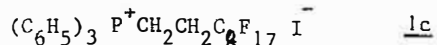
Yield : 95%

NMR 1H CD_3COCD_3 : 2.72 (2p, unresolved, $CH_2 \beta P$) ; 4.00 to 4.57 (2p, m, $CH_2 \alpha P$), 7.66 to 8.33 (15p, m, $(C_6H_5)_3P$).

1b

Yield = 94%

NMR 1H CD_3COCD_3 : 2.63 (2p, m, $CH_2 \beta P$) ; 4.23 (2p, m, $CH_2 \alpha P$) ; 7.40 to 8.40 (15p, m, $(C_6H_5)_3P$).



Yield = 85%

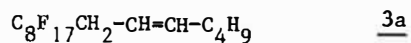
NMR 1H CD_3COCD_3 : 2.73 (2p, m, $CH_2 \beta P$) ; 4.27 (2p, m, $CH_2 \alpha P$) ; 7.67 to 8.37 (15p, m, $(C_6H_5)_3P$).

A.2. - Preparation of mixed olefins 3

Condensation of phosphonium halides 1 with aldehydes

General method

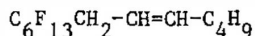
All aldehydes were purchased from Aldrich (95% min. purity) 0.025 mole of fluorinated phosphonium salt, 20 ml of dioxan-1,4 anhydride, 0.02 mole of aldehyde, 0.03 mole of potassium carbonate and $1.67 \cdot 10^{-2}$ mole of water or formamide are placed in a round bottomed flask. The reactants are shaken at 95°C for 2 h. The reaction mixture is then filtered, and the solvent evaporated under vacuum. The residue is taken up in cyclopentane to remove most of the triphenylphosphine oxide. The cyclopentane phase is extracted with water to remove the dioxan, the cyclopentane is evaporated and the residue is distilled under vacuum (10^{-2} mm Hg).



Yield = 55%

NMR 1H $CDCl_3$: 2.4 to 3.2 (2p, split triplet, $CH_2 \alpha F$) ; 5 to 6 (2p, m, $CH=CH$) ; 0.6 to 2.2 (9p, m, C_4H_9).

NMR ^{19}F $CDCl_3$: 7.5 (3f, CF_3), 40 (2f, $CF_2 \alpha CH_2$) ; 48 to 50 (10f, $(CF_2)_5$) ; 53 (2f, $CF_2 \alpha CF_3$).

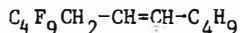


3b

Yield = 35%

RMN ^1H CDCl_3 : 2.4 to 3.2 (2p, split triplet, CH_2) ; 5.2 to 6.2 (2p, m, CH=CH) ; 0.8 to 2.2 (9p, 3M, C_4H_9).

RMN ^{19}F CFCl_3 : 6.5 (3f, CF_3), 39.5 (2f, CF_2 CH_2) ; 48 to 50 (10f (CF_2) $_3$) ; 53 (2f, CF_2 CF_3).

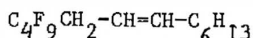


3c

Yield = 23%

RMN ^1H CDCl_3 : 2.3 to 3.2 (2p, split triplet, CH_2) ; 5 to 6 (2p, m, CH=CH) ; 0.6 to 2.2 (9p, 3M, C_4H_9).

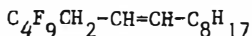
RMN ^{19}F CDCl_3 : 6.5 (3f, CF_3), 40 (2f, CF_2 \propto CH_2) ; 51 (2f, CF_2 CH_2) ; 53 (2f, CF_2 \propto CF_3).



3d

Yield = 30%

NMR ^1H CDCl_3 : 2.4 to 3.4 (2p, split triplet, CH_2) ; 5.2 to 6.1 (2p, m, CH=CH) ; 0.9 to 2.2 (13p, 3m, C_6H_{13}).



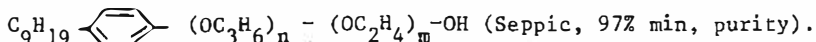
3e

Yield = 60%

NMR ^1H CDCl_3 : 2.4 to 3.2 (2p, split triplet, CH_2) ; 5.2 to 6.1 (2p, m, CH=CH) ; 0.9 to 2.2 (17p, 3m, C_8H_{17}).

B. Determination of monophasic zones in the microemulsions

Surfactants used were cetyltrimethylammonium bromide (C.T.A.B Merck, 99% min. purity) and ethoxylated nonylphenol



Cosurfactants was 1-butanol (Merck, spectroscopy grade, 99/7% min. purity).

Transparency criteria were used to determine the monophasic microemulsion zone on the pseudoternary phase diagram. A visual method was used (11) at a temperature of $37 \pm 0.1^\circ\text{C}$. All systems were stable over a period of several months.

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