

Pseudo-ternary Phase Diagrams of Lecithin-based Microemulsions: Influence of Monoalkylphosphates

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Abstract

The formation of macroscopically homogeneous, stable, fluid, optically transparent, isotropic solutions (microemulsions) was delineated, at 25°C, for systems containing water, soybean lecithin, sodium monoalkylphosphate (hexyl or octyl), alcohol and isopropyl myristate. Six straight or branched alcohols (1-butanol, 2-butanol, isobutanol, 1-pentanol, 2-pentanol, 3-pentanol) were investigated as co-surfactants. A constant lecithin/alcohol mixing ratio was used, while the aqueous phase consisted of a solution of alkylphosphates at different concentrations.

An increase of the microemulsion domain was seen by increasing the concentration of the alkylphosphate. With 0.2 M hexylphosphate, as aqueous phase, the microemulsion domain consisted of a single region, that, in the presence of butylic alcohols, spanned the greater portion of the phase diagram. In the presence of amyl alcohols the area of this region was much smaller. With 0.2 M octylphosphate the realm of existence of the microemulsions, except for 1-pentanol, consisted of two regions separated by a liquid-crystal region. With all the alcohols examined, the liquid-crystal phase solubilized a larger amount of oil in the presence of octylphosphate than in the presence of hexylphosphate.

The stability ranges of microemulsions in systems containing soybean lecithin, alcohol, water, and isopropyl myristate can be greatly increased by using a second hydrophobic amphiphile, such as hexylphosphate, to adjust the hydrophilic-lipophilic balance or the spontaneous peaking properties of lecithin-alcohol systems.

Microemulsions containing naturally-occurring amphiphiles are of considerable interest as potential delivery systems; phospholipids constitute a group of lipids of particular interest in this regard. Lecithin is a naturally-occurring non-toxic and safe material, and attempts to use it as an amphiphile to prepare microemulsions containing pharmaceutically-acceptable oils, such as isopropyl myristate, have been reported (Gallarate et al 1988; Gasco et al 1991).

Pseudo-ternary phase diagrams of water-isopropyl myristate-lecithin systems prepared using a range of short-chain alcohols at several surfactant/co-surfactant mixing ratios have been reported (Aboofazeli & Lawrence 1991, 1993; Attwood et al 1992); these authors found that the size and shape of the isotropic realms was dependent upon both the nature of the co-surfactant and the lecithin/co-surfactant mixing ratio.

Recently, lecithin-based microemulsions containing a second amphiphilic molecule have been used as putative vehicles for drug delivery (Trotta et al 1990; Gallarate et al 1993). A marked increase in the amount of solubilized oil was noted upon addition of monoalkylphosphates.

To elucidate the effect of alkylphosphates on the microemulsification process, the enthalpies of solubilization of butanol in aqueous sodium monoalkylphosphate solutions with or without lecithin were measured (Trotta et al 1993a); the enthalpy values were mainly ascribed to alkylphosphate-butanol interactions. Quantitative relationships of the

critical micellar concentration (CMC) of hexylphosphate in the presence of a series of alcohols with physicochemical properties and structural descriptors of the alcohols could be described (Trotta et al 1993b).

This paper reports the pseudo-ternary phase diagrams of water-isopropyl myristate-lecithin-monoalkylphosphate-alcohol systems, in order to determine the effect of the nature and concentration of the second amphiphilic molecule on the formation of microemulsions.

Materials and Methods

Materials

Soybean lecithin (Epikuron 200) was obtained from Lucas Meyer Co. (Hamburg, Germany) and used without further purification. Isopropyl myristate, 1-butanol, 2-butanol, isobutanol, 1-pentanol, 2-pentanol and 3-pentanol were from Aldrich Chemical Co. (Dorset, UK). Sodium dihydrogen phosphate was from Merck (Darmstadt, Germany). Sodium monoethylphosphate and sodium mono-octylphosphate were prepared from monoalkylphosphoric acid (Brown et al 1955) and recrystallized twice from ethanol. Water was freshly bidistilled.

Methods

The boundaries of the isotropic, liquid crystal and heterogeneous phases were determined at 25°C for a constant value of lecithin/alkanol weight ratio of 1:0.6.

In the phase diagrams, the isotropic phases are designated by the letter L. The subscripts 1 and 2 indicate oil-in-water and water-in-oil microemulsions, respectively. In some cases

L_1 and L_2 regions are connected and there is a single isotropic phase; this phase is denoted L. The liquid crystal phase is designated LC and the heterogeneous phase EM.

Appropriate amounts of lecithin/alcohol mixture and isopropyl myristate were weighed into well-capped glass ampoules. Samples were shaken for sufficient time to attain equilibrium; the three-component mixtures were then progressively enriched with water (added drop by drop) or with water containing 0.1 or 0.2 M alkylphosphate. The amounts of added water (or water containing alkylphosphate) at which transitions occurred were derived from weight measurements. By repeating this experimental procedure for other combinations of lecithin/alcohol to isopropyl myristate weight ratio, the phase boundaries were determined. Cross-polarizers were used to determine the presence of the LC phase.

The phase boundaries reported are accurate to 2–4%.

Results and Discussion

Neither the addition of lecithin alone, nor the addition of an alkanol alone, can efficiently promote the mutual solubilization of water and isopropyl myristate. By adequately mixing water, isopropyl myristate and suitable amphiphilic compounds, such as lecithin plus alcohol, it is possible to obtain stable, single-phase, isotropic systems over a wide range of composition (Fig. 1a–c).

Systems containing lecithin, a double-chain surfactant, would be expected to form lamellar phases by efficient geometric packing (Israelachvili et al 1976; Cornell et al 1986). In the presence of short-chain alcohols, these very weakly amphiphilic co-surfactants would be expected to be partitioned between the phases of the microemulsion. A decrease in the polarity of the polar medium and the incorporation of alcohol molecules in the lipid layer, via an increase in the area per lipid polar group, would produce a change in the hydrophilic/lipophilic balance of lecithin that can be shifted as appropriate to form microemulsions (Shinoda et al 1991).

The pseudo-ternary diagrams of the system 0.2 M sodium dihydrogen phosphate-lecithin-1-butanol (1-pentanol)-isopropyl myristate are reported in Fig. 1. Phase diagrams similar to those obtained in the absence of phosphates were obtained, indicating that the size and shape of the microemulsion realms were not affected by their presence.

The pseudo-ternary diagrams of the systems containing monoalkylphosphates are reported in Figs 1, 2.

The general trend of the changes induced by the presence of hexylphosphate is that the microemulsion realm becomes larger as the monoalkylphosphate concentration increases.

Systems containing 0.2 M hexylphosphate-1-butanol exhibit a single region (Fig. 1b) which covers most of the diagram. The same behaviour is observed in the case of

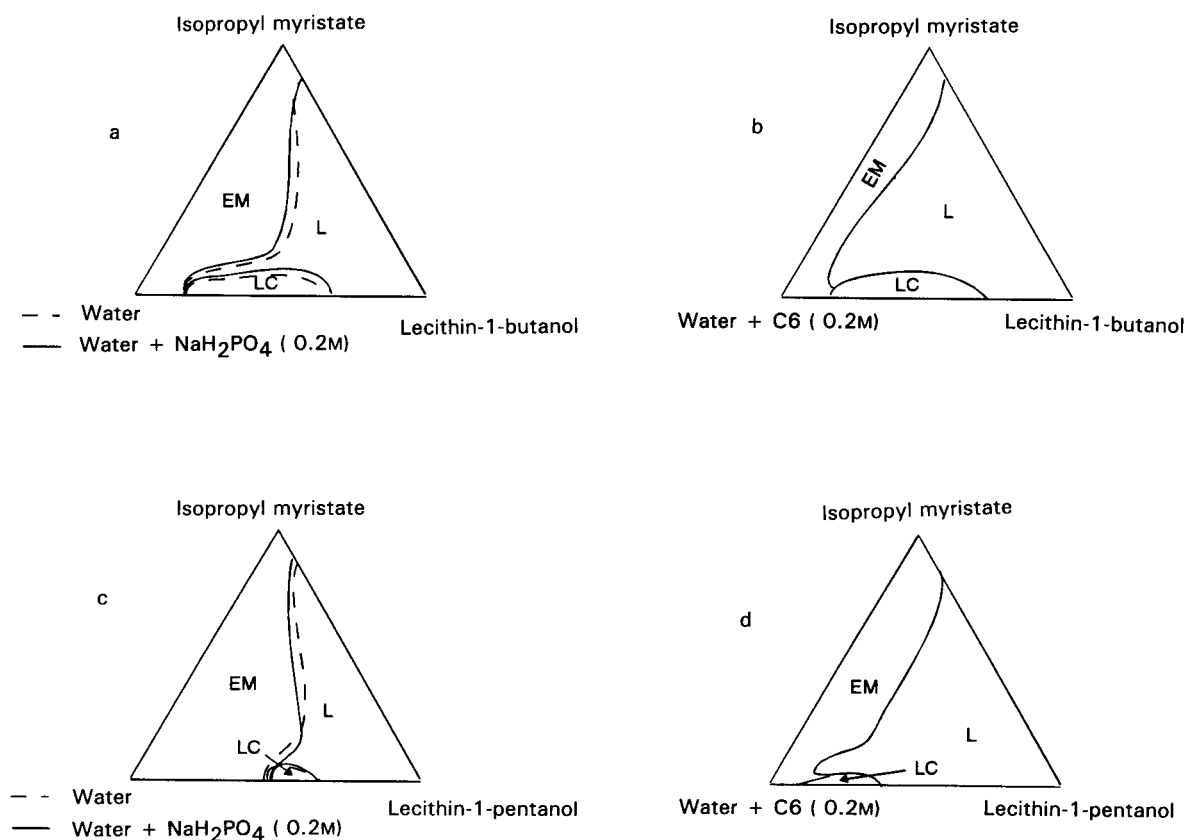


FIG. 1. Pseudo-ternary phase diagrams at constant K_m value of systems. L, isotropic phase; LC, liquid crystal phase; EM, heterogenous new phase.

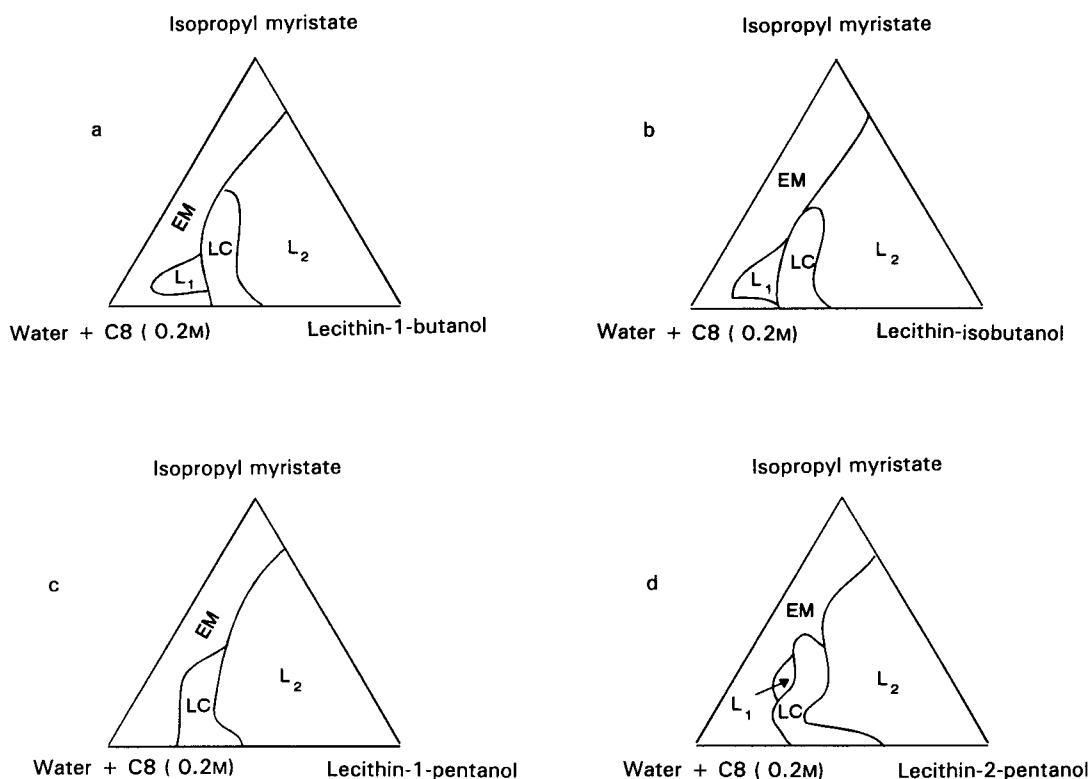


FIG. 2. Pseudo-ternary phase diagrams at constant K_m value of systems. L_1 , oil-in-water microemulsion; L_2 , water-in-oil microemulsion; LC, liquid crystal phase; EM, heterogenous phase.

isobutanol and 2-butanol, indicating that the alcohol isomers are not significantly different in their influence on the microemulsion domain.

The range of formation of isotropic solution is reduced in systems containing 1-pentanol (Fig. 1d) compared with those obtained with butyl alcohols, especially in the water-rich area. In this case the substitution of one amyl alcohol for another (2-pentanol, 3-pentanol) does not induce significant changes in the microemulsion pseudo-ternary domain.

No attempt was made to recognize microemulsion structure at different parts of the microemulsion realm but, owing to the continuity between the water-poor and the water-rich regions, it may be predicted that the microemulsion structure varies greatly, but progressively, as the composition varies.

In contrast, the LC domain of all the systems containing hexylphosphate does not differ fundamentally from that of the systems obtained in the presence of sodium dihydrogen phosphate.

Hexylphosphate is an amphiphilic molecule (Chevalier & Chachaty 1984) with a large hydrophilic head and a relatively small hydrocarbon volume. The partition of this molecule at the interface can affect the curvature of the interface, favouring the formation of the water-rich isotropic phase. Although all the diagrams correspond to only one lecithin/alcohol weight ratio, these results indicate that the effect of hexylphosphate on the microemulsion is high in the water-rich part of the phase diagram. The presence of octylphosphate also increases the formation of monophasic

solutions (Fig. 2), which in all systems containing 0.2 M octylphosphate, except for 1-pentanol, consists of two separate highly asymmetrical areas, L_1 which corresponds to direct solubilization and L_2 , which corresponds to inverse solubilization. The region L_1 varies in shape and extent with alcohol solubility (Hansch et al 1968). As alcohol solubility in water decreases, L_1 first enlarges, becomes maximum in the presence of isobutanol, then shrinks and vanishes in the presence of 1-pentanol, the least soluble of the alcohols studied. The existence of a liquid crystal phase was also seen. Contrary to the case for the LC structures based on lecithin-hexylphosphate, these LC phases solubilized a large amount of oil; a maximum isopropyl myristate percentage of 50% of total weight was reached.

It is difficult to explain the differences observed in the extent of the phases obtained with the two alkylphosphates. The differences in hydrocarbon volume, even if small, should lead to a different location of the alkylphosphates. The formation of a large microemulsion domain, favoured by the presence of hexylphosphate, which is more hydrophilic than octylphosphate, should be principally due to its location in the polar head group region. The influence on the dielectric constant of the medium due to the presence of the negatively charged hexyl derivative should not influence the extent of the microemulsion domain, as the pseudo-ternary phase diagrams obtained in the presence and in the absence of sodium dihydrogen phosphate show.

The LC phase, however, is favoured by octylphosphate, probably because of its larger hydrophobic core and its higher incorporation in the interfacial region.

In conclusion, the stability ranges of microemulsions in systems containing soybean lecithin, alcohol, water and isopropyl myristate can be greatly increased by using a second hydrophilic amphiphile, such as hexylphosphate, to adjust the hydrophilic-lipophilic balance or the spontaneous packing properties of lecithin-alcohol systems. Of the different alcohols examined as co-surfactants in this study, butyl alcohols were found to have the optimum properties.

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