ELSEVIER

International Journal of Pharmaceutics 143 (1996) 67–73

international journal of pharmaceutics

Phase behaviour of microemulsion systems containing lecithin and lysolecithin as surfactants

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Received 4 June 1996; accepted 1 August 1996

Abstract

Phase diagrams were constructed at 25°C to investigate the phase behaviour of systems containing water, isopropyl myristate, commercially-available soybean lecithin and lysolecithin at different mixing ratios, as surfactant mixture, and alcohol, as cosurfactant. Lysolecithin was obtained by enzymatic hydrolysis from soybean lecithin. The lysolecithin:lecithin mixing ratios were 0.7:1, 1.4:1 and 2.1:1, for the systems containing 1-butanol, and 1.4:1, for the systems containing 1-propanol or ethanol. The surfactant/cosurfactant mixing ratios (Km) were 1/2, 1/1 and 2/1 for 1-butanol, 1/1 and 1/2 for 1-propanol and ethanol. A liquid crystalline region was observed only in systems containing 1-butanol at Km 2/1. The stability range of microemulsions containing lecithin was greatly increased by adding lysolecithin. The extension of the microemulsion domain was very dependent upon the nature of the cosurfactant and on the lysolecithin:lecithin and surfactant/cosurfactant mixing ratios. Infinitely dilutable microemulsions were obtained using 1-propanol or ethanol.

Keywords: Lysolecithin; Microemulsion; Cosurfactant; Phase diagram

1. Introduction

Microemulsions are thermodynamically stable, clear, isotropic, usually four-component mixtures that contain a surfactant, a cosurfactant, an oil and water.

Recently microemulsions have attracted considerable interest as putative drug delivery systems. A great deal of dosage-form development activity has focused on the use of microemulsions as oral delivery systems (Kovarik et al., 1994; Constantinides et al., 1995). Furthermore, microemulsions have shown themselves to be effective ways of delivering active ingredients transdermally for both pharmaceutical and cosmetic applications (Gasco et al., 1990).

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PII S0378-5173(96)04688-1

Lecithin, a naturally-occurring surfactant, is attracting increasing interest as a component of microemulsions, due to its low toxicity, and numerous studies have reported it to solubilize pharmaceutically-acceptable oils, in the presence of short chain alcohols, alkanoic acids, amines and glycols (Aboofazeli et al., 1994). The possibility of using a second amphiphilic molecule in formulating microemulsions, though, has received very little attention.

In a previous study, we examined the stability ranges of microemulsions containing soybean lecithin, alcohol, water, isopropyl myristate and a second amphiphilic molecule, such as hexylphosphate (Trotta et al., 1995): the extension of the microemulsion domain increased markedly.

Lecithin itself is unstable, so that associated degradation products may also be present. Two main degradation mechanisms are involved: oxidation of the acyl chains at unsaturated sites or hydrolysis at the polar head, especially in the presence of water. The latter mechanism gives rise to mono acyl(lyso) derivative or, ultimately, the corresponding glycerophosphoryl compound.

The amount of lyso derivatives was found to increase after heat sterilization of large-volume parenteral emulsions containing lecithin (Kemps and Crommelin, 1988); from the physical standpoint, the particle size of the disperse phase droplets remained unchanged or decreased after sterilization (Lee and Groves, 1981; Hansrani et al., 1983). There is some evidence that the stability of these emulsions is enhanced on sterilization.

Lysolecithins are amphiphilic molecules: the critical micellar concentrations are very low. The phase diagrams of lysolecithin/water systems (Arvidson et al., 1985) show that, at room temperature, the isotropic micellar solution is followed, with decreasing water content, by a hexagonal phase, a cubic phase and lamellar phase. In general, the lysolecithins seem to behave similarly to many soaps and detergents.

The aim of the present study was to investigate whether lysolecithin, used as a second hydrophilic amphiphile, would allow microemulsion formation with the surfactant lecithin, in the presence of short chain alcohols.

2. Materials and methods

2.1. Material

Soybean lecithin (Epikuron 200®, phosphatidylcholine content > 94%) was obtained from Lucas Meyer (Hamburg, G) and used without further purification. Isopropyl myristate (IPM), ethanol, 1-propanol and 1-butanol were from Aldrich Chemical Co. (Dorset, UK).

Lysolecithin was prepared by the action of an aqueous solution of phospholipase A_2 (Sigma, Dorset, UK) on an ethereal solution of Epikuron 200®, and purified as described by Perrin and Saunders (1960). The crystallized product had a purity (Sheely et al., 1987) of $96 \pm 1\%$; the major impurity was lecithin.

All other chemicals were reagent grade and were used as received. Water was freshly bidistilled.

2.2. Construction of pseudo-ternary phase diagrams

To investigate the microemulsion regions, phase diagrams were constructed titrating a series of surfactant/cosurfactant-IPM mixtures with water at 25°C.

The boundaries of the microemulsion domain were determined for different values of the surfactant/alcohol weight ratio (Km). Kms of 2/1, 1/1 and 1/2 were used in the case of 1-butanol, while Kms of 1/1 and 1/2 were used for 1-propanol and ethanol. The lysolecithin:lecithin (surfactant mixture) weight ratio was 0.7:1, 1,4:1 or 2.1:1 for the systems containing 1-butanol and 1.4:1 for 1-propanol and ethanol.

Appropriate amounts of lecithin/alcohol or surfactant mixture/alcohol and IPM were weighed into glass ampoules. Samples were shaken for sufficient time to attain equilibrium and then progressively enriched with water (added drop by drop). The amounts of added water at which transition occurred were derived from weight measurement. By repeating this experimental procedure for other combinations of lecithin/alcohol or surfactant mixture/alcohol to IPM weight ratio, the phase boundaries were determined.

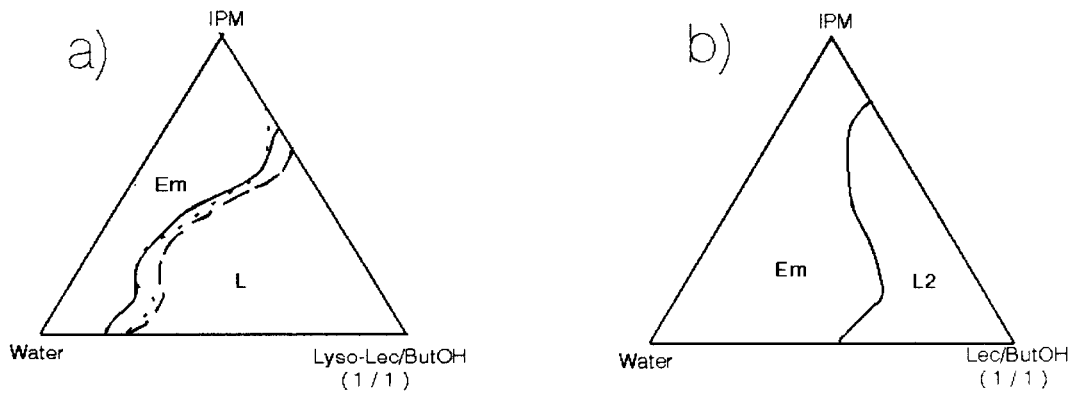

Fig. 1. Phase diagrams of systems containing IPM/water/surfactant/ButOH at a Km of 1/1, a) lysolecithin:lecithin weight ratio 0.7:1 (●●●); 1.4:1 (—); 2.1:1 (- - -); b) lecithin.

The microemulsion domain was determined by visual observation for transparency; the presence of liquid crystalline mesophase structures, designated LC, was determined by using cross polarizers.

The L2 regions, indicated in the phase diagrams for low water-content mixtures, were fluid isotropic w/o microemulsions. Systems exhibited a single isotropic phase, which spanned a great part of the pseudo-ternary diagrams continuously, from the region of water-poor compositions to the region of water-rich compositions, were designated as L region, although at low oil contents (below 15%) it would not be unreasonable to assume the presence of oil droplets, i.e. oil-in-water microemulsions.

Light-scattering measurements were carried out at 25°C using a Malvern light-scattering photometer model PCS 100 and an angle of 90°. The solutions were clarified prior to examination by pressure filtration through a 0.2 μm millipore filter directly into a cell.

3. Results and discussion

In the presence of water and IPM, lecithin, a double-chain surfactant, forms lamellar phase or reverse microemulsions, over a limited range of composition, because of its geometric packing parameter (Israelachvili et al., 1976; Cornell et al., 1986). A decrease in polarity of the polar medium, and/or the incorporation of cosurfactant molecules into the interfacial film, can reduce the geometric packing parameter of lecithin, via an increase in the area per lipid polar group, allowing the formation of balanced microemulsions (Shinoda et al., 1991). An increase of the microemulsion domain could then be obtained in the presence of weakly amphiphilic cosurfactants (Chew et al., 1988; Aboofazeli et al., 1994). An alternative way to obtain balanced microemulsions would be the partial substitution of lecithin by a more hydrophilic amphiphile, such as lysolecithin.

The lysolecithin used in these experiments was not chemically homogeneous, but a mixture originating from soybean lecithin treated with phospholipase A_2. Therefore the influence of the acyl-chain structure on the phase diagrams could not be elucidated.

Fig. 1a shows the pseudo-ternary phase diagrams of systems containing water/IPM/lecithin:lysolecithin/1-butanol at Km 1/1 and lysolecithin:lecithin at mixing ratios of 0.7:1, 1.4:1 and 2.1:1.

No attempt was made to recognize microemulsion structures in different parts of the microemulsion realm but, owing to the continuity between the water-poor and the water-rich

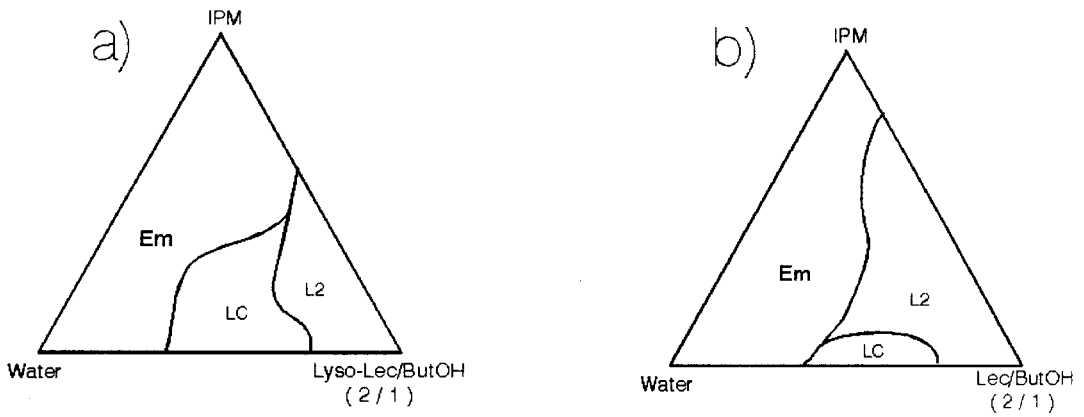

Fig. 2. Phase diagrams of systems containing IPM/water/surfactant/ButOH at a Km of 2/1, a) lysolecithin:lecithin weight ratio of 1.4:1; b) lecithin.

regions, it may be predicted that the microemulsion structure will vary greatly, but progressively, as the composition varies over such a wide range.

As the lysolecithin:lecithin ratio increased, the L region first enlarged, achieving its maximum extension at a ratio 1.4:1, then shrank as it neared a ratio 2.1:1. The L phase was shifted towards the aqueous corner, and contained low surfactant concentrations, and a higher concentration of solubilized oil. The phase diagrams show that it is possible to form microemulsions over a wider range of compositions in the presence of lysolecithin.

As can be seen from the phase diagram (Fig. 1b), the microemulsion region was drastically reduced in the absence of lysolecithin.

The explanation for the differences in the phase diagrams might be ascribed to the increased hydrophilicy of the surfactant mixture, with a reduction of the effective geometrical packing parameter of the lecithin, producing more balanced microemulsions. It is well established that the nature of the surfactant aggregate is governed by the ratio between hydrophobic volume, head group area and hydrocarbon tail length of the surfactant molecule (Israelachvili et al., 1976); the spontaneous curvature of the surfactant is determined by this ratio. For lecithin, the large hydrophobic volume relative to the head group area, and the increase of the effective hydrocarbon volume due to the penetration of oil into the surfactant chain, favour the formation of inverse microemulsions. The increase in head group area and the decrease in the hydrocarbon volume in the presence of lysolecithin molecules at the interface led to the formation of direct microemulsions, by affecting the spontaneous curvature of the surfactant.

For the same reason, the L region became even smaller towards the oil corner as the lysolecithin:lecithin ratio increased. At Km 1/1 the LC phase was not present.

At Km 2/1 (Fig. 2), the existence of a LC phase in the surfactant-rich, oil-poor, part of the phase diagram considerably reduced the extent and altered the appearance of the L2 region; the extent of the LC region in the presence of lysolecithin (Fig. 2a) was greater than in it absence (Fig. 2b).

In general, the number of cosurfactant molecules positioned at the interface reduces as Km increases (Aboofazeli and Lawrence, 1993); thus, the increased rigidity of the interface causes the LC phase to extend. It would appear that, by increasing the area per lipid polar group, and thus changing the spontaneous curvature of the lipid layer from being curved toward water to becoming more planar, lysolecithin would increase the stability of the LC phase.

It is known that liquid crystalline mesophases could be destroyed by adding short chain alco-

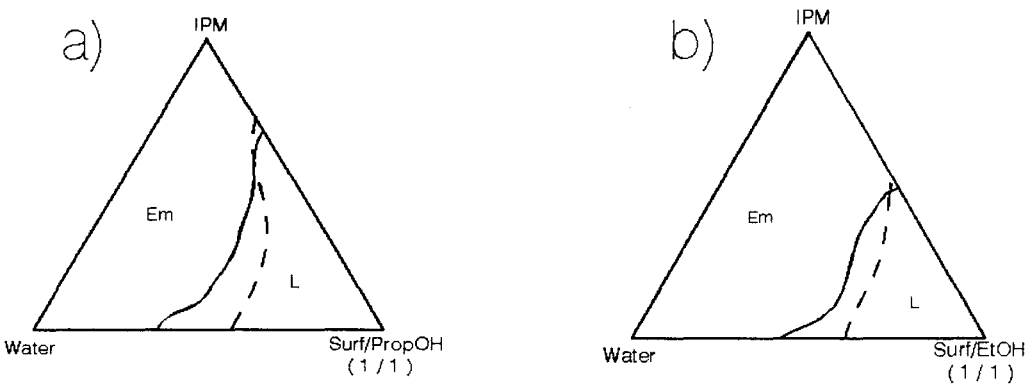

Fig. 3. Phase diagrams of systems containing IPM/water/surfactant/alcohol at a Km 1/1, a) 1-propanol and lysolecithin:lecithin weight ratio of 1.4:1 (——), lecithin (– – –); b) ethanol and lysolecithin:lecithin weight ratio of 1.4:1 (——), lecithin (– – –).

hols. These cosurfactants promote micellization of the lamellar or the hexagonal phases, by favouring large head groups. Friberg and Kayali (1991) have pointed out that triglyceride microemulsions could be obtained by forming a liquid crystalline phase, which is destabilized by the addition of suitable compounds. Such behaviour of the LC phases was obtained by decreasing the Km ratio; butanol destroyed these structures and isotropic properties were detected at Km lower than 2/1 over a wide range of compositions.

At Km 1/2, the extent of the microemulsion domain was drastically reduced, whether in the presence or not of lysolecithin (data not reported). Although the diagrams correspond to limited ranges of variation of the surfactant/cosurfactant weight ratio, Figs. 1 and 2 show that the microemulsion domains were highly sensitive to the Km. The patterns of the modification undergone by the microemulsion pseudo-ternary domains obtained in the presence of lysolecithin indicate that, to enlarge the microemulsion domain, the optimum value of Km was about 1/1.

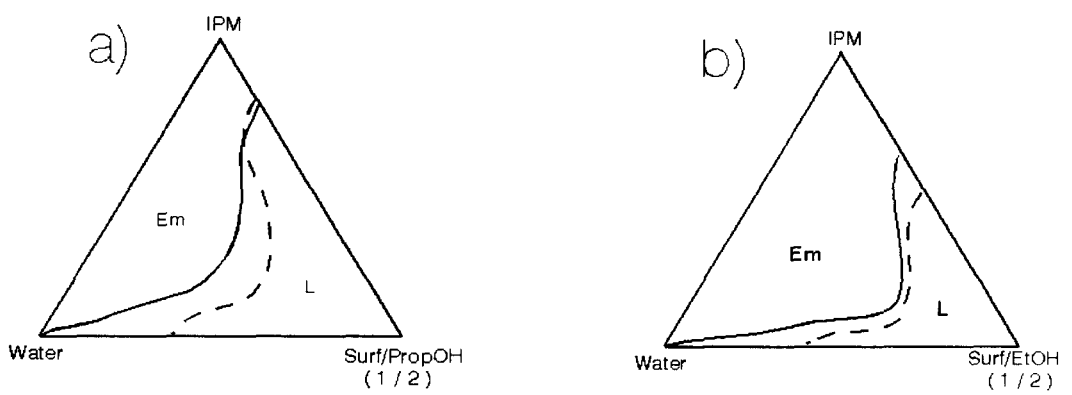

Fig. 4. Phase diagrams of systems containing IPM/water/surfactant/alcohol at a Km 1/2, a) 1-propanol and lysolecithin:lecithin weight ratio of 1.4:1 (——), lecithin (– – –); b) ethanol and lysolecithin:lecithin weight ratio of 1.4:1 (——), lecithin (– – –).

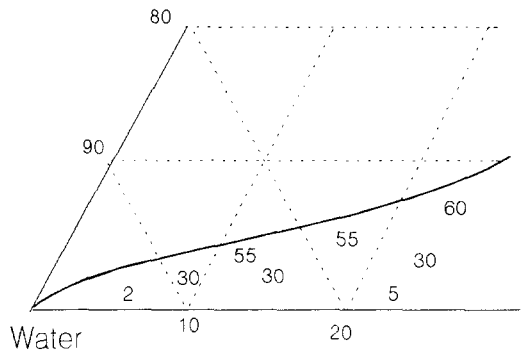

Fig. 5. Mean droplet diameters (nm) of systems containing IPM/water/PropOH (Km 1/2)/lysolecithin:lecithin weight ratio of 1.4:1.

The phase diagrams for systems containing 1-propanol and ethanol at Km 1/1 are depicted in Fig. 3. The effectiveness of alcohols as cosurfactants also depends on the extent of their distribution in the interface. The hydrophilic 1-propanol and ethanol would be expected to distribute mainly in the aqueous phase, whereas the more hydrophobic butanol is expected to partition preferentially in the interfacial layer. Due to the increased number of butanol molecules at the interface, less alcohol was necessary to adjust the geometric packing of surfactant in the interface, to facilitate the formation of balanced microemulsions. Besides this, the microemulsion region in the phase diagrams was larger when butanol was used as cosurfactant. The more hydrophobic alcohol (1-pentanol) distributed primary in the oil and gave only a narrow L2 region (data not reported).

Stable, clear regions independent of water-content were obtained with 1-propanol (Fig. 4a) and ethanol (Fig. 4b) at Km 1/2 in the presence of lysolecithin. 1-propanol and ethanol reside predominantly in the aqueous phase (the partition of 1-propanol between water and IPM is roughly 95:5); thus, the formation of balanced microemulsions should be due principally to the decrease in the polarity of the polar medium, so that it balanced the properties of the surfactant mixture better, even if some alcohol molecules, especially those of 1-propanol, produced changes in the same direction. The gradual transition from the oil-droplet-in-water continuum to mixed micelles (Fig. 5) might allow the production of infinitely dilutable lysolecithin:lecithin based microemulsions, without the formation of a turbid phase.

In conclusion, the stability range of microemulsions containing lecithin can be greatly increased by using a second hydrophilic amphiphile, such as lysolecithin, to adjust the spontaneous packing properties of lecithin alcohol systems. The extent of the microemulsion domain was very dependent upon the nature of the cosurfactant, the lysolecithin:lecithin mixing ratio and that of the surfactant/cosurfactant. Infinitely dilutable lysolecithin:lecithin based microemulsions can be obtained using 1-propanol or ethanol.

Acknowledgements

This work was supported by a grant from Ministero dell'Università e della Ricerca Scientifica e Tecnologica.

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