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Rapid Communication

Phase studies on oil-in-water phospholipid microemulsions

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Summary

Phase studies on systems composed of egg or soya lecithin, *n*-butanol, isopropyl myristate and water have identified stable, oil-in-water microemulsion regions. The influence of the lecithin/butanol ratio on the area of existence of the microemulsions has been examined.

The high stability, small droplet size, transparency and low viscosity of microemulsion systems has led to considerable interest in their potential as delivery systems for lipophilic drugs. Phosphqlipids are an obvious choice as the emulsifying agent, particularly if the microemulsion is intended for parenteral use and several formulations prepared using these surfactants appear in the patent literature (see, for example, Gauthier and Levinson, 1988). Inspection of such patents, however, reveals that prolonged sonication or microfluidisation is usually required for their preparation. Such systems are clearly not microemulsions in the accepted sense of this term since they do not form spontaneously. The small droplet sizes of true microemulsions are a consequence of the ultralow interfacial tension between the oil and water phases which arises from the presence of co-surfactant molecules which intercalate between the surfactant molecules at the oil/water interface (Prince, 1977). Short-chain alcohols are suitable cosurfactants for use with lecithin since, in addition to their incorporation into the interfacial layer, they also have the effect of making the aqueous phase less hydrophilic so shifting the hydrophilic-lipophilic balance of the lecithin enabling spontaneous microemulsification to occur (Shinoda et al., 1991). A detailed study of the phase behaviour of lecithin-based microemulsions containing *n*-hexadecane as the oil phase and *n*-propanol as the cosurfactant has recently been reported (Shinoda et al., 1991). Aboofazeli and Lawrence (1991) have reported the influence of the nature of the cosurfactant (short-chain alcohol) on the area of existence of water-in-oil microemulsions prepared using isopropyl myristate and lecithin. Other authors (Gallarate et al., 1988; Gasco et al., 1988, 1989, 1990) have investigated drug release from both oil-in-water and water-in-oil lecithin-containing microemulsions but have not reported phase studies on these systems.

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In this study, we have examined the phase properties of an oil-in-water microemulsion reported by Fubini et al. (1988) composed of lecithin (egg or soya), *n*-butanol, isopropyl myristate and water. The influence of the ratio of surfactant to cosurfactant on the area of existence of the oil-in-water microemulsion region has been investigated.

The phospholipids used were egg lecithin, Ovothin 200 (O200) and soya lecithin, Epikuron

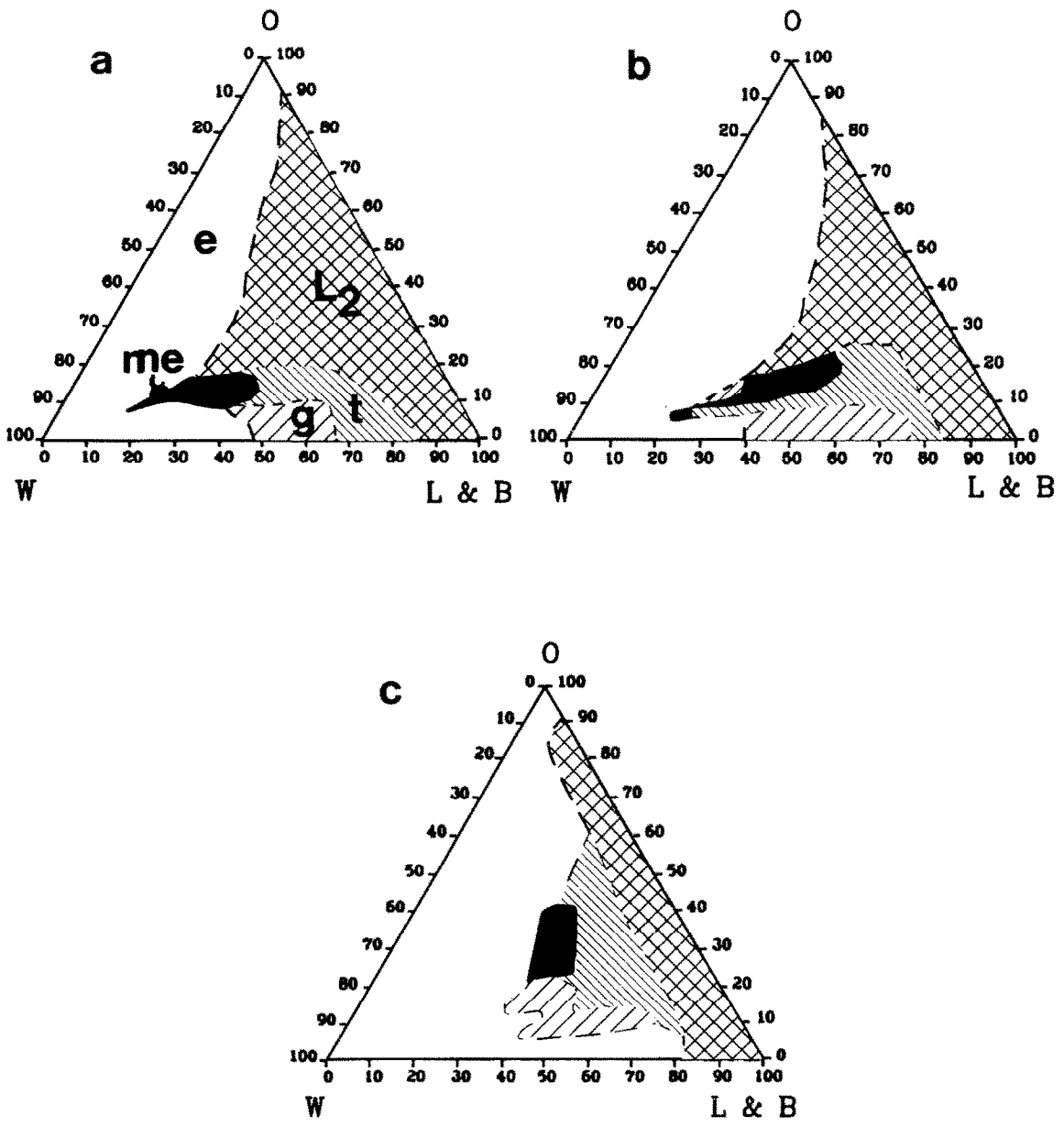

Fig. 1. Partial phase diagrams of the system O200/butanol/IPM/water showing stable oil-in-water microemulsion (me), gel (g), monophasic turbid (t), unstable emulsion (e) and isotropic (L_2) regions, for O200/butanol weight ratios of (a) 1:0.6; (b) 1:0.45 and (c) 1:0.33 O, IPM; W, water; L&B lecithin + butanol.

200 (E200), which contain 94–95% phosphatidylcholine (Lucas Meyer Ltd). Isopropyl myristate (IPM) and *n*-butanol (Sigma Chemical Co.) were used as supplied.

Phase studies were carried out by slowly titrating weighed monophasic mixtures of the phospholipid and cosurfactant in the required ratio, with distilled water. The temperature was maintained at 50°C with continuous stirring. The samples were assessed visually to determine clarity and fluidity. The microemulsion region was identified as a fluid transparent area. Samples with compositions within these areas were stable for up to at least 1 year at room temperature. Clear systems which did not show a change in meniscus after tilting to an angle of 90° were classified as gels. No attempts were made to identify in detail other regions of the phase diagram which have been described only in terms of their visual appearance and stability.

Fig. 1 shows the influence of the O200/butanol weight ratio on the phase properties. As the lecithin content increased with change of ratio from 1:0.6 to 1:0.33, the amount of IPM incorporated into the microemulsion increased from between 8 and 19% by weight (for the 1:0.6 ratio) to between 24 and 42% by weight (for the 1:0.33 ratio). From a formulation viewpoint, the increased oil content obtained with the 1:0.33 ratio may provide a greater opportunity for the solubilisation of poorly water-soluble compounds. It was not possible to form oil-in-water microemulsions with ratios of 1:0.25 presumably because of insufficient cosurfactant to produce adequate lowering of the interfacial tension.

Comparison of Figs 1 and 2 shows the effect of substitution of the egg lecithin by soya lecithin (E200) of approximately the same purity. The oil-in-water microemulsion regions of the two systems with lecithin/butanol ratios of 1:0.6 differed only in that the O200 systems extended over a wider surfactant region (18–42% compared with 22–42% for E200 systems). A greater difference was observed for O200 and E200 systems containing lecithin/butanol ratios of 1:0.45. Microemulsions prepared with E200 had a lower IPM content (3–13% compared with 8–26% for O200 systems) and were formed over a narrower range of total surfactant + cosurfactant concentration (22–42% compared to 20–52% for O200 systems). Such differences illustrate the importance of the nature of the fatty acid impurities in the two types of lecithin in determining the phase behaviour of the systems.

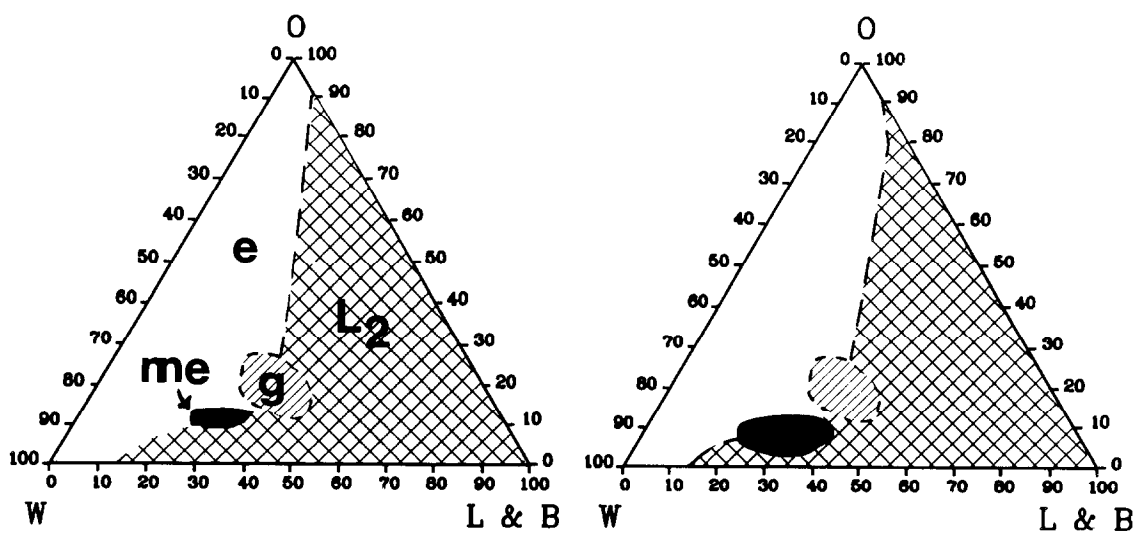

Fig. 2. Partial phase diagrams of the system E200/butanol/IPM/water showing stable oil-in-water microemulsion (me), gel (g), unstable emulsion (e) and isotropic (L_2) regions, for E200/butanol weight ratios of (a) 1:0.6 and (b) 1:0.45. O, IPM; W, water; L&B lecithin + butanol.

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