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Investigations into the formation and characterization of phospholipid microemulsions. III. Pseudo-ternary phase diagrams of systems containing water-lecithin-isopropyl myristate and either an alkanoic acid, amine, alkanediol, polyethylene glycol alkyl ether or alcohol as cosurfactant

R. Aboofazeli [a], C.B. Lawrence [a], S.R. Wicks [b], M.J. Lawrence [a,*]

[a] *Drug Delivery Group, Chelsea Department of Pharmacy, King's College London, London SW3 6LX, UK*
[b] *Pharmaceutical Research and Development Department, Pfizer Central Research, Sandwich, Kent, UK*

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Abstract

The phase behaviour of quaternary systems composed of lecithin/isopropyl myristate/water/cosurfactant, at a lecithin:cosurfactant mixing ratio (K_m) of 1:1 (on a weight basis) have been investigated by the construction of phase diagrams. The lecithin used in this study was the commercially available soybean lecithin, Epikuron 200 (purity greater than 94% phosphatidylcholine) and the cosurfactants examined were either short (alkyl chain length 4–6) straight-chain alkanoic acids, amines, alkanediols, diethylene glycol alkyl ethers or alcohols. With the exception of the amines which appeared to react with lecithin, all the systems showed the area of existence of a stable isotropic region along the surfactant/oil axis (i.e., reverse microemulsion area; L_2). In no case was a second isotropic region (i.e., normal microemulsion area; L_1) observed, although in certain systems a single clear isotropic region covered virtually the whole of the phase diagram and may have included an L_1 region. A liquid crystalline (LC) region was observed only in systems containing either an alkanediol or polyethylene glycol alkyl ether as cosurfactant. It was concluded that the area of existence of the various phase regions was very dependent upon the nature of the cosurfactant used.

Key words: Microemulsion; Soybean lecithin; Phase diagram; Phase behavior; Cosurfactant

1. Introduction

Microemulsions are thermodynamically stable microstructured mixtures containing oil and water stabilized by a surfactant and often a small amphiphilic molecule called a cosurfactant. Recently, microemulsions have attracted considerable pharmaceutical interest as putative drug delivery systems.

With the exception of systems stabilized by a nonionic surfactant (see, for example, Malcolmson, 1992), the majority of microemulsions require for their production the presence of a co-

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[*] Corresponding author.

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surfactant. The most commonly used cosurfactants are simple low molecular weight alcohols such as *n*-butanol; unfortunately, such alcohols are generally considered to be unacceptable pharmaceutically. To date, however, very little work has examined the use of alternative cosurfactants. Other cosurfactants that have been investigated include short straight-chain amines (Ahmad et al., 1974; Venable et al., 1986; Wormuth and Kaler, 1987) and glycol derivatives (Desnoyers et al., 1983; Shinoda et al., 1984; Chew et al., 1988). With the exception of the investigation by Wormuth and Kaler (1987), most of the studies performed to date are limited in the fact that they have only compared the ability of two different types of cosurfactant to form microemulsions. None of the studies have investigated the potential of non-alcohol cosurfactants to produce microemulsions with lecithin. The aim of the present study was to investigate the ability of a number of alternative cosurfactants to allow microemulsion formation with the surfactant lecithin. Although not all the cosurfactants examined are pharmaceutically acceptable, it was hoped that by altering both the nature of the head group and the length of the hydrophobic chain, it would be possible to gain an indication of the physico-chemical properties of the cosurfactants required to produce pharmaceutically acceptable microemulsions stabilized by lecithin.

2. Materials and methods

2.1. Materials

Epikuron 200 (E200, soybean lecithin, phosphatidylcholine content greater than 94%) was obtained from Lucas Meyer (Germany). Isopropyl myristate (IPM) and *sec*-butylamine were supplied by Sigma Chemical Co. (Dorset, U.K.). *n*-Hexanol, 1,2-butanediol, 1,2-pentanediol, 1,2-hexanediol, *n*-butylamine, *n*-pentylamine, *n*-hexylamine, *tert*-butylamine, 2-aminopentane, diethylene glycol monobutyl ether, diethylene glycol monopentyl ether and diethylene glycol monohexyl ether were purchased from Fluka Chemicals Ltd (Glossop, U.K.). 2-Pentanol, 3-pentanol, *n*-hexanoic acid, *n*-pentanoic acid and 3-aminopentane were from Aldrich Chemical Co. Ltd (Dorset, U.K.). All reagents were of the highest purity available and were used without further purification. Triple-distilled water from a well-seasoned, all-glass still was used throughout the study.

2.2. Construction of pseudo-ternary phase diagrams

Phase diagrams were constructed by titration with triple distilled water of a series of three-component IPM-lecithin-cosurfactant mixtures at room temperature, using the method of Aboofazeli and Lawrence (1993).

In order to ensure equilibrium had been achieved, several series of samples were prepared for long-term storage, typically 1 month. Of particular interest were systems near a phase boundary. With the exception of the samples prepared using the straight-chain amines, the results of the long-term stability study agreed with those obtained by titration.

The phase behaviour of the systems investigated was mapped on pseudo-ternary phase diagrams. The top apex of the diagram represents the lecithin/cosurfactant K_m of 1:1 and the other two apices represent oil and water. The regions, L_1 and L_2, indicated on the phase diagrams at low oil and low water content, respectively, were fluid transparent isotropic microemulsions which were stable for a sufficiently long time (i.e., at least a month). Unless indicated, the liquid crystalline (LC) areas were stable for greater than 1 week. Some systems exhibited a clear area extending over most of the possible oil/water/lecithin:cosurfactant combinations, in such cases the clear area was designated a BM (balanced microemulsion). It must, however, be realised that it is unlikely that only one type of phase structure exists over such a wide range of compositions (Rushforth et al., 1986).

3. Results

The pseudo-ternary phase diagrams of systems containing water/IPM and E200 with the different cosurfactants at a mixing ratio (K_m) of 1:1 lecithin : cosurfactant are shown in Fig. 1–5. The pseudo-ternary phase diagrams of the corresponding straight- and branched-chain alcohols at the same K_m are shown in Fig. 6–8; the phase diagrams obtained using *n*-hexanol, 2-pentanol and 3-pentanol are from this study, while those depicting the use of all other alcohol cosurfactants are from the work of Aboofazeli and Lawrence (1993) and are included for purposes of comparison.

3.1. Alkanoic acids as cosurfactant

As can be seen in Fig. 1, the phase diagrams obtained when using either *n*-pentanoic acid or *n*-hexanoic acid as cosurfactant are very similar. An L_2 region is formed over the whole range of possible surfactant/oil concentrations. However, in both cases this L_2 region can solubilize only a small amount of water; a maximum of 20% for *n*-pentanoic acid and 17% for *n*-hexanoic acid. No LC or L_1 region was seen in either of the systems.

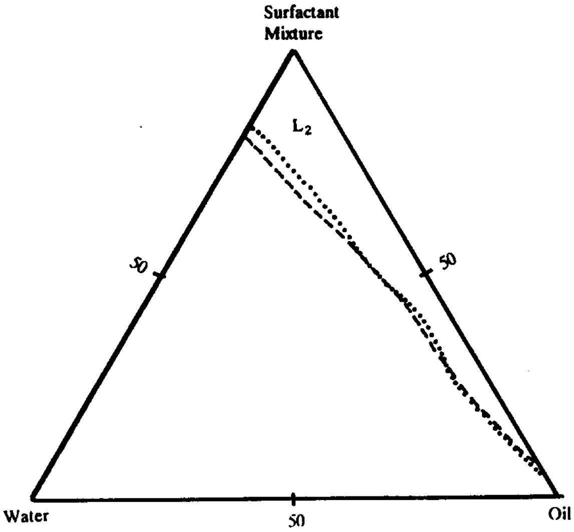

Fig. 1. Phase diagrams of systems containing E200/IPM/water/alkanoic acid at a K_m of 1:1; (dashed line) *n*-pentanoic acid, (dotted line) *n*-hexanoic acid.

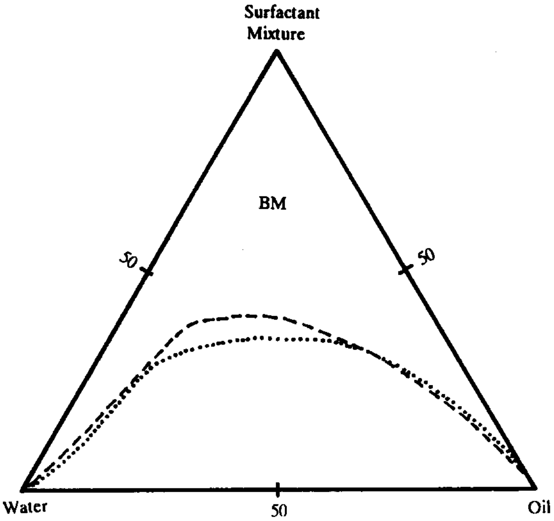

Fig. 2. Phase diagrams of systems containing E200/IPM/water/branched-chain butyl amines at a K_m of 1:1; (dashed line) *sec*-butylamine, (dotted line) *tert*-butylamine.

3.2. Amines as cosurfactant

When either *n*-butylamine, *n*-pentylamine or *n*-hexylamine was used as cosurfactant, a large clear (L_2) region was obtained (data not shown). Although no L_1 or LC region was seen with

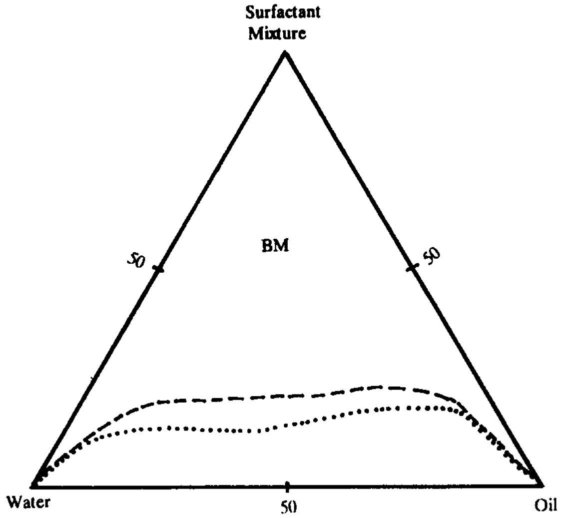

Fig. 3. Phase diagrams of systems containing E200/IPM/water/branched-chain pentyl amines at a K_m of 1:1; (dashed line) 2-aminopentane, (dotted line) 3-aminopentane.

either *n*-butylamine or *n*-pentylamine, *n*-hexylamine exhibited small LC and L_1 areas. Upon standing, samples from the clear L_2 regions, and in the case of *n*-hexylamine the L_1 region, became cloudy and ultimately phase separated. It was not possible to reproduce these phase diagrams as the extent of the clear regions appeared to critically depend upon the rate of titration of the water; a slow titration gave a much smaller L_2 region, suggesting the presence of a reaction in the system. This reaction occurred even in the absence of water as samples containing only oil, surfactant and cosurfactant remained clear for no more than a few hours.

The situation was different when a branched-chain butyl or pentylamine was substituted for a straight-chain amine. Here stable clear regions, independent of the rate of titration, could be obtained. Fig. 2 and 3 illustrate the phase behaviour for systems containing the cosurfactants *sec*-butylamine and *tert*-butylamine and, 2-aminopentane and 3-aminopentane, respectively.

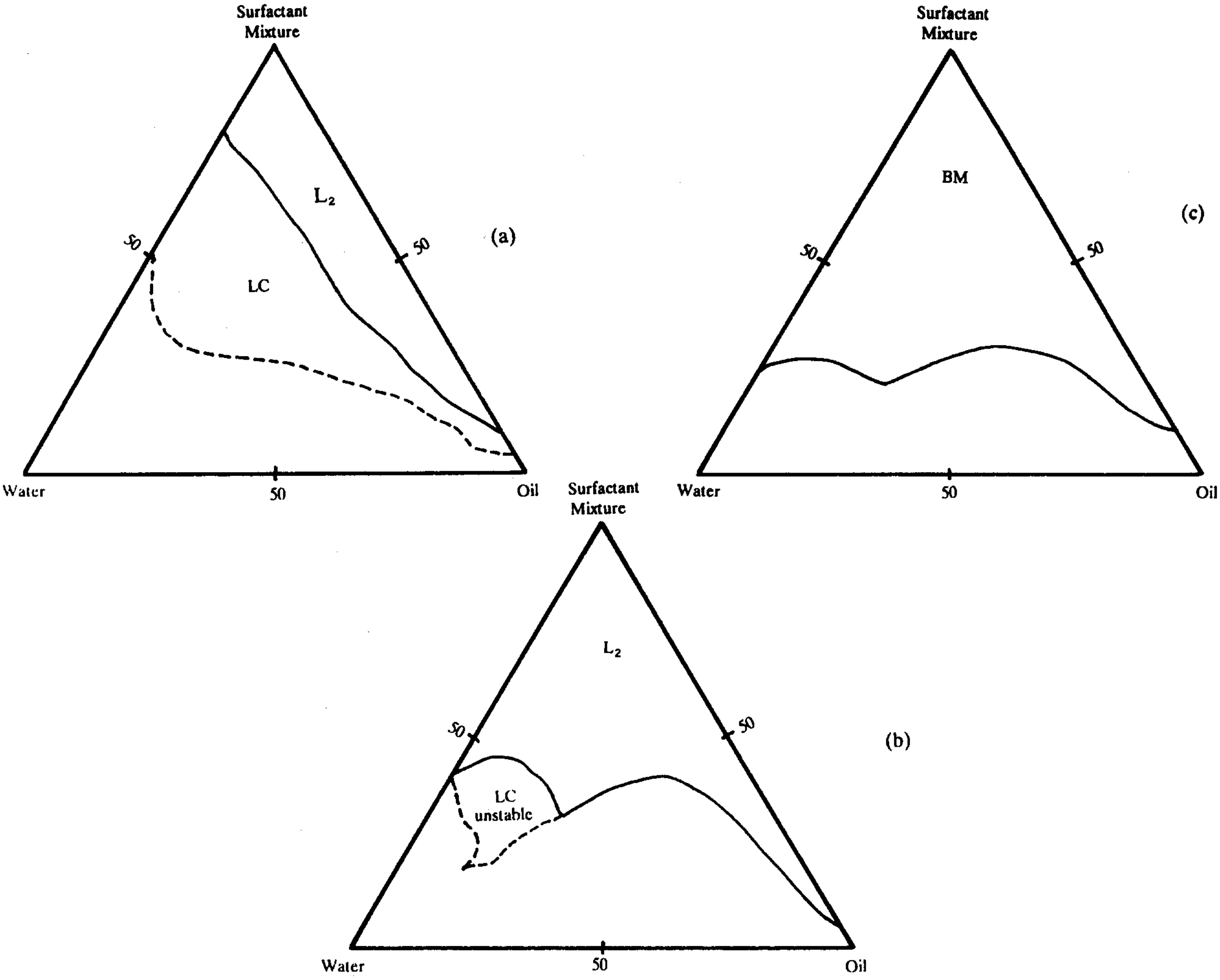

Fig. 4. Phase diagrams of systems containing E200/IPM/water/alkanediols at a K_m of 1:1; (a) 1,2-butanediol, (b) 1,2-pentanediol, (c) 1,2-hexanediol.

The phase behaviour of each pair of amines was very similar. In each of the systems, the existence of a large clear isotropic area over the whole range of surfactant concentrations and in both water and oil rich parts of the phase diagrams is noticeable. The extent of this clear region was significantly larger with the branched-chain pentylamines than the branched-chain butylamines. No LC domain was observed with any of the branched-chain amines. Similarily, no second clear (L_1) region was seen, although at low oil contents (less than about 15%), it would not be unreasonable to assume the presence of oil droplets, i.e., oil-in-water microemulsion. The transition between water droplets (water-in-oil microemulsion; L_2) observed at high oil concentrations to oil droplets (L_1) at high water contents would be expected to occur via bicontinuous microemulsions (Safran et al., 1986). The clear region is thus designated BM.

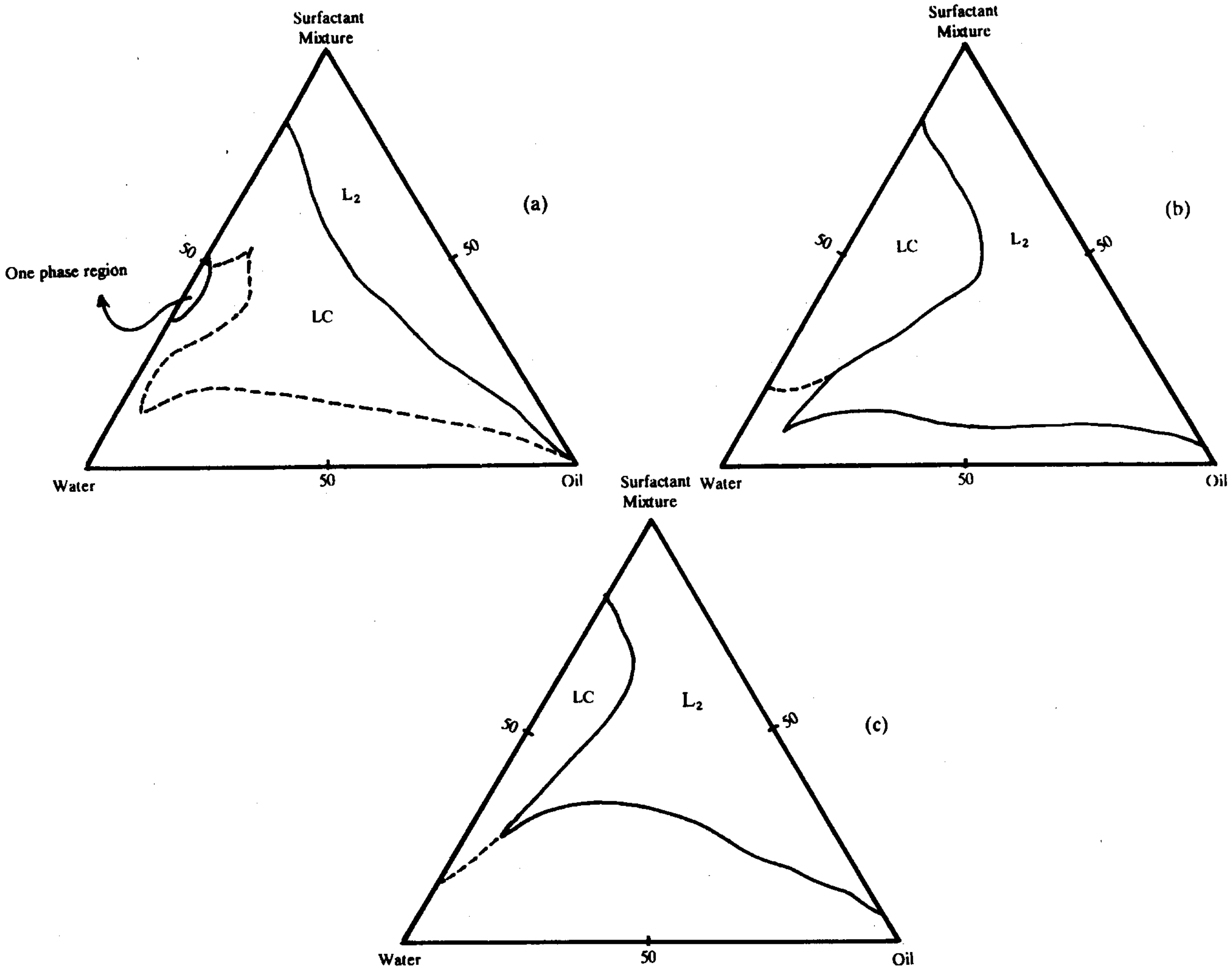

Fig. 5. Phase diagrams of systems containing E200/IPM/water/polyethylene glycol alkyl ethers at a K_m of 1:1; (a) diethylene glycol monobutyl ether, (b) diethylene glycol monopentyl ether, (c) diethylene glycol monohexyl ether.

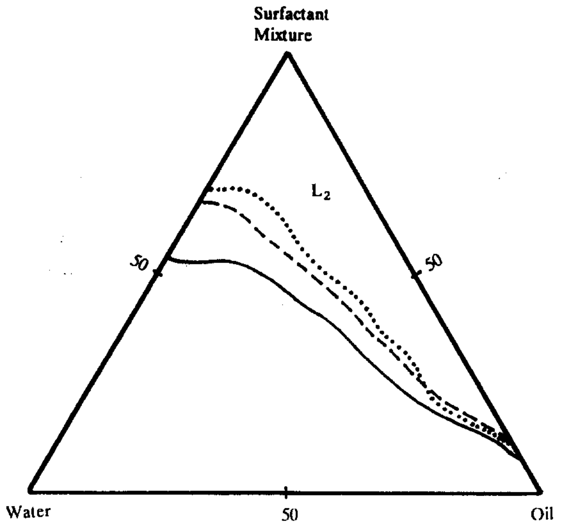

Fig. 6. Phase diagrams of systems containing E200/IPM/water/alcohol at a K_m of 1:1; (continuous line) *n*-butanol, (dashed line) *n*-pentanol, (dotted line) *n*-hexanol.

3.3. Alkanediols as cosurfactants

The phase diagrams for systems in the presence of 1,2-butanediol, 1,2-pentanediol and 1,2-hexanediol are depicted in Fig. 4. Comparison between the phase diagrams reveals, in all cases the presence of a clear region covering all oil/surfactant combinations, the extent of which is greatest in the presence of 1,2-hexanediol and least with 1,2-butanediol (in the system containing 1,2-hexanediol the large clear area was designated a BM). It appears that increasing the chain length of the hydrocarbon moiety results in an increase in the extent of the clear region. Although the phase diagram obtained with 1,2-butanediol exhibited an extensive LC region covering all surfactant/oil combinations, when 1,2-hexanediol and 1,2-pentanediol were examined, no stable LC phase was detected. In no system was a second clear (L_1) region observed.

3.4. Polyethylene glycol alkyl ethers as cosurfactant

Fig. 5 compares the phase properties of systems prepared with either diethylene glycol monobutyl ether, diethylene glycol monopentyl ether or diethylene glycol monohexyl ether as cosurfactant. The phase diagrams obtained show some similarities to those obtained when using the alkanediols in that all systems exhibited an L_2 region covering all surfactant/oil combinations, the extent of which increased with increasing alkyl chain length of the cosurfactant. Interest-

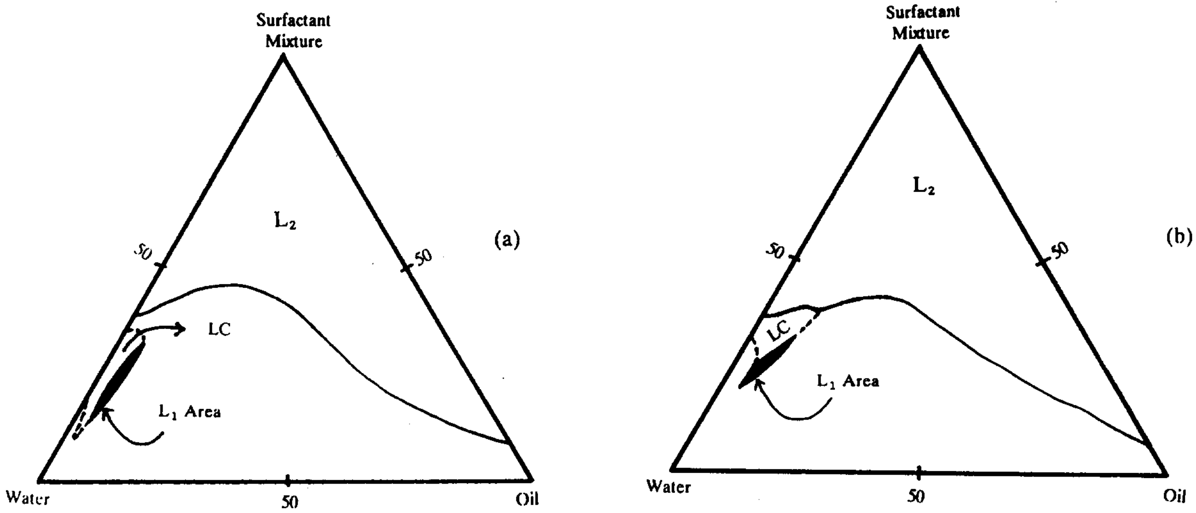

Fig. 7. Phase diagrams of systems containing E200/IPM/water/branched-chain butyl alcohols at a K_m of 1:1; (a) *sec*-butanol, (b) *tert*-butanol.

ingly, however, it was the diethylene glycol monopentyl ether system that produced the greatest water solubilizing capacity (about 80 wt%). In contrast, the maximum amount of water incorporated when using diethylene glycol monohexyl ether was 72% and diethylene glycol monobutyl ether only 20%. Unlike the alkanediols, all glycols produced an LC region, which was most extensive in the case of diethylene glycol monobutyl ether and least extensive with diethylene glycol monohexyl ether. None of the diethylene glycol alkyl ethers exhibited an L_1 region, with the exception of diethylene glycol monobutyl ether which produced a very small clear (L_1) area containing 1–2% oil.

3.5. Alcohols as cosurfactant

Fig. 6 shows the phase diagrams produced when the straight-chain alcohols were used as cosurfactant. Each alcohol produced an L_2 which covered almost all of the possible oil/surfactant combinations. As the chain length of the cosurfactant increased the extent of clear L_2 region slighty decreased; for example, *n*-hexanol incorporated a maximum of 32% water, while *n*-butanol incorporated about 45%. In no case was an LC or L_1 region observed.

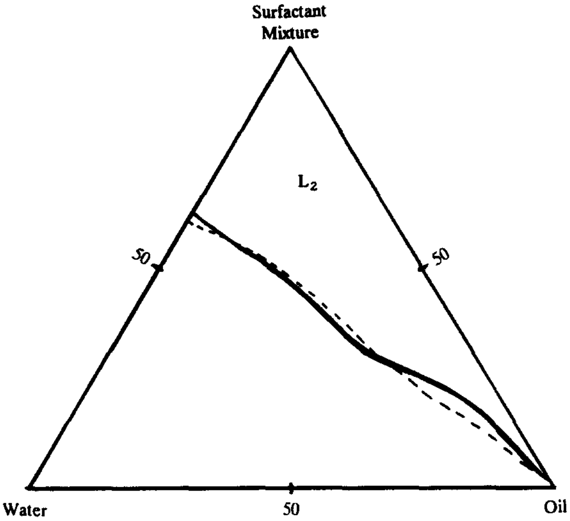

Fig. 8. Phase diagrams of systems containing E200/IPM/water/branched-chain pentanols at a K_m of 1:1; (dashed line) 2-pentanol, (dotted line) 3-pentanol.

The phase diagrams shown in Fig. 7 are those produced when *sec*-butanol and *tert*-butanol were used as cosurfactant (Aboofazeli and Lawrence, 1993). As can be seen, both alcohols behaved in a similar way, each producing L_1, L_2 and LC domains. Fig. 8 shows the phase diagrams for the branched-chain pentanols; 2-pentanol and 3-pentanol. The phase diagrams obtained with both alcohols were virtually identical in that they both produced an L_2 region of similar extent covering all the possible surfactant/oil combinations. The extent of this region was, however, much smaller than that seen with the branched-chain butanols. Unlike the branched-chain butanols, the branched-chain pentanols did not produce an LC or L_1 region.

4. Discussion

When lecithin (phosphatidylcholine) alone is used as a single surfactant it will not produce balanced microemulsions, i.e., microemulsions that cover most of the possible oil, water and surfactant compositions (Shinoda et al., 1991). Generally, in the absence of a cosurfactant, lecithin forms reverse microemulsions over a very limited range of concentrations (Schurtenberger et al., 1993). This is because the lecithin molecule is too lipophilic; it has a critical packing parameter (CPP) of approx. 0.8 (Cornell et al., 1986) favouring the formation of lamellar phases or bilayers (Israelachvili et al., 1976). This CPP is further increased in a microemulsion if the oil phase of a microemulsion penetrates into the long alkyl chains of the lecithin molecule (Evans et al., 1986).

In order to produce a balanced lecithin microemulsion, it is necessary to reduce its effective CPP. This can be achieved by the use of cosurfactants. Cosurfactants can alter the effective CPP in one of two ways; either by making the aqueous phase less hydrophilic and/or by their incorporation into the interfacial film. The cosurfactant can also have a third effect, in that it can reduce the tendancy of lecithin to form highly rigid films (Binks et al., 1989), thus allowing the interfacial film sufficient flexibility to take up the different curvatures required to form balanced microemulsions (Osipow, 1963; De Gennes and Taupin, 1982).

The explanation for the differences in the phase diagrams produced by the cosurfactants in this study is their distribution between the three domains, namely, the aqueous phase, oil phase and interfacial film (Biais et al., 1987) and their influence on the effective CPP of lecithin. However, it is not trivial to determine the distribution of a cosurfactant between the various phases of a microemulsion (Graciaa et al., 1986; Guo et al., 1992). To a first approximation, it is possible to gain an idea of the influence of a cosurfactant on the effective CPP by estimating its likely distribution by reference to its aqueous solubility. Water-soluble, hydrophilic cosurfactants would be expected to be distributed primarily between the aqueous phase and in the polar part of the interfacial layer, thereby decreasing the CPP and producing more balanced microemulsions. In contrast, oil-soluble, hydrophobic cosurfactants would be expected to be distributed mainly between the oil phase and in the hydrocarbon parts of interfacial layer, thus increasing the CPP.

A further indication of the probable relative distribution of a range of putative cosurfactants can be obtained from the partitioning data of Wormuth and Kaler (1987). They found in order of decreasing hydrophilicity, potential cosurfactants containing a primary amine > triethylene glycol > nitrile > alcohol = carboxylic acid > aldehyde = ketone head group. Their results suggest that, in comparison to the equivalent carboxylic acid, more of the primary amine resides in the aqueous phase. A microemulsion produced by a primary amine would thus be anticipated to be more balanced than that produced by the corresponding carboxylic acid or alcohol.

It is obvious from Fig. 1 that the carboxylic acids examined, do not form balanced microemulsions. As the carboxylic acid head group is relatively hydrophobic (Wormuth and Kaler, 1987), it is not surprising that *n*-pentanoic and *n*-hexanoic acid gave only a narrow L_2 region. The fact that this region was reduced in comparison with that obtained with the corresponding alcohol indicates that the carboxylic head group is more hydrophobic than an hydroxyl group. This was unexpected in the light of the study by Wormuth and Kaler (1987) and may be due to the fact that carboxylic acids are known to form dimers in certain oils. These dimers would be expected to reside mainly in the oil phase, leading to the decreased number of cosurfactant molecules in the interfacial film in comparison to the corresponding alcohol. This would have the effect of reducing the extent of the L_2 area.

In contrast to the phase diagrams obtained with the carboxylic acids, the equivalent amines would, due to their increased hydrophilicity, be anticipated to form microemulsions over a wider range of compositions. Unfortunately, as a result of their reactivity, it was not possible to determine reliable phase diagrams with the straight-chain amines. However, both pairs of branched-chain amines tested, produced reasonably balanced microemulsions in that they produced only one clear isotropic region extending over much of the phase diagram (Fig. 2 and 3). This was in marked contrast to the phase diagrams obtained with *sec*-butanol and *tert*-butanol (Fig. 7) and 2- and 3-pentanol (Fig. 8). The existence of balanced microemulsions with the amines is a consequence of their increased hydrophilicity and is in agreement with trends indicated by the work of Wormuth and Kaler (1987).

Interestingly, in marked contrast to the trend seen with the corresponding alcohols, the clear region obtained with the branched-chain pentylamines was greater than that achieved with the butylamines. This result suggests that, due to their high aqueous solubility, the butylamines reside almost exclusively in the aqueous phase, exerting less of an effect on CPP than the pentylamines which are distributed between both the aqueous phase and the head group region of the interfacial layer. The latter distribution may more favourably alter the CPP.

The results obtained with the alkanediols are interesting in that the shorter chain 1,2-butanediol produced both L_2 and LC regions, while the longer chain 1,2-hexanediol was able to produce a fairly balanced microemulsion. This result implies that the very water soluble, shorter chain 1,2-butanediol resided predominately in the aqueous phase and did not greatly disrupt the packing of the LC phase, whereas 1,2-hexanediol resided both in the aqueous phase and interfacial region, thus preventing the production of an LC domain, and thereby allowing the formation of a balanced microemulsion. This observation is in agreement with the work of El-Nokaly et al. (1981) who found, in a system containing lecithin and alkanediol, that increasing the chain length of the alkanediol decreased the stability of the lamellar structure. Their results showed that the long-chain alkanediols were mainly positioned between the lecithin molecules while those with a short chain were located primarily in the aqueous regions between the lecithin layers.

A similar trend was seen in the systems containing polyethylene glycol alkyl ethers. The pentyl and hexyl derivatives were much more effective cosurfactants than diethylene glycol monobutyl ether. Therefore, if we assume that the hydrophilicity of these compounds decreases with increasing the chain length, the implication of the result is that the number of cosurfactant molecules positioned at the interface increases with akyl chain length. The presence of the cosurfactant in the interfacial region causes the destruction of the LC phase thereby allowing the production of balanced microemulsions.

So far, in this and previous studies (Aboofazeli and Lawrence, 1993, 1994), we have investigated the effect of a wide range of putative cosurfactants on the formation of lecithin microemulsions. However, the detailed interpretation of phase behaviour is complicated and depends upon the delicate balance between the nature of the lecithin, oil and cosurfactant. As yet, no one existing theory is able to adequately forecast and explain microemulsion phase behaviour. We have tried to explain the results by considering the role of the cosurfactant in adjusting the effective CPP of surfactant systems, either by altering its hydrophilicity (Wormuth and Kaler, 1987; Trotta et al., 1989) and/or by its effect on the interfacial film (Osipow, 1963; De Gennes and Taupin, 1982), the spontaneous curvature of which is governed by geometric constraints (Israelachvili et al., 1976; Chen et al., 1986).

Our results suggest that in order for cosurfactant to produce balanced lecithin microemulsion, it needs to act in the bulk aqueous phase (to decrease the effective CPP) and in the interfacial layer (both decreasing the effective CPP and rigidity of the lecithin monolayer). For most pharmaceutical purposes, however, the ideal cosurfactant would exert an effect only on the interfacial surfactant layer. In this way, it would allow the infinite dilution of the microemulsion without destruction due to the dilution of the cosurfactant below effective levels. For a cosurfactant to exert its effect exclusively in the interfacial layer, it requires an alkyl chain of sufficient length to ensure it resides only in the interfacial layer. However, the alkyl chain of the cosurfactant cannot be too long or else it will prevent the destruction of the rigid interfacial monolayer known to be formed by lecithin. It addition, it is imperative that the hydrophilic head group of the cosurfactant is of sufficient size to reduce the effective CPP. To this end, a short alkyl chain molecule with a large head group probably offers the best hope as a potential cosurfactant to allow the production of infinitely dilutable lecithin-based microemulsion.

Acknowledgments

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