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Effect of Short-Chain Alcohols as Co-surfactants on Pseudo-ternary Phase Diagrams Containing Lecithin

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Abstract–Lecithin is a natural amphiphilic molecule, the microemulsions of which are often employed as a transdermal delivery medium of drugs and cosmetics. However, it constructs a microemulsion and lamellar phase in a phase diagram without co-surfactant only at a narrow range of composition. In this study, the effect of several short-chain alcohols on pseudo-ternary phase diagrams composed of lecithin, water and dodecane containing 1.0 wt% lidocaine (local anesthetic) was investigated in relation to the application of lecithin-based microemulsion for transdermal drug delivery. The phase diagram for an aqueous solution containing 80.0 wt% ethanol showed a lamellar structure (LC) and bicontinuous isotropic regions. When the mixing ratio of lecithin to alcohols (1-propanol, 1-butanol and n-pentanol) was 2 : 1, water-in-oil (L2) and oil-in-water (L1) microemulsions and LC were obtained in a certain range of compositions. The maximum solubilization of water into L2 phase was 38 wt% when the total surfactant was 43 wt% with butanol as cosurfactant.

Key words : Lecithin, Phase Diagram, Short-Chain Alcohol, Lidocaine, Solubilization

INTRODUCTION

Microemulsion systems, which are obtained by mixing water, oil and surfactant, are homogeneous, transparent, thermodynamically stable solutions that contain high proportions of oil and water. Since these systems were first described by Hoar and Schulman in 1943, microemulsions have been of great interest in pharmaceutical and cosmetic applications because of their transparent appearance, long stability, ease of preparation and high solubility of drugs [Garti and Aserin, 1996].

It has long been known that various types of microemulsion structures, which are two isotropic phases and an anisotropic phase, may be encountered as the composition of a surfactant solution is varied as shown in Fig. 1 [Bourrel and Schechter, 1988]. The L1 phase is a clear isotropic solution in which the oil is dispersed as fine droplets in water and called an oil-in-water microemulsion. The second isotropic phase, L2, appears at a high concentration of the water-insoluble component, which is called a water-in-oil microemulsion in which the oil is the continuous phase and the water is the dispersed phase. The micelles within this phase are 'reversed', i.e., the polar groups are directed inwards forming a polar pool for the hydrophilic solubilizate. The liquid crystal phase, which is clear anisotropic, usually consists of double layers of surfactant molecules with the polar groups protruding into the intervening layers of water molecules. The bicontinuous phase is the mesophase appearing between L1 and L2 [Attwood and Florence, 1983].

Lecithin-based microemulsions are extensively studied as pharmaceutical drug delivery systems because lecithin is natural, non-

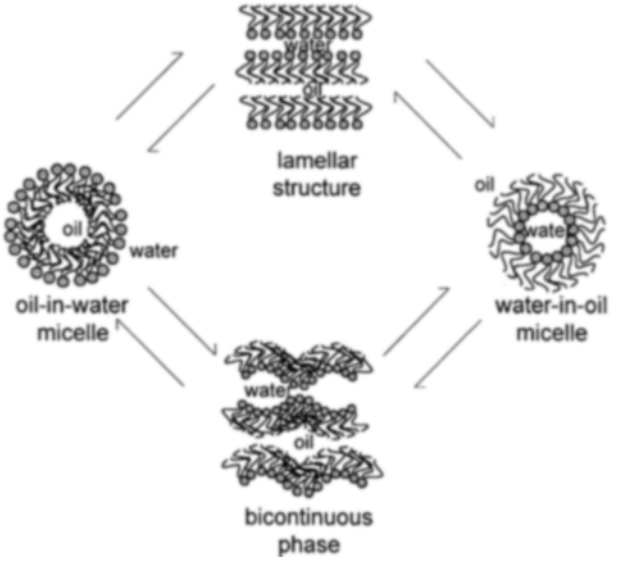

Fig. 1. Intermicelle equilibrium and associated phase changes shown by certain series of amphiphilic solutions.

toxic and has amphiphilic molecules [Aboofazeli et al., 1995; Bonina et al., 1995; Trotta et al., 1995]. However, it is too liphophilic to form balanced microemulsions without co-surfactant. Lecithin has a strong tendency to form liquid crystal structure over a limited concentration [Shinoda et al., 1991]. This might be due to the fact that lecithin has a fairly high packing parameter (the ratio R) of around 0.8 [Cornell et al., 1986]. In order to form microemulsions in a wide range of concentration, the ratio R needs to be reduced for the formation of the L1 phase or increased for the L2 structure. The short chain co-surfactant decreases the ratio R by its incorporation into the interfacial

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surfactant film and dissolving in the aqueous phase, thereby making water less hydrophilic. In the case of a long and double hydrophobic chain surfactant like lecithin, a short chain co-surfactant can also act to increase the fluidity of the interfacial surfactant layer, thereby reducing the tendency of lecithin to form highly rigid films and allowing the interfacial film sufficient flexibility to take up the different curvatures required to form balanced microemulsions [Binks et al., 1989].

Lidocaine, discovered by Löfgren in 1946, has widely been used as a local anesthetic agent, which is a drug that produces the loss of sensation and motor activity in the body by reversibly blocking the conduction in nerve fibers. Local anesthetics are generally prepared as solutions for an easy injection [Burm and van Kleef, 1994]. Lecithin-based microemulsion containing an oil-soluble local anesthetic can be a proper medium for transdermal drug delivery without the toxic problem.

In this study, we have investigated the different pseudo-ternary phase diagrams of systems containing the water, the oil (dodecane), the lecithin and the co-surfactant of several short chain alcohols such as ethanol, 1-propanol, 1-butanol and 1-pentanol. Lidocaine used as local anesthetic drug is dissolved in the oil phase by 1.0 wt%. The pseudo-ternary phase diagrams of these mixtures were constructed through titration method.

EXPERIMENTAL

1. Materials

Lecithin (Lipoid 80) extracted from egg yolk was obtained from Dongkook Pharmaceutical company in Korea; it is composed of phosphatidyl choline (75.2 %), phosphatidylethanolmine (15.3 %), sphongomyelin (2.5 %), lysophosphatidylcholine (1.7 %) and triglyceride (2.7 %). Dodecane(99+%) and n-pentanol (99+%) were purchased from Aldrich Chemical Company. Ethanol (99.8 %) was supplied from J. T. Baker in Holland, 1-propanol (min.95 %) by Kanto Chemical (Japan), 1-Butanol (min.98 %) by Showa (Japan). Lidocaine (99+%), a local anesthetic drug, was purchased from Sigma. All reagents were of the highest purity available and were used as received. Double-distilled water of 18.2 MΩ electrical resistivity was obtained through ELGA system and used as aqueous phase. All-glass vials were used throughout this study.

2. Construction of Pseudo-Ternary Phase Diagrams

Phase diagrams were constructed using a traditional titration method. The samples were prepared at twenty points of different compositions. Appropriate amounts of lecithin, dodecane containing lidocaine (1 wt%) and cosurfactant were weighed into glass vials and the samples were stirred until a clear solution was obtained. The mixing ratio of lecithin to cosurfactant except ethanol was 2 : 1 by weight and ethanol was added into water at 80 wt%. The sealed glass vials were placed in the incubator at 37.5 °C. Titrating with water (or water containing ethanol) drop by drop, the mixing solution was vigorously shaken with the mixer. After this procedure, samples were kept in the incubator at 37.5 °C for a few days. After equilibrium was reached, the mixtures were checked both visually for clarity, and through the cross polarizer for the presence of a liquid crystalline (LC) phase. All mixtures produced optically clear solutions at low water concentrations, forming the reverse microemulsion (L2). When birefringence was observed by the cross polarizer, the mixtures were construed as LC structure. The titration was continued in order to observe the presence (or absence) of a second clear region (L1).

The pseudo-ternary phase diagrams were represented as a ternary diagram, which contained three components of water, oil (1 wt% lidocaine), surfactant/co-surfactant. The boundary of the phase diagram was drawn within a tiny error.

RESULTS AND DISCUSSION

Studies on the pseudo-ternary phase diagrams (Fig. 2-5) showed the existence of oil-in-water (L1), water-in-oil (L2) microemulsion regions and lamellar (LC) regions in the systems using lecithin as surfactant and the various short-chain alcohols as co-surfactants. Lecithin extracted from egg yolk and soy bean

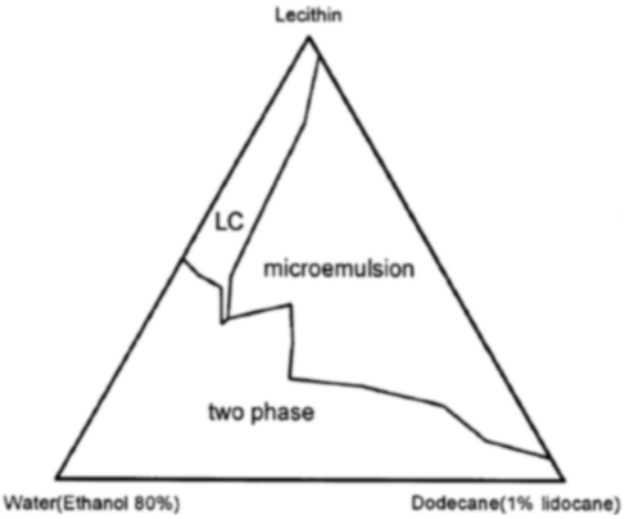

Fig. 2. Pseudo-ternary phase diagram for lecithin-dodecane (1 % lidocaine)-water (Ethanol 80 %).

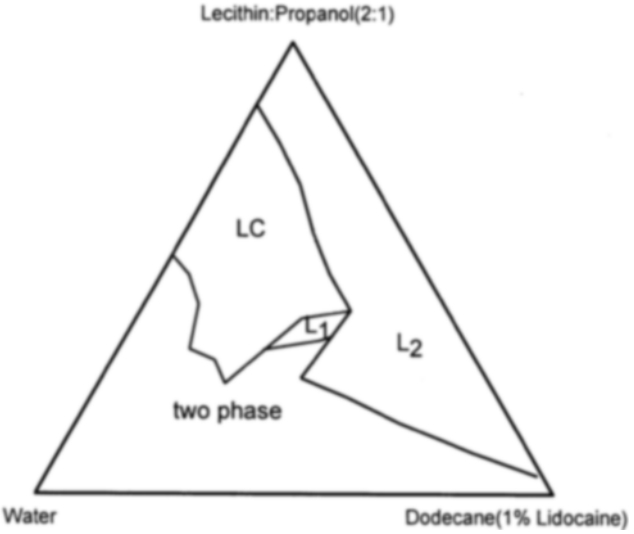

Fig. 3. Pseudo-ternary phase diagram for lecithin/1-propanol (2 : 1)-dodecane (1 % lidocaine)-water.

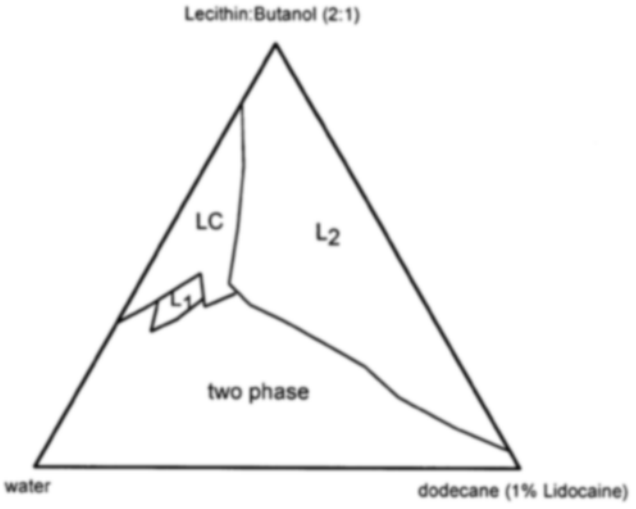

Fig. 4. Pseudo-ternary phase diagram for lecithin/1-butanol (2 : 1)-dodecane (1 % lidocaine)-water.

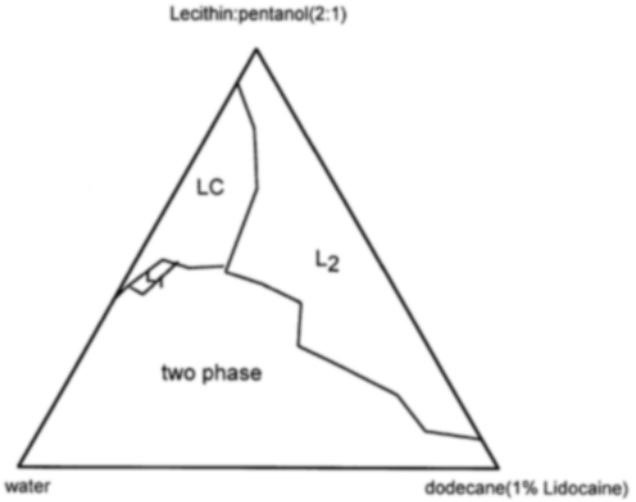

Fig. 5. Pseudo-ternary phase diagram for lecithin/n-pentanol (2 : 1)-dodecane (1 % lidocaine)-water.

is of interest in transdermal medium of drugs and cosmetics as it is a biological amphiphilic molecule and membranes of plant and animal cells are typically composed of 40-50 % lipid and 50-60 % protein. But microemulsion is never formed with only lecithin as surfactant [Kabalnov et al., 1996].

Israelachvili et al. [1976] have proposed a simple rule to explain the geometrical micellar property, spherical, cylindrical and lamellar structures with packing parameter R,

$$R = \frac{v}{al} \quad (1)$$

where v is the real volume of the hydrocarbon chain, a is the cross-sectional area of the surfactant, and l is the approximate length of the surfactant hydrocarbon chain. The ratio R, so called Packing Parameter, is the ratio between the cross area of hydrophilic group and the mean area of hydrophobic group in surfactant. When the range of R is below 1/3, the structure is spherical normal micelle. In the range of 1/3-1/2, it is the mesophase of a cylinder, in 1/2-1, lamellar structure, over the range of 1, reverse micelle. Since the R of lecithins used generally is around 0.8, its solutions mainly form a lamellar structure.

Shinoda et al. [1991] emphasized the intrinsic properties of lecithin which should be taken into consideration in preparation of lecithin-based microemulsions. Lecithin exhibits a very strong hydrophobicity due to two long hydrocarbon chains, as well as a strong hydrophilicity due to the zwitterionic polar head groups which have dipole moments and are strongly hydrated. Thus, lecithin has a close balance between hydrophilic and lipophilic properties, although slightly inclined toward the lipophilic properties. And lecithin has a strong tendency to form liquid crystals, notably of lamellar structure due to the proper packing ratio for the formation of bilayer.

The cross-sectional area of the hydrophilic group of Lipoid 80 used in this study is 60 $Å^2$ [Choi et al., 1998]. In calculating R for Lipoid 80 by Eq. (1), its value of the ratio R is near to 0.71. Thus it is necessary that co-surfactant is added into the surfactant in order to obtain microemulsion by Lipoid 80. It has been reported that it is proper to keep the ratio of lecithin to co-surfactants (1-propanol, 1-butanol and n-pentanol) as 1.94 : 1 to get a clear phase at a wide range of compositions in the mixtures of pure water/lecithin/alcohols/isopropyl mystrate [Aboofazeli and Lawrence, 1993]. For ethanol, when it is mixed with water to 4 : 1, microemulsions are formed at a wide region with isopyl mystrate as an oil phase [Ruth et al., 1995]. As alcohols are used as solvent, a great quantity of alcohol is dissolved in surfactant as well as in oil and a few alcohols do not break lamellar structure. Thus, the solution in which surfactant was prepared so that the ratio between lecithin and alcohol was 2 : 1 and ethanol : water was 4 : 1 was titrated with pure water drop by drop.

Fig. 2 illustrates the phase diagram obtained with ethanol in aqueous phase. Lamellar and microemulsion phases appeared in the wide region. Without regions being divided oil-in-water microemulsion (L1) into water-in-oil microemulsion (L2), they were bicontinuous from L2 to L1. The studies on the effect of 1-propanol, 1-butanol and n-pentanol are depicted in Figs. 3-5. For all co-surfactants except ethanol, L2 phase was produced in a wide range of surfactant/co-surfactant, LC phase was observed extensively but oil-in-water microemulsion realm was very narrow, incorporating only a very limited amount of water.

Fig. 6 shows the amount of solubilized water in water-in-oil microemulsion against the total surfactant. For the 1-propanol cosurfactant system, the water solubilizing capacity in the system was gradually increased to the maximum 36 wt% water for 25 wt% total surfactant. Above this maximum solubility of water, with increase in the amount of total surfactant, the water solubility slowly decreased. A similar trend was observed with 1-butanol and n-pentanol. The maximum solubility of water in phase studies on the 1-butanol system was 38 wt% for 43 wt% total surfactant ; in n-pentanol the maximum water capacity was 33 wt% for 47 wt%. Thus reverse micelle containing 1-butanol as cosurfactant solubilized a greater amount of water than other alcohols.

The LC region gradually increased in the following order to ethanol < 1-butanol < n-pentanol < 1-propanol. The L1 region was observed in the narrow region for all alcohols except eth-

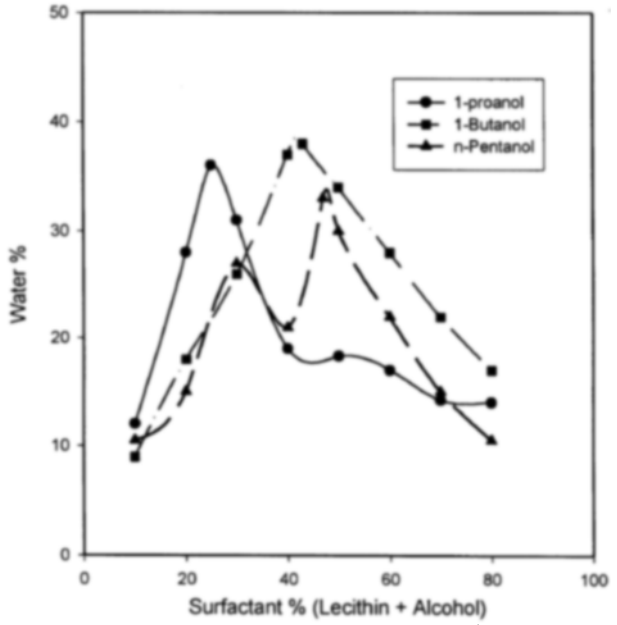

Fig. 6. Water solubilization in water-in-oil micelle.

anol. The L1 region was not observed with ethanol in all regions of the phase diagram. Surfactant systems containing lecithin and ethanol could not solubilize dodecane into the water continuous phase in all compositions.

The distribution of the alcohols between the aqueous phase, oil phase and the interface is dependent on their partition coefficients. The more hydrophilic alcohols would be expected to be distributed first between the aqueous and the interfacial layer. However, the more hydrophobic alcohols would be expected to be distributed mainly between the oil and interfacial layer. The partition of this molecule at the interface can affect the curvature of the interface [De Gennes and Taupin, 1982]. The more partition of alcohols in the interfacial layer of micelle, the easier formation of an isotropic region at the lecithin-based phase diagram. The solubility of alcohol in water is decreased in order of ethanol, 1-propanol, 1-butanol, n-pentanol. Without lidocaine, 1-propanol mostly favored the formation of an extensive clear area, then decreasing with 1-butanol, n-pentanol in similar systems with triglyceride, soybean oil, miglyol 812 or oleic acid as oil phases [Aboofazeli et al., 1995]. From this study, we found that more 1-butanol penetrated into the interfacial layer of lecithin between oil and water than 1-propanol, followed by the reduction in rigidity of the film and easy formation of spontaneous curvature obtaining a clear region. Since oil-soluble lidocaine molecules are located in the hydrophobic region of lecithin and oil phase, lidocaine molecules contract the monolayer of lecithin in a mixed system as proven in our previous study [Choi et al., 1998]. The more hydrophobic molecule (1-butanol) seems to favor the situation in the interfacial layer than 1-propanol.

CONCLUSION

The phase behaviors of lecithin-based microemulsions with short chain alcohols as cosurfactants have been studied in relation to transdermal drug delivery systems. In order to examine its micellar shape, the ratio of R (packing parameter) was calculated, which was about 0.71 for the lecithin used in this study. This value is suitable for the formation of lamellar structure. It cannot form a wide range of microemulsion and lamellae without co-surfactant. When several short-chain alcohols (ethanol, 1-propanol, 1-butanol, n-pentanol) as co-surfactant mixed with lecithin, pseudo-ternary phase diagrams composed of water, dodecane (1 wt% of lidocaine) and lecithin/alcohol showed the wide region of water-in-oil (L2) microemulsion, lamellar structure and oil-in-water microemulsion (L1) in a very limited region. With the penetration of alcohols into the interfacial layer of micelle, the curvature of the interface is altered for the spontaneous formation of microemulsions. Solubilization of water was maximized 38 wt% for 43 wt% total surfactant at 1-butanol. In contrast to the largest realm of L1 and L2 with propanol as cosurfactant when oil phase does not contain lidocaine as reported by other researchers, the butanol system formed the largest area of L1 and L2 when oil has lidocaine. This result may be due to the change in the hydorphobicity of interfacial lecithin layer due to the lidocaine.

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