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Effects of alcohols and diols on the phase behaviour of quaternary systems

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Abstract

The aim of the current study was to investigate the effect of different co-surfactants on the phase behaviour of the pseudoternary system water:ethyl oleate:nonionic surfactant blend (sorbitan monolaurate/polyoxyethylene 20 sorbitan mono-oleate). Four aliphatic alcohols (1-propanol, 1-butanol, 1-hexanol and 1-octanol) and four 1,2-alkanediols (1,2-propanediol, 1,2-pentanediol, 1,2-hexanediol and 1,2-octanediol) were used. The co-surfactant-free system forms two different colloidal structures, a water-in-oil microemulsion (w/o ME) and lamellar liquid crystals (LC) and two coarse dispersions, water-in-oil (w/o EM) and oil-in-water (o/w EM) emulsions. Microemulsion region area (%ME), liquid crystalline region area (%LC), amount of amphiphile blend required to produce a balanced microemulsion (%AMPH) and amount of water solubilised (%W) were used as assessment criteria to evaluate the co-surfactants. Seven calculated physico-chemical descriptors were used to represent the different co-surfactants. 1-butanol, 1,2-hexanediol and 1,2-octanediol produced balanced MEs capable of solubilising a high percentage of both oil and water. A similarity was observed between the descriptors attributed to 1-butanol and 1,2-hexanediol. The requirements of a co-surfactant molecule to produce a balanced microemulsion were: HLB value 7.0–8.0, a carbon backbone of 4–6 atoms, percentage carbon of 60–65%, percentage oxygen of 20–30%, log P value 0.2–0.9 and log $1/S$ (S: aqueous solubility) close to zero. © 2000 Elsevier Science B.V. All rights reserved.

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Microemulsions (MEs) are clear, thermodynamically stable optically isotropic systems. They form spontaneously upon mixing a suitable oil, water and an amphiphile blend (surfactants either alone or in combination with a co-surfactant) thereby overcoming the need for any additional input of energy. These properties render them useful as vehicles for drug delivery particularly as an alternative to coarse emulsions. MEs can be characterised as water in oil (w/o), oil in water (o/w) or bicontinuous systems in which water rich and oil rich domains are separated by surfactant-rich sheets (Bourrel and Schechter, 1988). A disadvantage of MEs is that they often require a high concentration of surfactant, which can lead

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to issues of bioincompatibility. The concentration of surfactant can sometimes be reduced by the addition of a co-surfactant (Prince, 1977). Low molecular weight alcohols can be used for this purpose. Such alcohols can influence the formation of MEs by both interfacial and bulk effects. Their amphiphilic nature, short hydrophobic chain and terminal hydroxyl group, enable them to interact with surfactant monolayers at the interface thereby affecting their packing, which in turn can influence the curvature of the interface and interfacial energy. The amphiphilic nature of low molecular weight co-surfactants also enable them to distribute between the aqueous and oil phase thereby altering the chemical composition and hence the relative hydro/lipophilicity (Cavalli et al., 1996). These two properties render short chain alcohols useful for the preparation of MEs having a decreased surfactant concentration. However, many of the short chain alcohols are regarded as toxic. 1,2-alkanediols have similar properties to aliphatic alcohols, but are reportedly less toxic and therefore may be suitable substitutes for use in the formulation of MEs (Kahlweit et al., 1995). The aim of the current study was firstly to investigate the effect of a series of related short chain alcohols and diols on the phase behaviour of a pseudo-ternary system which formed two types of colloidal structures namely, a ME and a liquid crystalline phase. Secondly, to identify physico-chemical characteristics of co-surfactants which facilitate the formation of microemulsions.

The effect of eight different co-surfactants on the phase behaviour of a pseudo-ternary system was investigated. Ethyl oleate (Crodamol EO) was used as the oil component of the co-surfactant free system, sorbitan monolaurate (Crill 1) and polyoxyethylene 20 sorbitan mono-oleate (Crillet 4 super) were used as surfactants. Deionised water was used as the aqueous phase. Four alcohols and four diols (1-propanol, 1-butanol, 1-hexanol and 1-octanol, 1,2-propanediol, 1,2-pentanediol, 1,2-hexanediol and 1,2-octanediol) were used as co-surfactants. Pseudo-ternary phase diagrams were constructed at a mass ratio of polyoxyethylene 20 sorbitan mono-oleate:sorbitan monolaurate:co-surfactant of 0.42:0.28:0.30, previously determined to be the optimal ratio for maximum water solubilisation. The pseudo-ternary phase diagrams of these systems were compared to the co-surfactant free system prepared at a mass ratio of polyoxyethylene 20 sorbitan mono-oleate:sorbitan monolaurate of 0.6:0.4, a combination previously determined to be the optimal ratio for maximum water solubilisation (Alany et al., 1999). Systems were prepared by mixing oil, surfactants and co-surfactants prior to the addition of the appropriate mass of water. The samples were vortexed and left overnight to equilibrate and then characterised by visual inspection, light microscopy (phase-contrast and polarised light microscopy) and conductivity measurements. Clear, isotropic, one-phase systems were designated as a ME; systems showing birefringence with characteristic oily streaks, maltese crosses or fan shaped textures, were designated as systems containing a lamellar mesophase. Non-birefringent two-phase systems as determined by visual inspection and microscopy were designated as coarse emulsions and the nature of the emulsion (o/w EM or w/o EM) was determined by conductivity.

Fig. 1 shows the pseudo-ternary phase triangles for the eight systems investigated together with that of the co-surfactant-free system. In all cases, addition of a co-surfactant resulted in changes in the phase behaviour of combinations of ethyl oleate, water and the surfactant mixture. The effect of each co-surfactant on the area of the ME in the phase diagram (%ME), the area of the LC region (%LC), the minimum amount of surfactant required to produce a ME with equal amounts of water and oil, (termed balanced ME, %AMPH) and the maximum water solubilised by the ME (%W) is listed in Table 1. No distinct trends were observed in the homologous series of either the alcohols or diols. Further, except for the similarity between 1-butanol and 1,2-hexanediol, no obvious relationship was observed between the alcohols and the diols investigated. This is in contrast to findings reported by Kahlweit et al. (1996), where a C6 diol behaved similar to 1-propanol and a C8 diol had similar effects to 1-butanol. However, any relationship between alcohols and diols may be influenced by the oil and surfactant combination used in the pseudo-ternary system.

In the absence of a co-surfactant, a maximum of 15% water can be solubilised by the ME formed by the surfactant blend and ethyl oleate, suggesting the formation of a w/o ME. At higher water concentrations, the system forms lamellar liquid crystals, typical of a lipophilic surfactant blend favouring long range ordered packing yielding surfactant films having a *true* zero curvature.

The formation of a LC phase was prevented by the inclusion of the lower molecular weight alcohols (C3 and C4). Hence, these short chain alcohols perturb the long range ordered packing of the two surfactants. The maximum % water solubilised by the ME formed by the inclusion of 1-propanol was much greater than that formed by the ME of the co-surfactant free system while the maximum% oil solubilised was only slightly reduced. This might suggest that 1-propanol reduces the hydrophilicity of the aqueous phase. However, 1-propanol produced a balanced ME (Shinoda et al., 1991) capable of solubilising a high % of both oil and water with a relatively high % (AMPH).

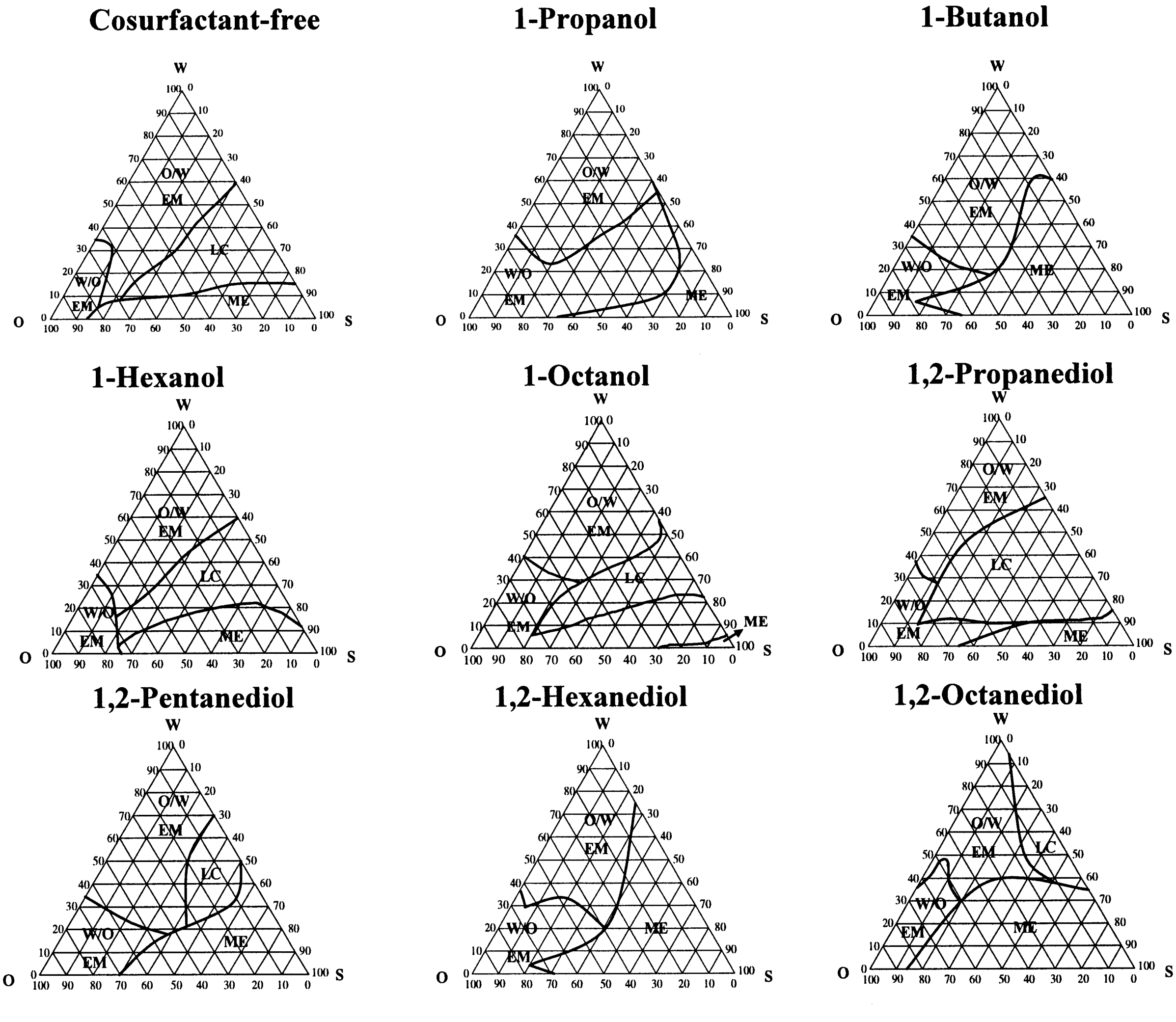

Fig. 1. Pseudoternary phase diagrams for the co-surfactant free system and systems formulated with different co-surfactants. O/W EM, water-in-oil emulsion; W/O EM, water-in-oil emulsion; ME, microemulsion; LC, area containing lamellar liquid crystals; W, water; O, oil; S, surfactant or surfactant + co-surfactant blend.

Table 1
Effect of co-surfactants on various parameters estimated for the constructed pseudo-ternary phase diagrams[a]

Co-surfactant	% ME	% LC	% AMPH	% W
Cosurfactant-free	19	28	67	15
1-Propanol	15	0	70	60
1-Butanol	43	0	40	62
1-Hexanol	23.5	29.5	60	22
1-Octanol	1.5	22.5	92	5
1,2-Propanediol	11.5	49	78	15
1,2-Pentanediol	30	13	50	52
1,2-Hexanediol	43	0	40	72
1,2-Octanediol	48	12	25	40

[a] % ME, area of microemulsion region; % LC, area of liquid crystalline region; % AMPH, amount of amphiphile blend required to produce a balanced microemulsion; % W, maximum amount of water solubilised.

For the homologous series of alcohols investigated, a balanced ME was only achieved by the use of 1-butanol and as such this was the most successful alcohol at optimising the amphiphilic properties of the surfactant blend to yield monolayers having the appropriate packing parameters and curvature characteristics. Balanced MEs capable of solubilising a high % of both oil and water would likely be bicontinuous in structure. In such a system, the net *mean* curvature of the surfactant monolayers is zero. The maximum % water solubilised by the ME was again reduced in systems containing 1-hexanol and 1-octanol with this region being almost non-existent in the latter case. Like the co-surfactant free system, LC regions were apparent in the pseudo-ternary phase diagram of both these alcohols although of slightly reduced area for 1-octanol. This would indicate that the longer chain alcohols (C6 and C8) did not adversely affect the ability of the surfactants to orderly pack along their linear axis.

For the homologous series of alkane diols, a large LC region was observed in the phase diagram when 1,2-propanediol was used as the co-surfactant, which reduced upon increasing the chain length to C6 in which case the LC region was absent. Increasing the chain length further to C8 resulted in the LC region re-appearing although to a lesser extent than that noted for the C3 diol. 1,2-propanediol therefore leads to long range ordered packing of the surfactant combination to yield surfactant films having a true zero curvature. This was not observed for 1-propanol which has a similar molecular length. The packing of the surfactant combination is disrupted by inclusion of 1,2-pentanediol, 1,2-hexanediol or 1,2-octanediol, yielding systems favouring the formation of MEs. Like 1-butanol, 1,2-hexanediol and 1,2-octanediol produce balanced MEs capable of solubilising a high percentage of both oil and water.

Eight descriptors were estimated for the alcohols and the diols used in order to ascertain whether any relationships exist between the physico-chemical properties of the co-surfactant and its ability to promote the formation of MEs, particularly balanced MEs produced at low surfactant concentrations. The descriptors chosen

Table 2
Calculated physico-chemical descriptors for the co-surfactants[a]

Co-surfactant	HLB	C No	C (%)	O (%)	log *P*	log *D*	log 1/*S*
1-Propanol	7.48	3	59.96	26.62	0.34	0.53	−0.4
1-Butanol	7.00	4	64.82	21.59	0.88	1.04	0.2
1-Hexanol	6.05	6	70.53	15.66	1.94	2.05	1.5
1-Octanol	5.10	8	73.78	12.29	3.00	3.07	2.8
1,2-Propanediol	9.38	3	47.35	42.05	−1.34	−0.71	−2.5
1,2-Pentanediol	8.43	5	57.66	30.72	−0.28	0.31	−1.2
1,2-Hexanediol	7.95	6	60.98	27.08	0.25	0.82	−0.5
1,2-Octanediol	7.00	8	65.71	21.88	1.32	1.84	0.7

[a] HLB, hydrophile–lipophile balance value; C No, number of carbon atoms in the backbone of the co-surfactant; C (%), weight percent of carbon content; O (%), weight percent of oxygen content; log *P*, logarithm of the partition coefficient in octanol/water; log *D*, logarithm of distribution coefficient at pH 7.0 in octanol/water; *S*, aqueous solubility at 25°C at pH 7.0.

were the number of carbon atoms in the backbone of the co-surfactant (C No), weight percent of carbon content (C (%)), weight percent of oxygen content (O (%)), hydrophile–lipophile balance value (HLB), logarithm of the partition coefficient in octanol/water (log P), logarithm of distribution coefficient at pH 7.0 in octanol/water (log D) and aqueous solubility (S) at 25°C at pH 7.0 expressed as $\log(1/S)$. The values for these descriptors for each co-surfactant are listed in Table 2. A similarity is observed between the descriptors attributed to 1-butanol and 1,2-hexanediol, co-surfactants which promoted the formation of a ME at low surfactant concentrations. It would therefore follow that for the present combination of oil and surfactant blend, a balanced ME with equal tendency to solubilise water and oil is favoured by a co-surfactant having the following physico-chemical properties: HLB 7–8, C No 4–6, C (%) 60–65, O (%) 20–30, log P 0.2–0.9 and log $1/S$ close to zero.

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