ELSEVIER International Journal of Pharmaceutics 122 (1995) 27-33

international journal of pharmaceutics

Phase behavior of aqueous solutions containing nonionic surfactant-polyethylene glycol mixtures

Nivedita K. Pandit *, Jayesh Kanjia, Kalpesh Patel, Dean G. Pontikes

College of Pharmacy and Health Sciences, Drake University, Des Moines, IA 50311, USA

Received 15 September 1994; revised 23 November 1994; accepted 10 January 1995

Abstract

The phase separation behavior of two nonionic surfactants, polyoxyethylene (10) oleyl ether (I) and polyoxyethylene (10) cetyl ether (II), was examined in solutions containing polyethylene glycols (PEGs) of various molecular weights. It was found that PEGs decrease the cloud points of both surfactants, and that this decrease is dependent upon the concentration and molecular weight of the PEG. This effect of PEGs on the cloud point can be explained by a depletion flocculation mechanism, which results in a segregative phase separation of the solution into surfactant-rich and polymer-rich phases. The Krafft point of II increased in the presence of PEGs, and this increase was dependent on the concentration of PEG, but independent of its molecular weight.

Keywords: Nonionic surfactant; Cloud point; Krafft point; Polymer; Polymer-surfactant

---

1. Introduction

Interactions between polymers and surfactants in aqueous solution have been investigated for more than two decades, and several books and reviews have been published on this topic (Saito, 1987; Dubin and Tong, 1993; Goddard and Ananthapadmanabhan, 1993). The interest in this area is because of the abundance in nature and commerce of aqueous systems containing both a polymer and a surfactant. In such systems, polymers and surfactants occur or are used together to take advantage of their characteristically different properties. When present together, they can interact to provide beneficial features or to cause unforeseen problems. Surfactant-polymer combinations occur in numerous pharmaceutical drug delivery systems and hence a systematic investigation into the behavior of pharmaceutically relevant surfactant-polymer systems is important.

Most of the work in this field has been with systems where at least one of the components is charged, i.e., uncharged polymer-ionic surfactant, charged polymer-nonionic surfactant or charged polymer-ionic surfactant systems. Nonionic surfactant-uncharged polymer mixtures have received comparatively little attention, probably because early results suggested that interactions in them are often weak or non-existent. For example, studies with polyvinyl alcohol (PVA), polyethylene oxide (PEO) and polyvinylpyrroli-

---

[*] Corresponding author.

0378-5173/95/$09.50
SSDI 0378-5173(95)00032-1

done (PVP) show no interaction with nonionic surfactants (Saito, 1987). However, a few reports have appeared demonstrating measurable interactions in such polymer-surfactant systems. A study of ethoxylated alcohols with PEO (Wormuth, 1991) found that the miscibility of the two components decreases significantly upon increasing the molecular weight of the polymer or the amphiphilicity of the surfactant. Karlstrom et al. (1990) demonstrated a weak interaction between ethylhydroxyethylcellulose and nonionic surfactants using cloud point measurements. Boscher et al. (1983) used light scattering to demonstrate an interaction between hydroxyethylcellulose (HEC) and an oxyethylene nonylphenyl ether. Other examples include the interaction between PEO and nonylphenol polyglycol ether (Szmerekova and Kralik, 1984) using gel permeation chromatography. The authors found a small decrease in the dimensions of the polymer with increasing concentration of the surfactant. In this study, the phenolic group may have determined the extent and type of interaction, since many types of water-soluble polymers are known to bind small protic substances like phenols and carboxylic acids in aqueous solutions (Saito, 1987). Penders et al. (1993) used cloud point (CP) and NMR self-diffusion measurements to demonstrate an interaction between agarose, a polysaccharide, and hexaethylene glycol mono-*n*-dodecyl ether, and found a decrease in the CP of the surfactant in the presence of agarose.

These few studies demonstrate that interactions can occur in certain combinations of uncharged polymers and nonionic surfactants in water. These interactions can be either associative, due to an effective attraction between the surfactant and polymer, or segregative, due to an effective repulsion between surfactant and polymer. Either type of interaction can affect several critical properties of both components, and result in unexpected behavior in the system. This unexpected behavior can either cause problems, or may suggest some unique new application for the polymer-surfactant mixture. However, considering the scarcity of literature reports showing significant interaction in nonionic surfactant-uncharged polymer systems, particularly those of pharmaceutical relevance, a formulation scientist usually assumes that no unusual behavior will occur when the components are mixed.

In the present study we provide strong evidence for a segregative interaction between polyethylene glycol (PEG) polymers and two alkyl POE ether surfactants – polyoxyethylene (10) oleyl ether, (I), and polyoxyethylene (10) cetyl ether (II) – in aqueous solution. PEGs and alkyl POE surfactants are common excipients in various pharmaceutical dosage forms and processing solutions, and are often present together. We have measured the effect of PEGs on the phase separation temperature of the surfactant to monitor the nature and extent of the interaction. Aqueous solutions of both surfactants show phase separation as the temperature is changed; I exhibits a cloud point (CP), while II exhibits both a CP and a Krafft point (KP).

CP measurements are used quite extensively to study the behavior of polyoxyethylene (POE) surfactants and polymers, and provide an excellent tool for studying polymer-surfactant interactions. This is a phenomenon where solutions of nonionic surfactants turn cloudy and separate into two phases upon heating; the temperature at which this phase change occurs is known as the CP or as the lower critical solution temperature of the surfactant. This property has been attributed to the progressive dehydration of the oxyethylene (OE) chain with an increase in temperature. CPs are very sensitive to changes in the system; an additive which interacts with either the surfactant or the solvent is expected to affect the CP significantly. The CP behavior of various POE ether surfactants has been thoroughly investigated (Mitchell, 1983), as has the effect of various salts on the CP (Schott, 1969; Schott and Han, 1975; Schott and Royce, 1984; Schott et al., 1984).

The KP is the temperature above which the solubility of a surfactant increases dramatically in aqueous systems, and is interpreted as the melting point of the hydrated solid surfactant. The concept of a KP has been applied extensively to ionic surfactants (Shinoda, 1978; Charbit et al., 1985, Heckmann et al., 1987), but has only rarely been observed for nonionic surfactants (Schott and Han, 1976; Schott et al., 1984). At the KP, the solubility of the surfactant is equal to its critical micelle concentration (CMC). Above the KP, the total solubility of the surfactant increases dramatically because of the formation of micelles, but below it only surfactant monomers are present, and the solubility is drastically limited. Thus, a surfactant solution is cloudy below the KP, but becomes clear at temperatures above the KP. If an additive significantly alters the hydrated solid surfactant-solvent equilibrium, we would expect the KP to change.

2. Materials and methods

2.1. Materials

Both I and II were kindly donated by ICI Surfactants, Wilmington, DE, and were used as received. PEG 400, 1000, 4600, 8000, 10 000 and PEO 100 000 were from Aldrich and were also used as received. Water was deionized and passed through a Millipore filtration system.

2.2. Cloud point and Krafft point measurements

All solutions were made on a w/w basis in water. The surfactant solutions were made by weighing out the appropriate amount of surfactant and mixing it with approx. 90% of the water required. This mixture was then heated slowly with stirring to rapidly hydrate the surfactant. When the surfactant was uniformly dispersed the solution was cooled, and enough water added to achieve the final total weight. Mixtures containing both surfactant and PEG were made similarly, with PEG being added to the cooled mixture, just before adjusting final weight. All mixtures were equilibrated at room temperature before KP or CP measurement. The exceptions to this were mixtures whose CPs were below room temperature. These were cooled in an ice bath until they were clear before CP measurement.

The CP was determined by heating about 20 ml of the sample mixture in closed containers with stirring at a rate of about 2° C/min. Slower heating rates gave the same readings. The phase separation temperatures were determined by visual observation against a black background. The KP was taken as the temperature at which the mixture became completely clear, and the CP as the temperature where the solution became distinctly cloudy. Slight haziness persisted in many solutions, presumably due to small amounts of impurities, and was not considered phase separation. The reproducibility of our measurements was ±1° C.

3. Results and discussion

3.1. Phase separation curves

Phase separation curves as a function of concentration are shown in Fig. 1 and 2 for surfactants I and II, respectively. Surfactant I shows the presence of a CP, while surfactant II displays a CP and a KP.

Aqueous solutions of surfactant I are clear between 0 and about 63° C and turn cloudy above this temperature, indicating a CP. The exact CP depends slightly on the concentration of I; e.g., a 2% w/w solution of I has a CP of 63° C. Upon

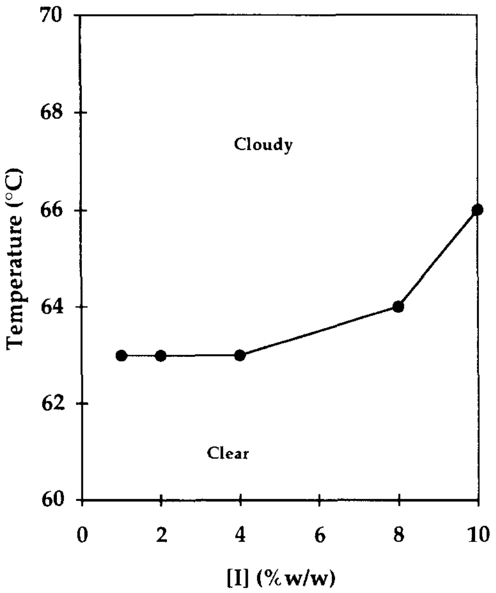

Fig. 1. Cloud point curve of aqueous solutions of surfactant I.

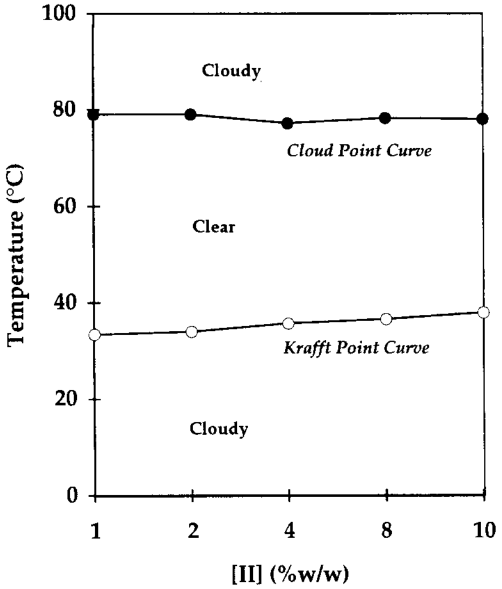

Fig. 2. Cloud point and Krafft point curves of aqueous solutions of surfactant II.

cooling, these solutions remain clear down to 2° C. Aqueous solutions of surfactant II are clear in the temperature range of about 34–77° C; the exact range depends on the concentration. This indicates the presence of a CP at 77° C, above which the solutions are cloudy, and a KP at 34° C, below which the solutions are cloudy.

The shapes of the CP and KP curves are similar to those reported for other alkyl OE ether surfactants (Schott and Han, 1976; Mitchell, 1983; Corti et al., 1984), in that the CP and KP do not vary much with surfactant concentration. The CPs of II are higher than those of I. Studies on the relationship of surfactant structure and CP (Schott, 1969) have shown that, at constant ethylene oxide content, the CP is lowered by an increase in molecular weight of the surfactant and branching of the hydrophobic group. This is consistent with our results. The effect of nonionic surfactant structure on the KP has also been discussed previously (Schott and Han, 1976). The authors found that the relationship of KP with structure parallels the melting point behavior of a homologous series of fatty acids.

3.2. Effect of PEGs on cloud points of I and II

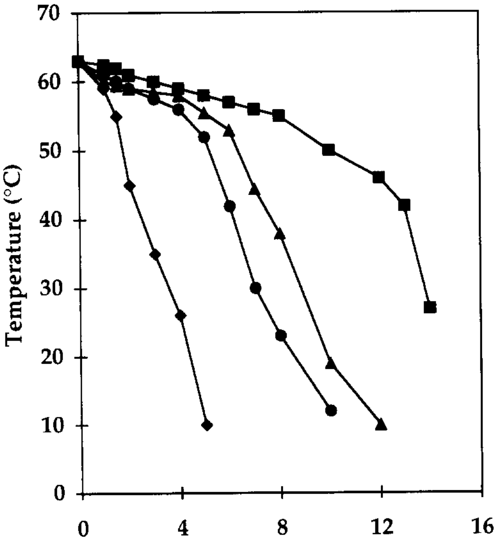

Fig. 3. Effect of PEG concentration and molecular weight on the cloud point of a 2% w/w solution of surfactant I. Filled symbols represent the cloud point curves with PEG. (■) PEG 4600; (▲) PEG 8000; (●) PEG 10000; (◆) PEG 100000.

Fig. 3 shows the effect of PEGs of increasing molecular weight on the CP of a 2% w/w solution of I, and Fig. 4 demonstrates the effect of the same PEGs on the CP and KP of a 2% w/w solution of II. All the higher molecular weight PEGs studied decrease the CP of I and II, and increase the KP of II, as a function of PEG concentration. The magnitude of CP lowering is dramatic, and increases as the molecular weight of PEG is increased. The magnitude of KP elevation is small, and is unaffected by the molecular weight of PEG. Although polyoxyethylene polymers themselves can also show cloud point behavior, the PEGs used in this study do not have CPs below 100° C in water, and thus did not interfere with determination of the CPs of the surfactants. The CP curves in the presence of PEG exhibit two distinct regions: at low PEG concentration, the slope of the CP vs % PEG curve is shallow, whereas at higher concentrations the curve is much steeper. As the molecular weight of the PEG increases, this transition from a shallow to a steep slope occurs at lower concentrations of

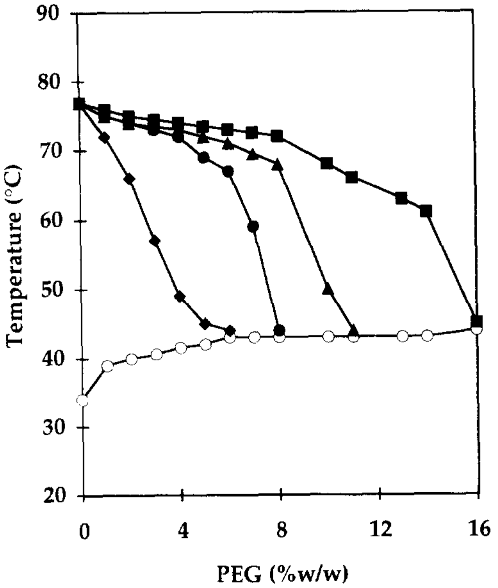

Fig. 4. Effect of PEG concentration and molecular weight on the cloud point and Krafft point of a 2% w/w solution of surfactant II. Filled symbols represent the cloud point curves with PEG. (■) PEG 4600; (▲) PEG 8000; (●) PEG 10000; (◆) PEG 100000. (○) Krafft Point curve, which is the same for all the PEGs studied.

PEG; for PEG 100000, only a steep slope is observed.

These effects can be explained using the analogy of flocculation of colloidal particle dispersions by polymers. Although soluble polymers are often used to stabilize particle dispersions such as lattices, they can also flocculate, or aggregate, colloidal particles, resulting in phase separation. The mechanism for depletion flocculation has been explained as follows (Saito, 1987; Everett, 1992; Dubin and Tong, 1993). When two colloidal particles come together in the presence of relatively high concentrations of a non-adsorbed or weakly adsorbed polymer, the polymer coils are excluded from the space between the particles; i.e., the polymer is negatively adsorbed. This depletion is a result of the polymer chains resisting a reduction of their conformational entropy, preferring to escape from the gap between the colloidal particles. To reduce the free energy of the system, the colloidal particles come together and share their depletion volumes, resulting in depletion flocculation. An alternative explanation for depletion flocculation is that the small gap between the colloidal particles prevents the polymer from entering this space. Thus, the gap behaves like an osmotic membrane permeable only to solvent. The solvent, therefore, leaves this space for the bulk, creating an osmotic pressure which forces the colloidal particles together, resulting in destabilization and coagulation of the colloidal particles.

In our system, micelles of I or II are the colloidal particles, and 'flocculation' of micelles results in micellar growth and eventual phase separation. As one would expect, the higher the molecular weight of the polymer, the lower the concentration at which phase separation of the micellar solution occurs at a given temperature. This is because the higher molecular weight polymer occupies a larger volume in solution, and is excluded from the gap between the micelles more readily. Similarly, the higher the molecular weight of the polymer, the lower the temperature at which phase separation occurs for a given polymer concentration, presumably because the higher molecular weight polymers approach theta conditions at progressively lower temperatures. Therefore, phase separation in these nonionic surfactant-PEG solutions is due to a combination of two effects: the dehydration of the OE chain with increasing temperature, causing micellar growth and aggregation, and the depletion flocculation of the micelles with increasing concentration and molecular weight of the PEG, causing flocculation. Although colloidal dispersions are often stabilized by polymers, we see no evidence of stabilization of the micellar solution by these PEGs, indicating that the PEGs probably do not adsorb onto the surface of the micelle.

The fact that the CP of I, even in the presence of PEGs, is not particularly sensitive to surfactant concentration (Table 2) is consistent with the flocculation mechanism, in that the temperature at which phase separation occurs is primarily dependent on polymer concentration and size. The slightly higher CPs observed for 1% w/w solutions of I may be due to the visual difficulty in detecting phase separation in dilute surfactant solutions.

Table 1
Effect of PEG 400 on the cloud point of 2% w/w surfactant I and cloud point and Krafft point of 2% w/w surfactant II solutions

PEG 400 (% w/w)	CP(I)	CP(II)	KP(II)
0	63	77	34
2	62	77	35
4	62	78	35
6	63	79	34
8	63	79	34
10	63	80	35
14	65	81	35
20	67	84	34

The net effect of these phenomena is that the concentration-temperature region where solutions of these nonionic surfactants remain clear is drastically reduced in the presence of PEGs. For example, a 2% w/w solution of I, which is normally clear up to a temperature of 63° C, will be cloudy at room temperature (around 22° C) if 5% w/w PEG 100 000 is added to it.

3.3. Effect of PEGs on the Krafft point of II

Only a single KP curve is shown for II in Fig. 4, because all the PEGs caused the same change in the KP at equivalent concentrations. The KP of II increased in the presence of all the PEG polymers studied, with the maximum increase being about 9° C (from 34 to 43° C); the magnitude of the increase depended on the concentration of the polymer, but not on its molecular weight. It has been reported (Schott and Han, 1976) that inorganic salts and urea have only a small effect on the KP of polyoxyethylene (10) stearyl ether, and raise it by between 1 and 4° C. In the only other study that looked at the KP of a nonionic surfactant in the presence of an uncharged polymer (Brackman et al., 1988), the authors found that the KP of *n*-octyl thioglucoside (OTG) decreased in the presence of polypropylene oxide (PPO), and the CP of the PPO increased in the presence of OTG. In other words, OTG and PPO increased each other's water solubility. The authors were unable to demonstrate whether this was a result of a decrease in the CMC of the surfactant, or an increase in the solubility of the surfactant monomers in the presence of the polymer. In any event, PPO is more hydrophobic than PEG, and significant hydrophobic interaction is possible between PPO and surfactants, resulting in the mutual solubility increases seen.

An increase in the KP of II in the presence of PEGs indicates that PEG polymers either reduce the solubility of II monomers, or increase the CMC of II, both of which could result in an increase of the KP. Further investigations are needed to distinguish between these possibilities. In any event, this elevation in the KP of II by PEGs narrows the temperature region where solutions of II are clear. Below the KP, solutions of II and PEG are cloudy and contain hydrated solid surfactant, dissolved surfactant monomers and dissolved PEG. Above the CP, the solutions are also cloudy and separate into surfactant-rich and polymer-poor phases. In the region between the CP and KP curves, the II-PEG solutions are clear, containing dissolved PEG, surfactant monomers and micelles.

The CP and KP curves of II meet at a certain 'critical' temperature and a certain critical concentration of PEG. The critical temperature for the II-PEG system appears to be about 43° C; the critical PEG concentration decreases as the molecular weight of PEG increases. Solutions of II containing PEG above its critical concentration are cloudy at all temperatures between 0 and 100° C. Presumably, II in these systems undergoes a transition at 43° C, from hydrated solid surfactant below 43° C, to large hydrated micelles that separate as a surfactant-rich phase above 43° C.

Table 2
Effect of concentration of surfactant I on the magnitude of cloud point decrease by PEG 10000

PEG 10000 (% w/w)	CP	
	[I] = 2% w/w	[I] = 1% w/w
0	63	63
1	61	61
2	59	60
4	56	56
6	42	46
8	23	27
10	12	14

3.4. Effect of PEG 400 on CP and KP

Although the higher molecular weight PEGs had a significant effect on the KP and a dramatic effect on the CP, PEG 400 showed no significant effect on the KP of II, but showed a slight increase in the CPs of both I and II (Table 1). This shows that PEG 400 is behaving very differently compared to higher molecular weight PEGs in our systems. Since PEG 400 is a small molecule and not a polymer, its effect on the CP may be considered more a solvent effect rather than a polymer-surfactant interaction effect. PEG 400 is widely used in aqueous solutions to increase the solubility of poorly water-soluble compounds. Thus, the solubility of the hydrophobic part of the surfactant, and therefore the surfactant as a whole, will be higher in PEG 400-water solutions. The CP occurs at a temperature where the hydration of the OE groups is not sufficient to overcome the water insolubility of the hydrophobic chain. Since the hydrophobic chain is more soluble in PEG 400-water mixtures, the CP is increased in the presence of PEG 400, and this increase is proportional to the amount of PEG 400. As the KP is considered to be the melting point of the hydrated solid surfactant, it is not affected by the presence of a cosolvent.

In conclusion, we have shown evidence for a repulsive interaction between alkyl polyoxyethylene ether surfactants and PEG polymers in water. This interaction reduces the aqueous solubility of the surfactants and dramatically reduces the temperature range where the surfactants are soluble. The interaction is manifest as an increase in the KP and a decrease in the CP of the surfactants. Further studies will examine such interactions in other surfactant-polymer systems, the effect of inorganic ions on the phase separation in such systems, and the influence of these interactions on ability of the surfactant-polymer mixtures to solubilize hydrophobic drugs.

References

Boscher, Y., Lafuma, F. and Ouivoron, C., Light-scattering studies of hydroxyethylcellulose in water/nonionic surfactant binary mixtures. *Polym. Bull.*, 9 (1983) 533–536.

Brackman, J.C., Van Os, N.M. and Engberts, J.B.F.N., Polymer-nonionic micelle complexation. Formation of poly(propylene oxide)-complexed *n*-octyl thioglucoside micelles. *Langmuir*, 4 (1988) 1266–1269.

Charbit, G., Dorion, F. and Gaboriaud, R., Phase equilibria between solid amphiphile and micellar solutions. *Fluid Phase Equilib.*, 20 (1985) 233–240.

Corti, M., Minero, C. and Degiorgio, V., Cloud point transition in nonionic micellar solutions. *J. Phys. Chem.*, 88 (1984) 309–317.

Dubin, P. and Tong, P., *Colloid-Polymer Interactions*, ACS Symposium Series 532, American Chemical Society, Washington, DC, 1993.

Everett, D.H., *Basic Principles of Colloid Science*, Royal Society of Chemistry, London, 1992.

Goddard, E.D. and Ananthapadmanabhan, K.P., *Interactions of Surfactants with Polymers and Proteins*, CRC Press, Boca Raton, FL, 1993.

Heckmann, K., Schwarz, R. and Strnad, J., Determination of Krafft point and cmc of hexadecylpyridinium salts in electrolyte solutions, *J. Colloid Interface Sci.*, 120 (1987) 114–117.

Karlstrom, G., Carlsson, A. and Lindman, B., Phase diagrams of nonionic polymer-water systems. Experimental andtheoretical studies of the effects of surfactants and other solutes, *J. Phys. Chem.*, 94 (1990) 5005–5015.

Mitchell, D.J., Phase behavior of polyoxyethylene surfactants with water. Mesophase structures and partial miscibility (cloud points). *J. Chem. Soc. Faraday Trans. I*, 79 (1983) 975–1000.

Penders, M.H.G.M., Nilsson, S., Piculell and Lindman, B., Clouding and diffusion of nonionic surfactants in agarose gels and solutions. *J. Phys. Chem.*, 97 (1993) 11332–11338.

Saito, S., Polymer-surfactant interactions. In *Nonionic Surfactants – Physical Chemistry*, Surfactant Science Series Vol. 23, Dekker, New York, 1987.

Schott, H., Hydrophile-lipophile balance and cloud points of nonionic surfactants. *J. Pharm. Sci.*, 58 (1969) 1443–1449.

Schott, H. and Han, S.K., Effect of additives on solutions of nonionic surfactants: IV. Krafft points. *J. Pharm. Sci.*, 65 (1976) 979–981.

Schott, H. and Han, S.K., Effect of inorganic additives on solutions of nonionic surfactants: II. *J. Pharm. Sci.*, 64 (1975) 658–664.

Schott, H. and Royce, A.E., Effect of inorganic additives on solutions of nonionic surfactants: VI. Further cloud point relations. *J. Pharm. Sci.*, 73 (1984) 793–799.

Schott, H., Royce, A.E. and Han, S.K., Effect of inorganic additives on solutions of nonionic surfactants. Cloud point shift values of individual ions. *J. Colloid Interface Sci.*, 98 (1984) 197–201.

Shinoda, K., *Principles of Solution and Solubility*, Dekker, New York, 1978.

Szmerekova, V and Kralik, P., Interaction complexes between polymers and surfactants: I. Interactions of polyethylene oxide with surfactants studies by gel permeation chromatography. *J. Chromatogr.*, 285 (1984) 188–193.

Wormuth, K., Patterns of phase behavior in polymer and amphiphile mixtures. *Langmuir*, 7 (1991) 1622–1626.