SURFACTANT SYSTEMS

Their chemistry, pharmacy and biology

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D. Attwood
Department of Pharmacy
University of Manchester

A. T. Florence
Department of Pharmacy
University of Strathclyde

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6 *Pharmaceutical aspects of solubilization*

6.1 Introduction

Solubilization in surfactant solutions above the critical micelle concentration offers one approach to the formulation of poorly soluble drugs in solution form [1].

The objective of this chapter and of Chapter 7 is to review the state of the art of solubilization in surfactant systems with emphasis on the consequences of a surfactant presence in pharmaceutical formulations. In particular, emphasis will be placed on the effect of surfactants on bioavailability and the toxicity of formulations for neglect of these topics will, on the one hand, prevent the realization of the potential of surfactant systems and, on the other, might lead to the unwise use of surfactants in formulations. Some attempt will be made to place the topic in perspective and to answer the question as to the real value of surfactant solubilization in pharmaceutical formulation.

It is perhaps true that micellar solubilization has not made much impact on drug formulation. There are relatively few marketed products which could be considered to be isotropic solutions of drug and surfactant in either the UK or the USA, although surfactants are present in many formulations as minor adjuvants and to that extent their presence and influence is perhaps hidden.

The limiting factors in the use of solubilizers as effective formulation aids are (i) the finite capacity of the micelles for the drug, (ii) the possible short- or long-term adverse effects of the surfactant on the body, and (iii) the concomitant solubilization of other ingredients such as preservatives, flavouring and colouring matter in the formulation with consequent alterations in stability and effectiveness. Nonetheless, there is scope for development simply because there is a need for agents to increase the solubility of poorly soluble drugs even if only at the stage of pharmacological evaluation where, indeed, surfactants are used often without due regard to the implications. The use of co-solvents and surfactants to solve problems of low solubility has the advantage that the drug entity can be used without chemical modification and hence toxicological data do not have to be repeated as would be the case when alternative approaches are used to produce more soluble compounds. Some caution has, however, to be adopted in the

interpretation of animal pharmacology and toxicology on formulations which differ from the final marketed product, especially if the final preparation contains surfactant but early test formulations do not or *vice versa*. Surfactants, as we will see in Chapter 7, are not inert substances some having distinctive pharmacological actions. There is a demonstrable need for the development of less toxic surfactants; the polyoxyethylene–polyoxypropylene block co-polymers which will be discussed later seem to have fewer side effects than conventional surfactants and seem to be worthy of further investigation.

With the development of new dosage form technology in which control of drug release is achieved, it is conceivable that micellar systems will find some place because of the ability of the micellar phase to alter the transport properties of solubilized drug molecules. One can envisage the deliberate addition of surfactants to drug reservoirs to control the exit rate of drugs from polymeric devices. This will be explained in Chapter 7.

This chapter is restricted mainly to aqueous systems and the solubilization of water-insoluble and poorly soluble drug entities and pharmaceutical additives, and, because of the lesser toxicity of non-ionic surfactants, it will concentrate on non-ionic surfactant systems. Wherever possible cited work refers to systems which have potential utility in pharmacy as there is a danger that all our knowledge is gained on model systems (of toxic ionic surfactants which are used because they are available in a pure state, benzene or similar well-defined solutes, and other unacceptable additives such as propanol) while we remain blissfully unaware of how to solve the real problems that arise [1].

As we have seen in Chapter 1, the range of available surfactants is wide, and so, too, are the mechanisms of solubilization and the effects the surfactants have on the solubilized material. Examples are known of enhanced drug activity and of inactivation, of increased stability, and instability; the interactions of the surfactants with components of the body must also be considered. In the case of insoluble drugs, the presence of micelles may enhance their activity through solubilization and transport to the site of action, a process which otherwise might have been a slow one. This has, of course, dire consequences in the case of carcinogens: normally insoluble carcinogenic substances which may be ingested may become very active in combination with surfactants, and, as the latter are taken in increasing amounts in food (non-ionics in bread is one example), this is a problem which warrants further study. Drugs which are meant to act on the intestinal mucosa, such as sulphaguanidine, might be inadvertently solubilized. There is the problem, especially with non-ionic surfactants, of interactions with preservatives in pharmaceuticals and consequent loss of biological action.

Some drugs themselves are surface-active and form micelles. While surface activity may not, in all cases, be the cause of their biological activity, it must in some way influence it and modify their interaction with the components of dosage forms or the components of the body. Surface-active drugs and surfactant molecules will interact to form mixed micelles at sufficiently high concentrations, a phenomenon which has implications for the thermodynamic activity and possibly the biological activity of the drug molecule.

Since 1964 there have been several comprehensive reviews of solubilization in surfactant systems, notably those by Swarbrick [2], Mulley [3], Sjöblom [4], Droseler and Voight [5], Elworthy *et al.* [6], and Florence [1]. These reviews together cite over a thousand sources primarily concerned with pharmaceutical applications. Other major publications which deal with micellar systems implicating solubilized species include Cordes [7], Fendler and Fendler [8] and the collections of papers edited by Mittal contain several contributions on the topic [9].

In this chapter the solubilization of a number of classes of drugs and pharmaceutical products will be dealt with; in some cases the division into sections has had to be somewhat arbitrary, but, as far as possible, compounds with similar structures, such as the steroids, have been dealt with as a group.

6.2 Solubilization of drugs

6.2.1 Antibacterial compounds

(A) PHENOLIC COMPOUNDS

Solutions of cresol with soap were early pharmaceutical examples of solubilized systems. Phenol itself is soluble in water to the extent of 7.7% (w/v), but it has disadvantages; the alternatives, cresol, chlorocresol, chloroxylenol, and thymol, are much less soluble in water, and their use as disinfectants has led to the need for formulation in surfactant solutions.

Solution of cresol with soap (lysol) is a saponaceous solution containing 50% v/v cresol. Its monograph specifies no particular soap, although activity of the preparation depends to a large extent on the type of soap employed. Although still used, the absence of strict standards for lysol, the widely varying phenol fractions used in its preparation, and the varying properties of the soaps make it an unsatisfactory solution. The high toxicity of phenol and the cresols has mitigated against their more widespread use. Emphasis is now being placed on their chlorinated derivatives, chloroxylenol and chlorocresol. Chloroxylenol is a potent, non-irritant bactericide of low toxicity. It has, however, a low solubility in water, 0.031 g ml^{-1} at 20° C [10]; the official preparation, Solution of Chloroxylenol B.P., contains 5% v/v chloroxylenol with terpineol in an alcoholic soap solution. A modification of this, claimed to be less alkaline, has been described by Lloyd and Clegg [11]. There are numerous commercial formulations with a wide spread of Rideal–Walker coefficients.

Mulley and Metcalf [12] have carried out detailed investigations of the phase behaviour of non-ionic detergent systems containing chloroxylenol (4-chloro-3,5-xylenol). Two of their phase diagrams are reproduced in Fig. 6.1. The surfactant $C_6H_{13}(OCH_2CH_2)_6OH$ is an efficient solubilizer above its CMC, which is approximately 3% w/w, but high concentrations are required to form isotropic liquids containing reasonable quantities of chloroxylenol. $C_6H_{13}(OCH_2CH_2)_2OH$ requires concentrations above 50% w/w to achieve an isotropic solution, and this compound probably acts more as a hydrotrope than

as a micellar solubilizer in this concentration region. The former detergent forms only small aggregates of about 13 monomers in aqueous solution [13]. To obtain systems suitable for use it is essential to increase the alkyl chain length; $C_{10}H_{21}(OCH_2CH_2)_6OH$ has a low CMC and its micelles are reasonably large, containing 73 monomers at 25°C [14]. Isotropic micellar systems are formed at lower concentrations of detergent than for the shorter alkyl-chain homologues. However, there is a concomitant increase in the complexity of the phase diagram with the formation of liquid crystalline phases (Fig. 6.1).

There is apparently no evidence from these phase diagrams for the existence of simple phenol–glycol chain complexes: the liquid which separates at a solubility limit is a solution of variable composition. Ultraviolet spectroscopy shows that a hydrogen-bonded complex between the phenolic hydroxyl group and the other oxygens of cetomacrogol 1000 ($C_{16}H_{33}(OCH_2CH_2)_{23-24}OH$) is formed when chloroxylenol is solubilized by this commercial non-ionic surfactant. The

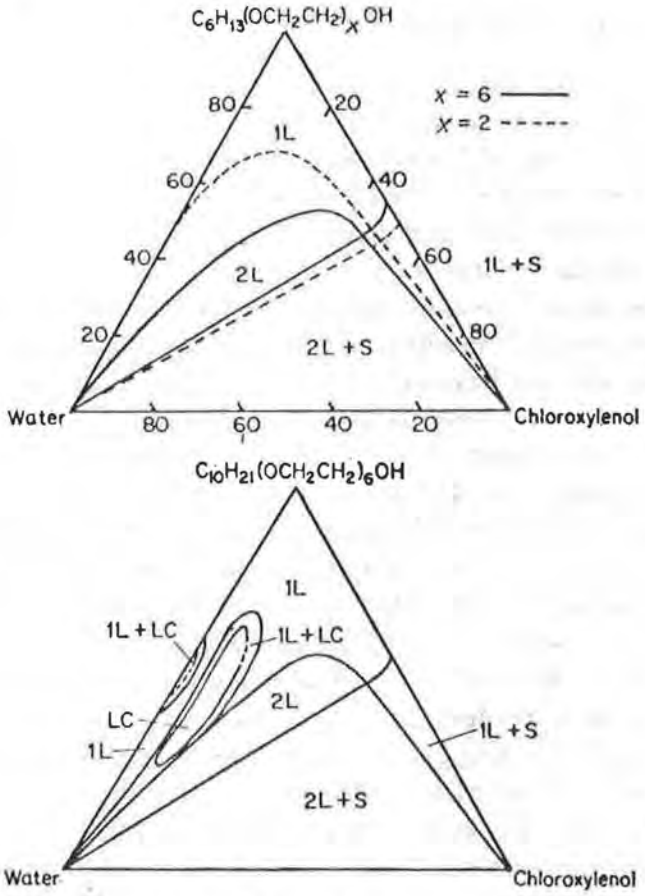


Figure 6.1 The upper phase diagram (after Mulley and Metcalf [12]) illustrates the phases existent in the system $C_6H_{13}(OCH_2CH_2)_xOH$: 4-chloro-3,5-xylenol: water at 20° C. The dotted line represents the behaviour when $x = 2$ and the solid lines where $x = 6$. The lower diagram shows the much more complex behaviour in the system: $C_{10}H_{21}(OCH_2CH_2)_6OH$: chloroxylenol: water. IL = isotropic liquid; LC = liquid crystalline; S = solid 2L = two liquids (immiscible.)

solubility of the chloroxylenol is directly proportional to the surfactant concentration, above the CMC [15]. However, rough determinations of the solubilities of resorcinol and phenol in cetomacrogol solutions, varying in concentration from 1 to 20%, showed these compounds to be less soluble than in water, although their solubility was proportional to detergent concentration [16].

Solutions of phenols in ionic systems exhibit similar behaviour. An initial fall in the solubility of 2-hydroxyphenol and 4-benzylphenol in potassium laurate solutions was noted below the CMC of the soap [17]. Few workers have commented on this 'insolubilization'; compounds with very low water solubility possibly do not show this property. That it is not restricted to phenols is shown by the results of Heller and Klevens [18] for ethyl benzene in potassium laurate. Ethyl benzene has a solubility in water similar to that of 4-benzylphenol.

The binding of series of phenols, cresols and xylenols to the non-ionic surfactant cetomacrogol 1000 can be described by a Langmuir adsorption isotherm [19]

$$x = K_1 K_2 c/(1 + K_1 c)$$

where x is the solute bound (mmol g^{-1} micelle), c is the concentration of free unionized solute (mmol), K_1 is the binding constant (1 $mmol^{-1}$) and K_2 the solute bound at hypothetical saturation (mmol g^{-1} micelle). The combined parameter $K_1 K_2$ is specific for each system and may be defined as the distribution coefficient of the solubilizate at infinitely dilute solubilizate concentration (P_0), Azaz and Donbrow [19] assert. Its value characterizes ideal behaviour both in the aqueous and micellar phases hence strictly would be subject to activity corrections. Binding capacity is inversely related to the water solubility of the phenol, cresol and xylenol, as can be seen in Table 6.1.

Values of P_0 in 0.1 M NaCl are also shown for a few compounds in this Table. A log–log plot of binding capacity and aqueous solubility yields a straight line. Azaz

Table 6.1 Aqueous solubility and distribution coefficient at infinite dilution (P_0) between cetomacrogol and water of phenols at 25° C

Compound	Solubility in water ($mol\,l^{-1} \times 10^3$)	P_0 in water*	Solubility in 0.1 M NaCl ($mol\,l^{-1} \times 10^3$)	P_0 in 0.1 M NaCl*
Phenol	1000	42.0	233	117
o-Cresol	240	79.5	188	80.6
p-Cresol	199	76.4	133	
m-Cresol	142	85.1		
2,4-Xylenol	51.0	125		
2,6-Xylenol	49.5	114		
3,5-Xylenol	40.0	132		190
3,4-Xylenol	39.0	151		
2,3-Xylenol	37.4	169		
2,5-Xylenol	29.0	197		

* Units: $(1/g) \times 10^3 = 1/1000$ g or dimensionless units assuming density of cetomacrogol is unity at 25° C. Measured in 2% cetomacrogol. From Azaz and Donbrow [19].

and Donbrow's work has supported earlier work [20–23] which demonstrated that in unsaturated systems the binding 'constants' of solubilizates to surfactants are concentration-dependent and not, in fact, constant as some authors have assumed (e.g. [24–26]). This variation may have important practical implications in formulation.

A wider range of 34 benzoic acid derivatives has been studied in detail by Tomida *et al.* [27]. Using a solubility method these workers obtained saturation solubilities of the benzoic acid derivatives in Brij 35 (a polyoxyethylene lauryl ether) over a range of concentrations. Solubility ratios, calculated as the solubility in the surfactant solution/solubility in HCl, were a linear function of surfactant concentration allowing the calculation of a partition coefficient P_m which can be defined as

$$P_m = \frac{C_m}{C_a}, \tag{6.1}$$

where C_m and C_a are the concentrations in the micellar and aqueous phases, respectively. P_m is obtained from the solubility data as

$$\frac{S_t}{S_a} = (P_m - 1)\bar{v}C_s + 1 \tag{6.2}$$

where S_t is the total solubility of solubilizate in the presence of surfactant at concentration C_s, S_a is the solubility in the absence of surfactant and $\bar{v}$ is the partial molar volume of the surfactant. Some of the extensive data is reproduced in Table 6.2 for the ortho, para and meta substituents. The data are consistent with the findings of Azaz and Donbrow: the order of aqueous solubilities is always ortho > meta > para and the order of P_m is the opposite except for the hydroxybenzoic acids for which the ortho compound was solubilized most, followed by para and meta compounds. Patel and Foss [21] obtained the

Table 6.2 Aqueous solubilities, S_a, and partition coefficients of benzoic acids, P_m, between aqueous and micellar phases obtained from solubility method*

Substituent	ortho		meta		para	
	S_a(mol l^{-1})	P_m	S_a(mol l^{-1})	P_m	S_a(mol l^{-1})	P_m
H			2.61×10^{-2}	57.4		
F	4.05×10^{-2}	43.1	1.65×10^{-3}	91.2	4.98×10^{-3}	94.6
Cl	8.66×10^{-3}	99.8	1.92×10^{-3}	346	3.48×10^{-4}	446
Br	5.29×10^{-3}	150	1.36×10^{-3}	505	1.42×10^{-4}	634
I	1.75×10^{-3}	271	2.74×10^{-4}	1150	9.16×10^{-6}	908
CH_3	6.55×10^{-3}	120	6.13×10^{-3}	166	2.23×10^{-3}	163
OCH_3	2.50×10^{-2}	32.0	1.18×10^{-2}	72.8	1.30×10^{-3}	109
OH	1.08×10^{-2}	116	5.71×10^{-2}	38.3	4.17×10^{-2}	42.2
NO_2	2.53×10^{-2}	47.5	1.57×10^{-2}	96.8	1.01×10^{-3}	117
CN			2.35×10^{-3}	50.1	5.60×10^{-3}	57.0
COOH	2.57×10^{-2}	22.4	4.42×10^{-4}	155	6.50×10^{-5}	69.8

* From [27].

magnitude of interaction of hydroxy-, chloro- and aminobenzoic acids in polysorbate 80 and cetomacrogol 1000; hydroxy and amino derivatives showed the order of interaction to be ortho > para > meta. Substitution of a hydroxy group in the ortho position results in more affinity for any surfactant than para and meta substituents. This can be explained by the fact that the intramolecular hydrogen bonding increases the proton-donating nature of the carboxylic group. The greater the dissociation constant of the acid group the greater the hydrogen bonding to the oxyethylene groups in the micelle.

Plots of log P_m versus log $P_{octanol}$ for the 34 compounds studied produced three groupings of results [27] to which the following equations applied.

	n	r	s	
$\log P_m = 0.921 \log P_{octanol} + 0.118$	21	0.986	0.080	(6.3)
$\log P_m = 0.881 \log P_{octanol} + 0.392$	5	0.999	0.014	(6.4)
$\log P_m = 0.968 \log P_{octanol} + 0.600$	3	0.999	0.036	(6.5)

where n is the number of points used in the regression, r is the correlation coefficient, and s is the standard deviation. Equation 6.3 applies to the majority of the compounds studied; Equation 6.4 to the nitro and cyano derivatives and the last equation to the compounds with dicarboxylic groups. The intercept values of the three groups are quite different; it is believed that the magnitude of the intercept is a reflection of the site of solubilization in the micelle. The closer the environment is to the nature of octanol used in the partitioning studies to obtain P_{oct}, the closer the intercept should be to zero. A negative intercept (for salicylic acid derivatives) has been identified with solubilization in the hydrocarbon core.

The site of solubilization while of little practical importance in the design of pharmaceutical formulations is of more than academic interest as the position of the solubilizate in the micelle may determine its stability and reactivity towards attacking species in the continuous phase (see Chapter 11).

To obviate the problem of the different affinities of ionized and unionized species for micelle, Tomida *et al.* [27] carried out their investigations at a pH such that ionization was suppressed. pH is rarely as low as that in this work and its influence on solubilization must be considered. Although the hydrogen ion concentration can influence the solution properties of non-ionic surfactants [28], the principal influence on uptake is exercised through the effect of pH on the equilibrium between ionized and unionized drug or solute species. This effect has been studied in most detail by Collett and Koo [29]. Increasing pH leads to a decrease in the micellar uptake of organic acids because of increasing solute solubility in the aqueous phase through increased ionization. This effect is clearly seen in Fig. 6.2 when the results of uptake of 4-chlorobenzoic acid between pH 3 and 4.40 are plotted as a ratio of its solubility in water of the appropriate pH, i.e. as the solubility ratio R. Considering the micellar species to form a phase or pseudophase allows a simple quantitative measure of the interaction between solubilizate and micelle. The concentration of solubilizate in the micelle is related to its concentration in the aqueous phase by a partition coefficient as defined in Equation 6.1.

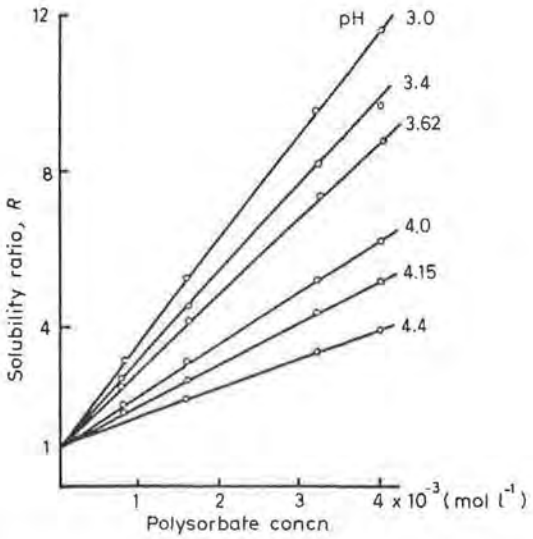


Figure 6.2 The influence of polysorbate 20 concentration and pH on the solubility ratio, R, of 4-chlorobenzoic acid. From Collett and Koo [29].

Curved Scatchard plots for the interaction of propyl *p*-hydroxybenzoate (propyl paraben) with four polyoxyethylene dodecyl ethers are shown in Fig. 6.3 [31]. The primary class of binding sites exhibited a high affinity and a low capacity for the preservative while the secondary sites had a low affinity and large binding capacity. Thus

$$r = \frac{n_1 K_1 D_f}{1 + K_1 D_f} + n_2 K_2 [D_f] \tag{6.6}$$

Analysis of these has allowed n_1, n_2, K_1 and K_2 to be estimated and related to the nature of the binding process in the micelles, especially in respect of the interaction with the hydrophilic polyoxyethylene layer [32].

Of great practical importance are the effects of additives on the binding of preservative molecules to surfactant micelles. Blanchard *et al.*, [33] have confirmed the negligible effect of sorbitol on the interaction of phenolic preservatives with polysorbate 80 using a Scatchard approach. The sorbitol is probably too hydrophilic to interact with the micelle and thus does not compete for binding sites. Similar conclusions were reached by Shimamoto and Mima [34] studying the effects of glycerol, propylene glycol and 1,3-butylene glycol on paraben–non-ionic surfactant interactions. These polymers had little effect on the binding of preservatives to the primary binding sites located at the core/PEG boundary of the micelle but they were thought to decrease binding at the secondary sites, 1,3-butylene glycol being most effective in displacing the preservatives. These secondary sites are reckoned to be non-specific and located in the PEG layer. As materials such as 1,3-butylene glycol may penetrate the PEG region they would probably displace solubilizate molecules. It would seem that displacement from the primary site would require much greater structural specificity (see discussion on interaction of preservative mixtures with micelles,

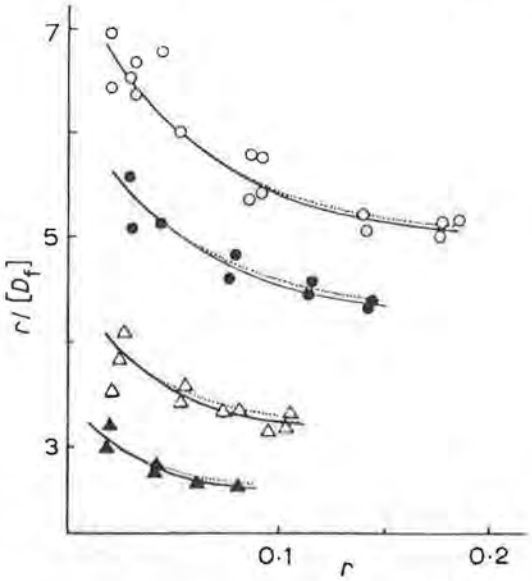


Figure 6.3 Scatchard plots for the interaction of propyl paraben with polyoxyethylene dodecyl ethers, n being the number of oxyethylene units.
○ $n = 15$; ● $n = 20$; △ $n = 30$; ▲ $n = 50$
From [31] with permission.

below). Any displacement of preservative from the micelle is likely to increase the preservative activity of the formulation.

The effects of added electrolytes on solubilized systems are discussed in Chapter 5. In Table 6.1 it can be seen that the addition of sodium chloride to a non-ionic system increases the P_m of the solubilizate. An electrolyte can have a dual effect, first on the properties of the surfactant and secondly on the solubilizate. If the electrolyte salts out the solubilizate P_m will increase, an effect observed with non-ionic surfactant systems whose micelles would be increased in size by such electrolytes. In ionic surfactant systems the effect can be more complex. The addition of electrolyte to an ionic surfactant results in a decrease in CMC, increase in micellar size and a decrease in effective charge per monomer, probably leading to a greater concentration of head groups and a more rigid micellar interior [35] which might result in decreased uptake of solubilizate into the micellar core. Uptake of methyl and ethyl paraben is increased by the addition of 10 mM NaCl to sodium lauryl sulphate [36] (see Table 6.3). As both electrolyte and the presence of paraben lowers the surfactant CMC, analysis of the results produced the unexpected conclusion that for all three compounds the partition coefficient to the micellar phase is reduced on addition of electrolyte. This is a problem which occurs and recurs in detailed studies of mechanisms of solubilization, being clearest when pH effects are studied. Generally the formulator is interested in total solubility which includes solubility in the aqueous and micellar phases. While the partitioning of a species to the micellar phase might be reduced, its increased solubility in the aqueous phase may compensate for this. In spite of the partition coefficient of the methyl, ethyl and butyl paraben

Table 6.3 Solubilization of alkylparabens in water and in 40 mM sodium lauryl sulphate solution at 27° C*.

Alkylparaben	Solubility (mmol l^{-1}) in		
	Water	40 mM NaLS	40 mM NaLS and 50 mM NaCl
Methylparaben	14.5	33.9	31.6
Ethylparaben	5.4	22.7	21.9
Butylparaben	1.1	24.3	26.7

* From [36, 38].

increasing towards the micellar phase from 1.2 through 3.2 to 21, respectively, in 40 mM sodium lauryl sulphate (NaLS) the total solubility is still highest for methyl paraben with a solubility limit of 33.9 mM. Ethyl paraben has the lowest solubility (22.7 mM) and butyl paraben has a solubility of 24.3 mM in 40 mM NaLS [38]. In a series such as the alkyl parabens their different locations in the micelle may be another factor complicating a ready understanding of the observation; the effect of the paraben on CMC which follows the order butyl > ethyl > methylparaben is of little importance when the total surfactant concentration is 40 mM as in the investigations in question but would obviously be important at surfactant concentrations close to the concentration (Fig. 6.4 shows this effect).

Uptake of solubilizate into surfactant micelles changes the physical state of the micelle (see Section 5.5). Sometimes the change in shape may result in drastic changes in the physical properties of the system as a whole – this may influence its use. The effect of additive on the cloud point of non-ionic surfactants

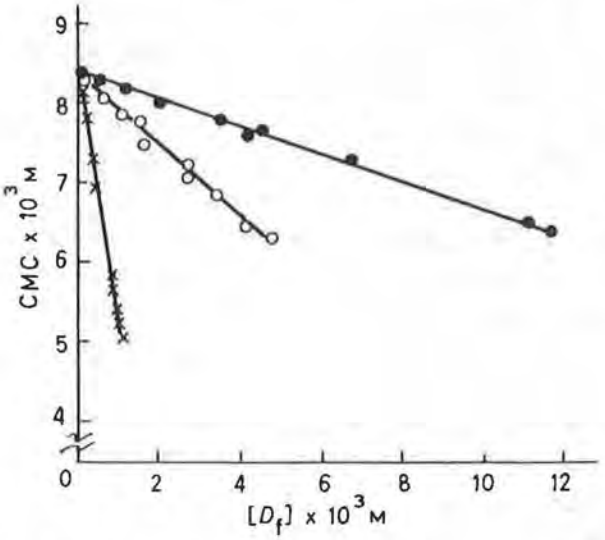


Figure 6.4 The CMCs of sodium lauryl sulphate solutions in the presence of alkyl parabens. ●, methylparaben; ○, ethylparaben; ×, butylparaben. From Goto and Endo [37] with permission.

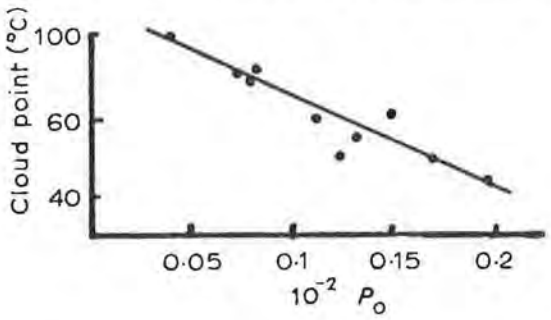


Figure 6.5 Relation between the cloud point and P_0 values for phenol and its homologues at concentrations of 0.05 mol l^{-1} in 2% cetomacrogol 1000. From Donbrow and Azaz [43]. Values of P_0 from Table 6.1.

[39–42] is of some practical importance as the cloud point may be lowered below room temperature. Fig. 6.5 shows the effect of a range of phenols on the cloud point of cetomacrogol solutions (cetomacrogol 1000 B.P. is $C_{16}H_{33}(OCH_2CH_2)_{22-24}OH$) where the relation between cloud point and the distribution coefficient of phenols, cresols and xylenols between micelles and water is demonstrated. The effect of a phenol on the cloud point is inversely related to its hydrophilicity. As the cloud point is thought to be due to the growth of the non-ionic micelles with increasing temperature, the binding of solute to the micellar structure could explain the lowering of the cloud point if the surfactant monomer–solute complex is more hydrophobic than the surfactant monomer itself.

Phenol–water systems display critical solution temperatures (CST). Addition of fatty acid soaps generally causes a lowering of CST. 3% sodium oleate lowers the CST of the phenol–water mixture from ~ 65 to 0° C [45]. 1% lowers it to 43° C and 1% sodium stearate lowers it to 49.1° C [46]. Prins [44] in investigations on cetyltrimethylammonium bromide (CTAB)–phenol–water mixtures, found striking effects caused by the detergent on the CST of the phenol–water system. Table 6.4 gives the concentrations of CTAB and phenol which have in admixture with water a CST of 20° C. The figures were obtained from a study of the phase diagram of the system.

Table 6.4 Concentrations of CTAB and phenol having a critical solution temperature of 20° C*

CTAB (% w/w)	Phenol (% w/w)
8.0	11.0
17.5	16.8
28.0	25.2
34.0	31.7
40.5	35.6
41.5	41.0
40.0	45.1

* From Prins [44].

Cetyltrimethylammonium bromide has a more complicated action than the fatty acid soaps. Although it generally enhances the mutual solubility of phenol and water, at some levels it has been shown to decrease the mutual solubility. Addition of more CTAB causes the mutual solubility to increase again until at 48 % CTAB, complete miscibility is attained. Prins has gone some way to explaining this behaviour. When phenol is added to an aqueous solution of CTAB consisting of spherical micelles the phenol induces the formation of rod-shaped aggregates (see simplified phase diagrams in Fig. 6.6).

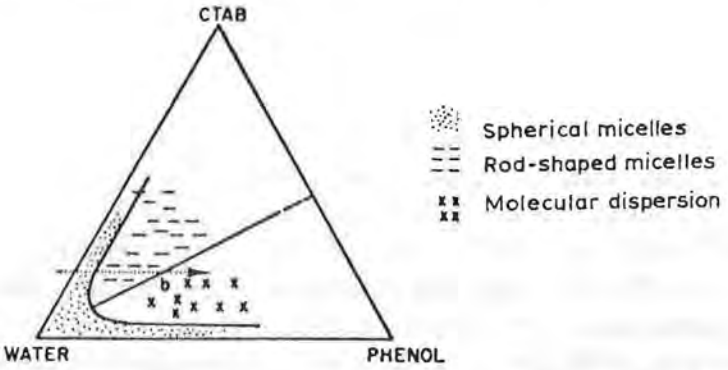


Figure 6.6 A diagrammatic representation of the cetyltrimethylammonium bromide–phenol–water system. (After Prins [44]). Horizontal arrow shows increasing phenol concentrations and passage from solutions containing spherical micelles, through solutions containing asymmetric micelles to a molecular dispersion on breakdown of the micelles.

The rod-shaped micelles can solubilize large quantities of phenol, but they reach a point (b) where they disintegrate, forming a molecular dispersion which results in a loss of mutual solubility. All systems containing more than 48 % CTAB are completely miscible. Examination of the interfacial tension curve of the co-existent phases in the water–phenol–CTAB system (phenol:water 40:60 by weight) shows that the curve mimics the solubility behaviour. A minimum at about 4 % is followed by an increase in interfacial tension, which falls again after 15 % concentration, falling to 0 $mN\,m^{-1}$ at about 40 %.

(B) INTERACTION OF PRESERVATIVE MIXTURES WITH SURFACTANTS.

In many formulations more than one solute will be a potential solubilizate whether or not this is desired. As discussed in Chapter 5, the effect, if any, of one solute on the solubilization of another will depend on the mechanisms of solubilization. If solubilization of one solute occurs at specific 'sites' within the micelles then molecules with similar binding affinities might compete for the available sites leading to a decreased solubilization of each. In some cases one solute might induce a reorganization of the micelle structure and allow increased uptake; both mechanisms might operate such that maxima and minima are seen in the plots of solubility versus the concentration of second solubilizate [47] (see Fig. 5.23). Benzoic acid, for example, increases the solubility of methyl paraben in

cetomacrogol solutions, but dichlorophenol decreases its solubilization [47]. Chloroxylenol reduces the solubility of methylparaben and methylparaben reduces the solubility of chloroxylenol in cetomacrogol, there being no effect on mutual solubilities in the absence of surfactant.

The distribution of a solubilizate between micelles and the aqueous phase does not obey necessarily a simple partition law when a second solubilizate is present [48]. A non-linear increase in solubilization with increasing surfactant concentration has been found with a second solubilizate present. Fig. 6.7 shows the change in micellar partition coefficient of *o*-hydroxybenzoic acid in the presence of increasing levels of benzoic acid when polysorbate 80 is the solubilizer [48]. At 1 % surfactant there is a marked decrease in partition coefficient, but at 3 % there is little change. Nalidixic acid does not alter the micellar distribution coefficient of *o*-hydroxybenzoic acid but chloramphenicol reduces the distribution. Nalidixic acid has no detectable effects on the cloud point of the polysorbate solutions, suggesting that it does not alter micellar structure. Alhaique *et al.* [48] conclude that if the added compound does not induce significant changes in micellar structure it will not alter the distribution into the micelle of another solubilizate; this problem requires further and more detailed examination, primarily because of its importance in pharmaceutical systems and because of the potential importance of the phenomenon in altering drug bioavailability from micellar systems. Preliminary work on permeation through polymer membranes [48] has shown that the reduction in permeation caused by solubilization of a solute can

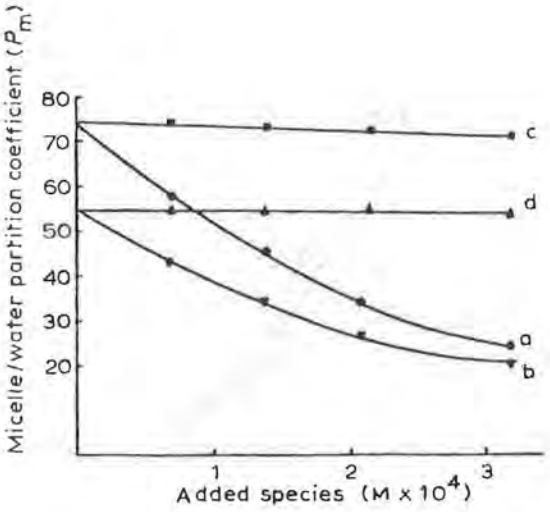


Figure 6.7 Changes in micelle/water apparent partition coefficient (P_m) of a solubilizate after progressive addition of a second species. Polysorbate 80 concentrations range from 1 to 3% w/v. Each plot refers to a constant concentration of the surfactant. *o*-Hydroxybenzoic acid partition coefficients on addition of benzoic acid ((a) 1 % and (c) 3 % w/v polysorbate 80). Benzoic acid partition coefficients on addition of *o*-hydroxybenzoic acid ((b) 1 % and (d) 3 % w/v polysorbate 80). Temperature, 25° ± 0.1°, pH = 2.0, and the initial solubilizate concentration, 3.2×10^{-4} M. Redrawn from Alhaique *et al.* [48].

be minimized to some extent by the addition of a second solute which would decrease the value of P_m; thus while nalidixic acid had no effect on the permeation rate of *o*-hydroxybenzoic acid, benzoic acid increases the permeation of this compound through polydimethylsiloxane from 5.61×10^{-10} mol cm^{-2} s^{-1} to 6.5×10^{-10} mol cm^{-2} s^{-1}.

An attempt to characterize the interaction of mixtures of preservative molecules with non-ionic surfactants using the theory of competitive binding was unsuccessful [49]. In the presence of a second preservative (C) which may act as a competitor, the binding equation may be rewritten

$$r = \frac{n_1 K_1 [D_f]}{1 + K_1 [D_f] + K_{c_1} [C_f]} + \frac{n_2 K_2 [D_f]}{1 + K_2 [D_f] + K_{c_2} [C_f]} \tag{6.7}$$

where $[C_f]$ is the concentration of free competitor and K_{c_1} and K_{c_2} are the intrinsic association constants of the competitors for binding sites of class 1 and class 2, respectively. Scatchard plots for the interaction of chlorocresol and cetomacrogol in the absence and presence of a constant concentration of methyl paraben are shown in Fig. 6.8. On increasing the concentration of methyl paraben there is a downward displacement of the curve suggesting competition between the solubilizates for the same binding sites. Theoretical lines obtained using Equation 6.7 are shown; reasonable agreement is shown, but this does not apply to chlorocresol–cetomacrogol systems in the presence of propyl paraben or

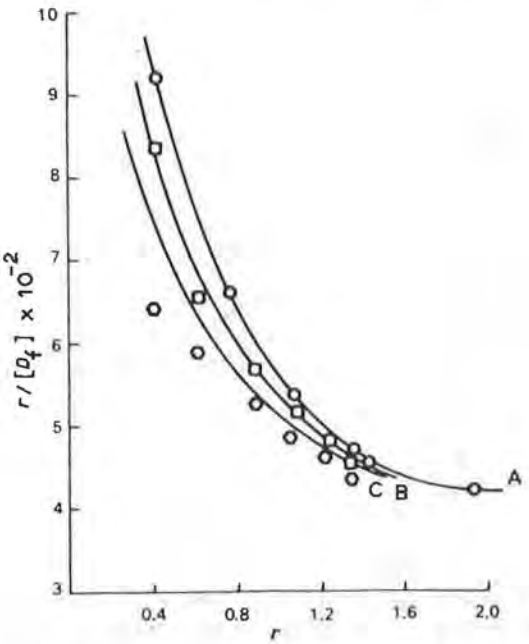


Figure 6.8 Scatchard plot for the interaction of chlorocresol with cetomacrogol in absence and presence of methyl paraben. Cetomacrogol concentration = 7.69×10^{-3} mol l^{-1}. Initial total methyl paraben concentration: ○, 0.0; □, 8.54×10^{-2}; ○, 13.14×10^{-2} mol l^{-1}. Points experimental, curves B and C calculated using Equation 6.7. From Kazmi and Mitchell [49].

perhaps surprisingly when the interaction of methyl paraben is measured in the presence of chlorocresol.

It is most likely that none of the preservative combinations used had exactly the same locus or are solubilized by the same mechanism, so that simple competition between the solubilizates in the micelle is unlikely; alternatively the interaction of some of the preservatives with the micelle (or monomers) leads to perturbations of micelle size and shape such that binding sites are altered in their capacity to accept solubilizate molecules.

For a mixture of two surfactants (S_I and S_{II}), Equation 6.11 becomes

$$r = 1 + \frac{n_1 K_1[M_1]}{1+K_1[D_f]} + \frac{n_2 K_2[M_1]}{1+K_2[D_f]} + \frac{n'_1 K'_1[M_{11}]}{1+K'_1[D_f]} + \frac{n'_2 K'_2[M_{11}]}{1+K'_2[D_f]}, \quad (6.8)$$

where M_1 and M_{11} are the molar concentrations of the two surfactants; n_1, n_2, K_1 and K_2 are constants for S_I and n'_1, n'_2, K'_1 and K'_2 are the corresponding constants for S_{II} as defined above. Kazmi and Mitchell [49] found that the extent of the interaction of a single preservative with a mixture of two surfactants can be predicted from a knowledge of the binding constants which characterize the interaction of the preservatives with the individual surfactants in the mixture. Variation of the free preservative concentration with total preservative concentration in mixtures of Texofor A16 and Texofor A60 are shown in Fig. 6.9a. The theoretical lines were calculated by substituting experimentally determined values of n_1, n_2 and K for each surfactant.

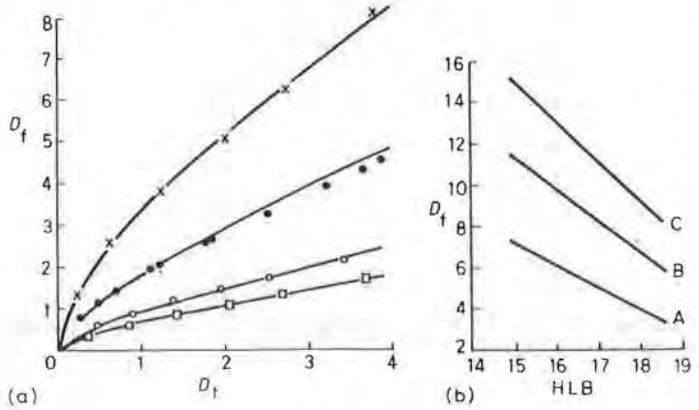


Figure 6.9(a) Variation of free preservative concentration $[D_f]$ with total preservative concentration $[D_t]$for the interaction of chlorocresol with mixtures of Texofor A16 and Texofor A60. Concentration of Texofor A16 and Texofor A60 in a mixture (mol l^{-1}): X, 50.89×10^{-3} A16 + 2.75×10^{-3} A60; ●, 10.57×10^{-3} A16 + 2.75×10^{-3} A60; ○, 10.57×10^{-3} A16 + 13.26×10^{-3} A60; □, 2.11×10^{-3} A16 + 5.51×10^{-3} A60. Points experimental, curves calculated.

(b) $[D_t]$ versus HLB at constant $[D_f]$ for the interaction of chlorocresol with Texofor A16, Texofor A60 and mixtures of Texofor A16 and Texofor A60. Total concentration of surfactant or surfactant mixtures = 1 % (w/v). Concentration of free chlorocresol $[D_f]$: A, 1.0×10^{-3}; B, 2.0×10^{-3}; C, 3.0×10^{-3} mol l^{-1}. HLB Texofor A16 = 14.88; HLB Texofor A60 = 18.67. Curves calculated from Kazmi and Mitchell [49].

When, for a given value of D_f, D_t is plotted as a function of the HLB of the surfactant mixtures, it is clear that in the Texofor mixtures a smaller total preservative concentration is required to maintain a given free concentration of chlorocresol as the HLB is raised (Fig. 6.9b). With cetomacrogol–polysorbate 80 mixtures there is a slight increase in the overall concentration of chlorocresol required, but these two surfactants have almost identical binding characteristics towards chlorocresol which is thought to reside in the ethylene oxide layer which is of about equal size in the two surfactants in question. It seems, therefore, that direct experimental verification of antibacterial and antifungal activities are still required in mixtures of surfactants and preservatives, although by judicious choice of preservative and surfactant once the characteristics of individual systems are known, reasonable calculations can be made of possible changes in activity.

Mitchell [50] has shown that the activity of chloroxylenol in water and in solutions of cetomacrogol 1000 is related to the degree of saturation of the system. A saturated solution of chloroxylenol in water was found to have the same bactericidal activity as saturated surfactant solutions containing up to 100 times as much chloroxylenol. It is thus apparent that the activity depends on the amount of the bactericide free in the aqueous phase; the compound has apparently no action inside the micelles. Table 6.5 shows some of these results and should emphasize the importance of these factors in formulation.

Table 6.5 Dependence of the death time of *E. coli* in chloroxylenol–cetomacrogol solutions on cetomacrogol concentration at 20° C at a constant chloroxylenol concentration of 1.5 %

Cetomacrogol conc. (mol l^{-1})	Saturation ratio*	Mean death time (min)
0.049	1.00	49
0.051	0.95	88
0.054	0.90	104
0.057	0.85	75–79 (h)

* The saturation ratio is the ratio of the amount of chloroxylenol present to its solubility in the solution.
From [50].

Of interest in this context are the results of Good and Milloy [51] (see Fig. 6.10). The partial pressure of phenol above CTAB–phenol–water solutions was determined as a function of phenol concentration by analysis of the gas phase above the solutions at 25° C. As P/P_0 is proportional to the activity of the phenol in the water, this, in accord with Ferguson's principle, should broadly determine its bactericidal activity. Studies of this nature on solutions with varying concentrations of surfactant would be valuable in interpreting the microbiological behaviour of such systems.

It has been suggested [52] that solubilization provides a means not only of

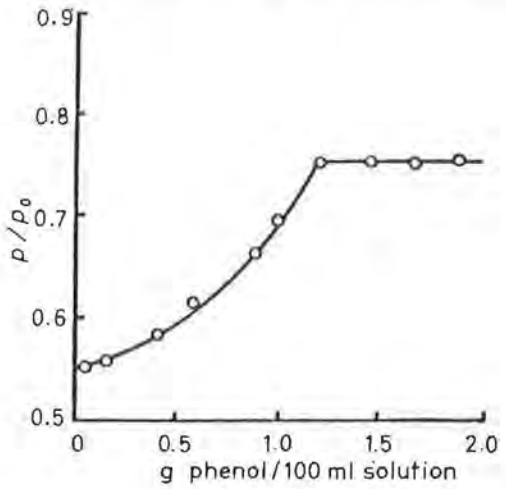


Figure 6.10 The partial pressure of phenol above solutions of phenol in 1% cetyltrimethylammonium bromide at 25°C; p = partial pressure of phenol in the surfactant solution; p_0 = the partial pressure of phenol in water. After Good and Milloy [51].

modifying the biological activity of the phenols but also of providing a reservoir of materials in the micelles which would prolong the duration of their action. The apparent divergence of opinion between Mitchell [50] and Bean and Berry [53, 54] probably results from the properties of the solubilizers used. If Mitchell's findings are of universal application, then the only point in having solubilized preparations of phenols is to provide a suitable form in which they may be distributed and diluted for use.

Note should be taken of the fact that Mitchell's results were obtained with a non-ionic detergent of the polyoxyethylene ether class in which tendency to complex with phenolic hydroxyls has been noted before: all evidence of synergism between surfactants and phenols have been with ionic soaps or with non-ionics of other classes. We may cite briefly some examples. Soaps of coconut oil, castor oil, or linseed oil increased the germicidal activity of various phenols in the absence of organic matter [55]; sodium riconoleate, sodium linoleate, resinate, and oleate enhanced the activity of chlorothymol, chlorocarvacol, thymol, chlorophenyl phenol, resorcinol, *n*-hexylresorcinol [56]; and sodium dodecyl sulphate has a similar effect on 2,4,6-trichlorophenol [57]. Shafiroff [58] quotes the synergistic effect of sucrose mono-laurate on *p-m*-chlorocresol against *Staph. aureus*. Sodium dodecyl sulphate, it should be remembered, has cytostatic and sometimes lytic activity by itself.

Calculations of free preservative concentrations in surfactant systems have been attempted by several workers. Evans and Dunbar [59] attempted with a simple approach to quantify the effects by calculating the free concentrations of antibacterial. Their derivation reproduced below leads to the relationship between $[D_a]$ the concentration of antimicrobial in the water phase, C_s the total concentration of solubilizer, $[D_m]$ the concentration of antimicrobial in the micelle, R the ratio of antimicrobial to solubilizer, and P_m the partition coefficient

of the antimicrobial substance towards the micelle phase

$$[D_a] = \frac{R[C_s]}{1 + P_m[C_s - \text{CMC}]} \tag{6.9}$$

where the critical micelle concentration of the surfactant is denoted by CMC. The assumption made in the derivation is that the concentration of monomers is constant above the CMC and that the surfactant has no effect on the intrinsic biological activity of the antimicrobial, which as we will see later is not always so.

Equation 6.9 is obtained as follows. $R = [D_t]/[C_s]$ and $P_m = [D_m]/[D_a]$

$$[D_t] = [D_m][C_m] + [D_a], \tag{6.10}$$

where $[D_t]$ is the concentration of the antimicrobial in the system in g g^{-1} and $[D_m]$ is the concentration in the micelle (g g^{-1} micelle). Using the product $[D_m][C]$ we convert this to g g^{-1} *system.*

$$\therefore \quad [D_a] = [D_t] - [D_m][C_m] \tag{6.11}$$

or

$$[D_a] = R.[C_s] - P_m.[D_a][C_m]. \tag{6.12}$$

As $[C_m] \approx (C_s - \text{CMC})$ we obtain, on rearrangement, Equation 6.9.

Evans and Dunbar's equation predicts a maximum biological activity at the CMC when R is constant at high P_m. Using this model and different values of P_m,

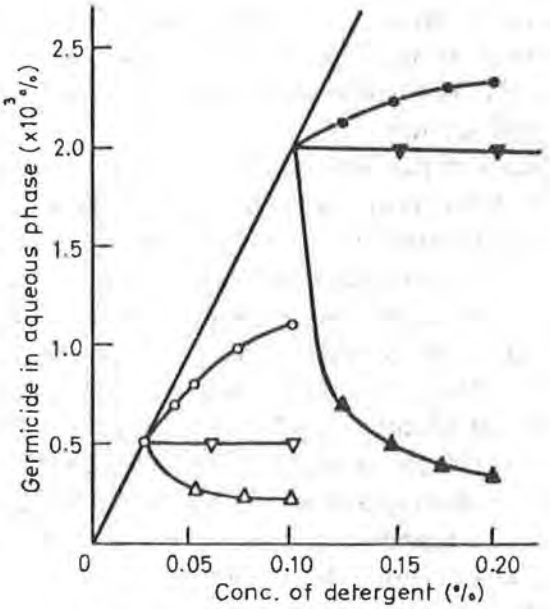


Figure 6.11 The effect of critical micelle concentration and solubilization on the concentration of germicide in aqueous phase, at a germicide: detergent ratio of 0.02. P_m is the distribution coefficient of germicide between aqueous and micellar phases

	P_m	CMC (%)		P_m	CMC (%)
○	1×10^3	0.025	●	7×10^2	0.10
▽	4×10^3	0.025	▼	1×10^3	0.10
△	1×10^4	0.025	▲	1×10^4	0.10

From Evans and Dunbar [59].

the concentration of active ingredient in the aqueous phase can remain the same, decrease, or increase slowly above the CMC (Fig. 6.11). The values of P_m used to construct Fig. 6.11 are reasonable. Methyl paraben has a $P_m = 3.24 \times 10^3$ and butyl paraben 7.29×10^4 in sodium lauryl sulphate solution [35]. Evans [60, 62] used a titration method to analyse preservative–non-ionic surfactant interactions, similar to that developed independently by Donbrow and Rhodes [61]. The method depends on the pH changes which occur when an acidic material is solubilized (see Chapter 5).

Knowing the total concentration of a substance, e.g. *p*-hydroxybenzoic acid, its dissociation constant, the concentration of detergent and P_m, it is a simple procedure to calculate the amount of acid dissolved in the aqueous and micellar phases at different pH values. The results of such a calculation assuming a total concentration of 0.1 % w/v *p*-hydroxybenzoic acid and 5.8 % w/v detergent are given in Table 6.6. If 0.1 % w/v is the optimum concentration of acid for a required preservative effect in water at pH 4, the concentration of the unionized acid – the active species – is 5.59×10^{-3} mol l^{-1}. Addition of 5.8 % of non-ionic detergent reduces this concentration to 1.14×10^{-3} mol l^{-1} as is seen in column 3 of Table 6.6.

The practical importance of these surfactant-preservatives is that much greater quantities of preservative must be added to a formulation containing a non-ionic to have an equivalent action to a specified amount in an aqueous solution. This is

Table 6.6 Effect of pH on solubilization of *p*-hydroxybenzoic acid in 5.8 % octylphenyl E 8.5, and percentage acid required to be equivalent to 0.1 % w/v acid

pH	[HA]* water	[HA]* detergent solution	% w/v required
3.5	0.00662	0.00118	0.56
4.0	0.00559	0.00114	0.49
4.5	0.00376	0.00104	0.36
5.0	0.00220	0.00081	0.27

* Molar concentration of unionized *p*-hydroxybenzoic acid in the aqueous phase.
From [60].

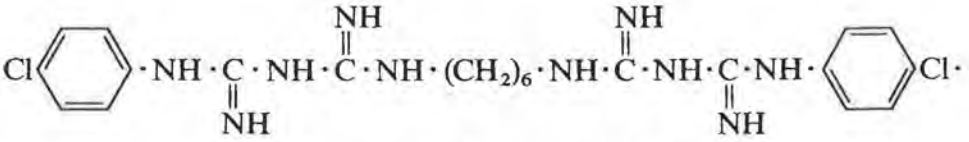
Table 6.7 Inhibitory concentrations of methylparaben in presence of polysorbate 80, observed for one month

Organism	Detergent conc. (%)	Inhibitory conc. (%)
A. aerogenes	0	0.075–0.08
	2	0.18–0.20
	4	0.28–0.30
	6	0.40–0.42
Asp. niger	0	0.045–0.05
	7	0.32–0.34

From [63].

illustrated in Table 6.7 after Pisano and Kostenbauder [63] which shows the inhibitory concentration of methyl paraben in the presence of polysorbate 80 against two organisms increases with increasing detergent concentration. Solubility data of methyl *p*-hydroxybenzoate in polysorbate at 27° C show that in a 5.8% solution it is five times more soluble than in water (1 mole benzoate for each 4 glycol units of detergent monomer [64]), and this agrees with the results of Table 6.7.

(c) CHLORHEXIDINE



Chemical structure of chlorhexidine available commercially as gluconate solution, acetate, and hydrochloride

(I)

Chlorhexidine possesses marked bactericidal action against a wide range of micro-organisms. The base has a low aqueous solubility (0.008% w/v); a wide range of salts have been prepared and their solubilities measured (Table 6.8). The dihydrochloride has a solubility of 0.06%, the diacetate 1.8% and as the gluconate has a solubility > 70% there would appear to be little need for the preparation of solubilized formulations. However, surfactants may be present in chlorhexidine formulations; because of the low solubility of chlorhexidine sulphate and related salts with inorganic ions present in water, extemporaneously prepared solutions diluted from concentrates may precipitate. Non-ionic and

Table 6.8 Chlorhexidine salts – water solubilities at 20° C

Salt	% w/v	Salt	% w/v	Salt	% w/v
(Base)	0.008	Diformate	1.0	Dilactate	1.0
Dihydriodide	0.1	Diacetate	1.8	Di-α-hydroxy*iso*butyrate	1.3
Dihydrochloride	0.06	Dipropionate	0.4	Digluconate	>70
Dihydrofluoride	0.5	Di-*iso*butyrate	1.3	Diglucoheptonate	>70
Diperchlorate	0.1	Di-*n*-valerate	0.7	Dimethanesulphonate	1.2
Dinitrate	0.03	Dicaproate	0.09	Di-isothionate	>50
Dinitrite	0.08	Malonate	0.02	Dibenzoate	0.03
Sulphate	0.01	Succinate	0.02	Dicinnamate	0.02*
Sulphite	0.02	Malate	0.04	Dimandelate	0.06
Thiosulphate	0.01	Tartrate	0.1	Di-isophthalate	0.008*
Di-acid phosphate	0.03	Dimonoglycolate	0.08	Di-2-hydroxynaphthoate	0.014*
Difluorophosphate	0.04*	Monodiglycolate	2.5	Embonate	0.0009*

* These are approximate values.
From [65].

quaternary ammonium surfactants serve to prevent this precipitation [65].

Surfactants may also be required as wetting agents and detergents and as emulsifiers in creams. Some non-ionic surfactant–chlorhexidine interactions are described by Senior [65]. 1 % and 3.3 % of polysorbate 80 reduces the activity of 0.1 % chlorhexidine acetate solution to 39 % and 14 %, respectively; corresponding figures for Lubrol W, a surfactant related to cetomacrogol, were 9 % and 5 %. Fig. 6.12 shows how the addition of ethanol to the formulation can reduce the interaction between the bactericide and the surfactant. The difference in surfactant uptake of two salts of chlorhexidine has been demonstrated by Wesoluch *et al.* [66] who conclude that the ion pair is solubilized into the micellar interior. The solubility of the diacetate is about six times that of the dihydrochloride in both Brij 96 and Tween 80. One might have expected the least soluble salt to have been solubilized to a greater extent but Fig. 6.13 demonstrates that this is not so and implies that the salt rather than the chlorhexidine ion is solubilized, a suggestion supported by the fact that the solubility of both salts increases in solvents of decreasing polarity. The surfactant properties of chlorhexidine diacetate [67] may induce the formation of mixed micelles in which the diacetate molecule retains its counter ions by orientating radially in the micelle with the surfactant monomers.

Differences in micellar uptake would affect the bactericidal effect of the chlorhexidine formulation; the choice of salt and surfactant must, therefore, involve a careful analysis of intrinsic solubilities and activities of the salts and their percentage solubilization in surfactant micelles.

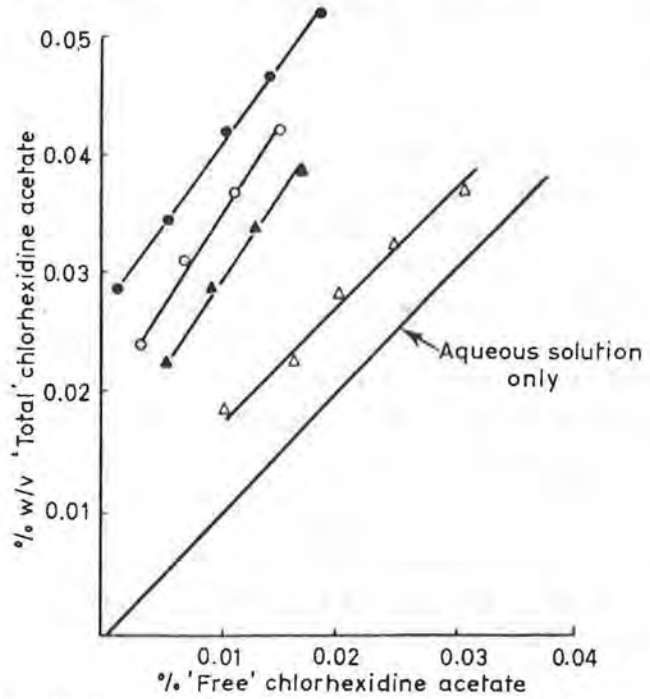


Figure 6.12 Effect of ethanol (v/v) on chlorhexidine acetate solubilization in 1 % w/v aqueous polysorbate 80. ●, 0 % ethanol; ○, 10 % ethanol; ▲, 20 % ethanol; △, 50 % ethanol. From Senior [65] with permission.

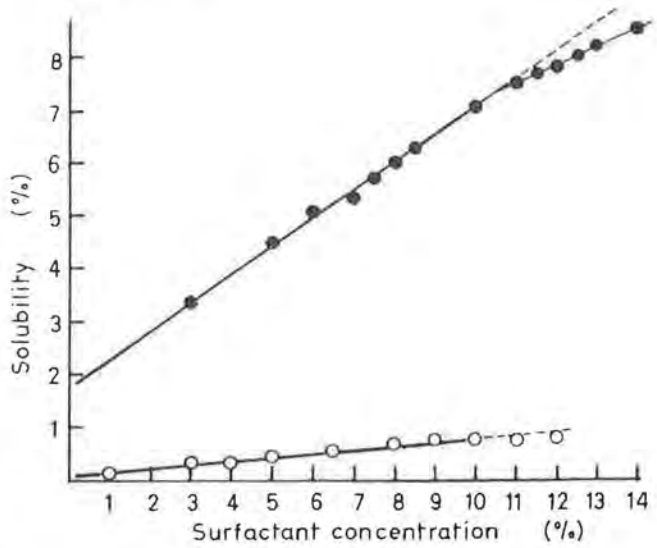


Figure 6.13 Solubility of chlorhexidine diacetate (●) and dihydrochloride (○) as a function of concentration of the decaoxyethylene oleic ether, Brij 96. Each point is the average of two or three independent determinations. From Wesoluch *et al.* [66] with permission.

(D) HEXACHLOROPHENE

The bactericidal properties of hexachlorophene in surfactant solutions have been studied by a number of workers [68–70]. Hexachlorophene is used in soaps for pre-operational scrubbing – the United States Pharmacopoeia has a hexachlorophene liquid soap which is a 0.225–0.26% w/v solution of hexachlorophene in a 10% potassium soap solution. Concern over the percutaneous absorption of hexachlorophene and its subsequent toxicity in infants has given fresh relevance to investigations of hexachlorophene–surfactant interactions. The effect of surfactants on skin permeability is discussed in Chapter 7.

Russell and Hoch [71] have claimed that the presence of non-ionic detergents in a number of shampoo formulations has no effect on the antibacterial action of bacteriostats (including hexachlorophene), but their results are difficult to interpret because of the presence in each formulation of additional surfactants. The biological action was, however, considered to be as great as or greater than that of preparations containing triethanolamine lauryl sulphate as the solubilizer and soap. The two detergents have, perhaps, some synergistic effects.

Anderson and Morgan [72] have related the solubilization of hexachlorophene with its biological activity, the bactericidal action being related to the concentration of unbound hexachlorophene, but the results of agar-plate diffusion tests could not be correlated with either the concentration of unbound agent or its total concentration.

(E) IODINE SYSTEMS

The term iodophor (phoros: bearer, carrier) is used to describe preparations of iodine in surfactant solutions. While all types of surfactant can be used to

solubilize iodine, non-ionic polyoxyethylene derivatives have been found most suitable, as the iodophor can be formulated without instability in acid conditions in which antibacterial activity is enhanced. Iodine may be solubilized to the extent of 30% by weight, of which three-quarters is released as available iodine when the iodophor is diluted. A cationic iodophor has, however, been used as an irrigant for the conjunctival sac and lachrymal passages.

Gershenfeld and Witlin [73] found that 1.49% iodine was soluble in a 1:1 mixture of propylene glycol and water. In most cases the bactericidal efficiency of iodine–iodide solutions prepared in aqueous propylene glycol was identical with that of Iodine USP XIII, and a satisfactory non-irritant formulation was given containing 2% iodine and 2.4% sodium iodide in distilled water containing 25–50% propylene glycol. Osol and Pines [74] investigated the solubility of iodine in aqueous ethylene, diethylene, triethylene, and propylene glycols and in glycerin, and cite evidence to support the presence of Lewis acid–base-type interactions in the solubilization process. To increase the solubility of the iodine to any great extent, large quantities of the glycols are required; this is a disadvantage.

Values for the solubility of iodine in water at 20° C vary between 0.335 and 0.285 $g l^{-1}$ [75]. The problem which occurs when such small quantities of iodine are dissolved results from the depletion of the solution through interaction of the iodine with the bacterial proteins. The use of non-ionic surfactants to produce systems with a high proportion of iodine was first described by Terry and Shelanski [76]. Unlike iodine–iodide systems, iodophors can be diluted without causing the precipitation of the iodine. Among other advantages claimed for iodine–surfactant systems are increased stability and decreased corrosion of metals, for example in instrument sterilization. Iodine is lost less readily from iodine–cetomacrogol solutions than from iodine solution (NF), as shown in Fig. 6.14 from Hugo and Newton [77]. It is an important consideration that the major proportion of iodine applied to a surface, for example, in the form of Strong Iodine Solution USP, is lost through sublimation [78]. Allawala and Riegelman [79] give evidence of the penetration of an iodophor solution (iodine–polyoxyethylene glycol nonylphenol) into the hair follicles of the skin, whereas iodine–iodide showed no such ability. This combination of less rapid sublimation and superior penetration results in enhanced activity. The product 'Wescodyne' (7.75% polyoxyethylene polypropoxyethanol–iodine complex; 7.75% nonylphenyl polyoxyethylene glycol ether–iodine complex and 0.1% HCl) is highly fungicidal and lethal to tubercle bacilli, the bactericidal action of the iodine being enhanced in the iodophors [80].

Iodophors are used in the dairy industry for sterilizing equipment and for application to cows' udders. In addition to the advantages already listed, the iodophor prevents the accumulation of milkstone by solubilization of the salts which are associated with the formation of these deposits [81].

The mechanism of solubilization of iodine by non-ionic surfactants has been discussed by a number of workers [82, 83], who have concluded in favour of the formation of a complex rather than true micellar solubilization. Polyoxyethylene

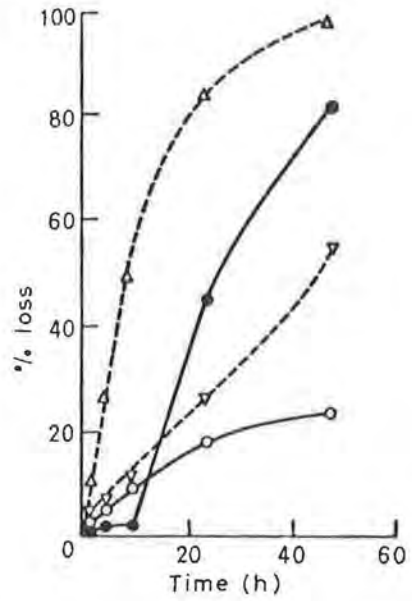


Figure 6.14 Changes in the weight and iodine content of iodine preparations stored in open beakers at room temperature. △ % weight of iodine solution; ▽ % weight of iodine–cetomacrogol complex; ● % weight of iodine lost from iodine solution; ○ % weight of iodine lost from iodine–cetomacrogol complex. From Hugo and Newton [77] with permission.

glycols increase the solubility of iodine in water, suggesting some complexation with the ether oxygens. Henderson and Newton [84] suggest that 1:1 charge transfer complexes are formed, characterized by a negative standard enthalpy change (ΔH^*). Negative ΔH^* values can also be observed for iodine–potassium iodide systems. If the reason for the increase in solubility is the formation of a complex with the ether oxygens one would expect little effect from the presence of micelles in solution. A comparison of Fig. 6.15a and b will show the great difference between the amount of iodine solubilized in cetomacrogol solutions (micellar) and in polyoxyethylene glycol solution (PEG 1540, 35 units) in the same concentration region. The molecular ratios of iodine to ether found for a series of monocetyl ethers and monolauryl ethers show that neither an ethylene oxide unit nor a molecule of ether associates with one molecule of iodine. The association must be more complex than the simple acid–base-type postulated for glycol–iodine interactions.

It should be remembered that evidence of complexation does not preclude the possibility of normal micellar solubilization.

Fig. 6.15 shows that the ratio of available iodine to total iodine in the cetomacrogol iodophor is approximately 0.86, a value which agrees well with those of Brost and Krupin [85] (0.775 and 0.80 for two non-ionic iodophors prepared with a nonyl phenylether).

The formation of solid polyoxyethylene glycol–iodine complexes is the cause of the incompatibility of potassium iodine–iodine solutions and certain glycol ointment bases [86]. A polyoxyethylene glycol 4000–iodine precipitate can be

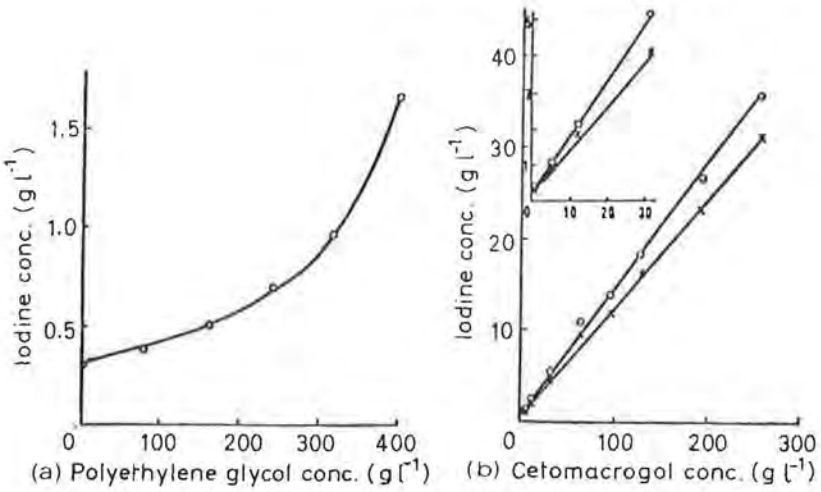


Figure 6.15(a) The solubility of iodine in aqueous solutions of polyoxyethylene glycol 1540 at 20° C. (b) The solubility of iodine in cetomacrogol solutions at 20° C is denoted by the open circles. The available iodine is shown by the crosses; the inset shows the effect at low cetomacrogol concentrations. The much higher solubility of iodine in the detergent solutions is evident. From Hugo and Newton [77] with permission.

assumed to have the iodine randomly distributed along its ether oxygens, not every oxygen being co-ordinated, according to Hiskey and Cantwell [87]. Their results are explicable in terms of a competing equilibrium for the iodine by the ether oxygens and iodide present in solution.

A complex between iodine and the micelles of non-ionic association colloids has been discovered in both aqueous and non-aqueous media [88]. Because of the similarity of the absorption spectra of the complex in aqueous and non-aqueous media – the ligand is shown to be the tri-iodide ion in both cases – Ross and Baldwin suggest that the site of the interaction between the tri-iodide species and the micelle is at the boundary between the hydrophobic and hydrophilic regions of the micelle. In aqueous and non-aqueous systems these regions are simply 'reversed', leaving the ions in identical environments.

(F) GLUTARALDEHYDE

Glutaraldehyde is an effective sporicide and chemisterilant. In alkaline solution it is effective but unstable; in acid conditions it is stable but weakly active. Cationic surfactants were suggested as stabilizing agents and the advantage of the addition of non-ionic surfactants has been demonstrated [89, 90]. As activity of glutaraldehyde has been enhanced by addition of divalent cations, various surfactant–cation combinations have been examined as possible potentiators and stabilizers of glutaraldehyde biocidal activity [91]. The magnesium salt of sulphated lauryl alcohol (Empicol ML 26A) was found to be effective in maintaining stability over 12 months and as a synergistic agent. Some of the effect may be on solution pH as Table 6.9 indicates. Table 6.9 compares bactericidal and fungicidal activity of two surfactant (Empicol) formulations with the activity of the simple solution and of an alkaline solution.

Table 6.9(a) Bactericidal activity of glutaraldehyde formations (0.01 % w/v) at 180° C (initial viable count: 1×10^8 ml^{-1})

Additive	Concentration (%)	Formulation pH	Time (min) for 99.9 % kill of:		
			E. coli	*Staph. aureus*	*Ps. aeruginosa*
Empicol	2.5	7.08	22	9	25
Empicol	10.0	7.60	15	7	20
None	—	4.6	120	100	65
$NaHCO_3$	0.3	7.9	20	12	35

(b) Fungicidal activity of glutaraldehyde formulations (0.5 % w/v) at 18° C (initial spore count: 1×10^6 ml^{-1})

Additive	Concentration (%)	Formulation pH	Time (min) for 99.9 % kill of:	
			A. niger	*T. mentagrophytes*
Empicol	2.5	4.8	110	75
Empicol	10.0	4.9	105	65
None	—	4.3	>180	>180
$NaHCO_3$	0.3	7.9	80	45

From [91].

6.2.2 Antibiotics and sulphonamides

The antibiotics and sulphonamides have been formulated in micellar solutions in the same way as other poorly soluble medicaments, but the range of chemical structures which exist would make it difficult to predict without experiment the solubilities of such drugs in surfactant solutions.

(A) CHLORAMPHENICOL

Chloramphenicol, soluble 1 in 400 of water at 20° C and 1 in 7 of propylene glycol, has been solubilized in Tween solutions [92, 93]. In spite of its superior solubility in propylene glycol, this compound cannot be used as a solvent for chloramphenicol in eye-drops or nasal preparations since it causes a marked burning sensation. Simple aqueous solutions of chloramphenicol lose about half their antibiotic activity by hydrolysis on storage for 290 days at 20 to 22° C [94].

Chloramphenicol 1 %, polysorbate 80 6 %, in water for injection has been suggested as an ophthalmic solution [95]. Other formulae have been given and some of these are collected in Table 6.10. A solution of the antibiotic has been prepared in 50 % *N*,*N*-dimethylacetamide as an intravenous injection. *N*,*N*-dimethylacetamide is a hydrotropic substance, a group of compounds whose actions are discussed in Section 6.7. Different crystal forms of chloramphenicol palmitate are soluble to differing extents in solutions of polysorbate 60. A detailed study of the solubilization of chloramphenicol in cetomacrogol solutions has been reported by Rogers [98]; Regdon-Kiss and Kedvessy [99] have studied the

Table 6.10 Solubilized chloramphenicol preparations

Chloramphenicol (%)	Solubilizer (%)	Reference
1	6% polysorbate 80	[95]
1.22	10% polysorbate 80	[96]
1.56	10% Brij 35	[96]
5.00	50% polysorbate 20	[97]
25.00	50% *N*,*N*-dimethylacetamide	
25.00	40% *N*-methyl-2-pyrrolidone	[98]

surface tension of polysorbate 20 solutions containing solubilized chloramphenicol.

(B) TYROTHRICIN AND RELATED SUBSTANCES

A mixture of gramicidin and tyrocidin, tyrothricin is stable in aqueous solutions of cationic and non-ionic surface-active agents. A 0.025% solution of the drug in 0.05% aqueous cetyltrimethylammonium bromide is stable for at least 6 months and the solution has a somewhat greater bactericidal action than solutions of either component alone. Levin [100] describes tyrothricin solutions containing 0.02% w/v of the antibiotic and employing 0.05% polyoxyethylene sorbitan monolaurate or 0.02% cetylpyridinium chloride as solubilizer. The latter solution is unstable in the presence of high concentrations of electrolytes, and a non-ionic should be used wherever there is the possibility of electrolyte contact. An isotonic solution for topical application (Soluthricin^{R}) which contains 0.05% tyrothricin and 0.05% cetylethyldimethylammonium bromide is stable for at least 1 year at room temperature [101]. A concentrate containing 2.5% antibiotic and 2.5% surfactant which can be diluted for normal use has been marketed [102–104]. 4.98 g tyrothricin can be solubilized per gram 20% polysorbate 80 solution [105]. Such concentrates can be incorporated into jellies, emulsions, or ointments. In some manufacturing procedures it is convenient to evaporate off the aqueous phase, leaving a dried residue of surfactant and drug usable in tablet or ointment formulations; the requisite amount of solubilizer is then available when the dosage form is dissolved in the gastro-intestinal tract or in the body cavity and will promote the dissolution of the antibiotic.

Gillissen [104] finds that the antibacterial action of tyrothricin is influenced by the presence of solubilizers. Cationic surfactants have a synergistic effect (as mentioned above) on its activity against Gram-positive and Gram-negative bacteria, whereas polysorbate 80 inhibits its activity. It is thus important that these effects are borne in mind, and a compromise must be found between the stability and incompatibility characteristics of the solution and the activity of the product. The complexity of the situation is revealed by the fact that the activity of bacitracin is enhanced by the presence of cationic and non-ionic surfactants [106] but decreased by anionic agents. The effect of non-ionic surfactants on the bactericidal activity of tyrothricin has been measured [107]. Some results are shown in Table 6.11.

Table 6.11 Relation between HLB of polyoxyethylene glycol stearates and polyoxyethylene glycol sorbitan fatty acid esters and the minimum bactericidal concentration of tyrothricin. Surfactant concentration 2×10^{-3} mol l^{-1}

Surfactant	HLB	Min. bactericidal concentration (10^{4} mol l^{-1})
PEG-900-stearate	15.0	4.4
PEG-1800-stearate	16.9	6.8
PEG-4700-stearate	18.8	9.3
PEG-900-Sorbitan laurate	16.7	4.3
palmitate	15.6	5.6
stearate	14.9	6.7

From [107].

Tyrothricin is surface active (see Fig. 6.16). Its size would seem to preclude significant interaction with micelles but the data in Table 6.11 show clearly that interactions occur, possibly by formation of mixed micelles.

Substances such as gramicidin J_1 and chloramphenicol, although they are only slightly soluble in water, have a high antibacterial activity. This presents little problem in *in vitro* antibacterial testing, but where study of a series of antibiotic derivatives is being made, low activity combined with low solubility can cause obvious difficulties. Such a problem was encountered during an investigation into the activity of a series of acyl derivatives of gramicidin J_1. Solubilization of the antibiotics in detergent solutions was possible – gramicidin J_1, aureothricin, and trichomycin were solubilized in a variety of non-ionic and cationic surfactants – but activity was affected in a variety of ways. Chloramphenicol,

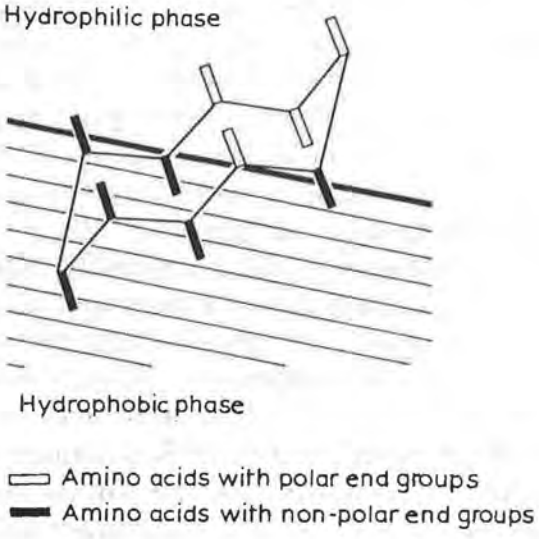


Figure 6.16 Schematic representation of the possible orientation of a tyrothricin molecule at the micellar interface between the hydrophobic core and the hydrophilic envelope of a non-ionic detergent. After Ullmann *et al.* [107].

dihydrostreptomycin, and colistin represent antibiotics suffering no, partial, and strong influence of surfactant, respectively. However, the activity of the antibiotics changed linearly with concentration and although polysorbate 80 and polyoxyethylene (15) octylphenol affect the colistin in opposite ways, extrapolation of results to zero surfactant concentration gives a value which agrees well with that determined in simple aqueous solution. This serves as a basis for the antibacterial test for poorly soluble substances: activities are determined at a number of surfactant concentrations and the minimum inhibitory concentration versus concentration (surfactant) plot is extrapolated to zero surfactant concentration [108].

Observations on the activity of antibiotic–surfactant combinations are not easy to collate. For example, although polysorbate 60 and Myri 52 (Polyoxyl 40 Stearate USP) do not impair the activity of bacitracin, oxytetracycline hydrochloride, polymixin B sulphate, or neomycin sulphate [109], Bliss and Warth [93] have concluded that polysorbate 80 potentiates the action of polymixins B and D and circulin. Brown and Winsley [110, 111] also reported that polymixin B and polysorbate 80 act synergistically against *Pseudomonas aeruginosa* on viability, cellular leakage and lysis, although the surfactant alone possessed little intrinsic activity. In attempts to elucidate this effect, spheroplasts of *Ps. aeruginosa* have been used as the test organisms for polysorbate 80-polymixin combinations [112]. The conclusion was that the synergism of action was probably due to the penetration of polysorbate 80 into the cytoplasmic membranes, facilitated by polymixin induced damage to the outer membrane and secondly to their combined action on the outer membrane structure and function. Concentrations of polysorbate 80 up to 10% w/v are required to reduce the growth rate of *Ps. aeruginosa* cultures [113] while less than 0.01% will lyse the corresponding spheroplast.

(c) GRISEOFULVIN

Orally administered griseofulvin is poorly and irregularly absorbed in rats and humans. Work has been directed towards increasing its absorption. Micronization of the drug has resulted in increased activity gram per gram [114, 115] but the effect of surface-active agents is not so obvious. Kraml *et al.* [116] believe that the addition of surfactants to either aqueous or corn-oil suspensions does not alter the levels of griseofulvin in the serum, yet Duncan *et al.* [117] observed that addition of butylated sodium naphthalene sulphonate (one of the compounds used by Kraml) to suspensions gave rise to higher serum levels of griseofulvin.

Griseofulvin has a low aqueous solubility – of the order of 1 mg per 100 ml – and solubilization as a means of improving its activity has been investigated [118]. In 2% NaLS at 30° C, the solubility of griseofulvin reaches 171 mg per 100 ml, too low to be of practical use as the oral dose is of the order of 125 mg. A comparison of griseofulvin plasma levels following oral administration of a solution (0.5% in polyoxyethylene glycol) and a suspension showed that higher levels were obtained with the solution. Sodium lauryl sulphate improved

the blood levels of griseofulvin with a specific surface area 0.41 $m^2\ g^{-1}$, but reduced the levels obtained with samples of specific surface area of 1 $m^2\ g^{-1}$. It did not enhance the activity when given in multiple doses. Apparently, multiple dosing improved the efficiency of absorption as much as the surfactant could.

Bates *et al.* [119] have studied the solubilization of griseofulvin by bile-salt solutions in order to gain insight into the possibility that insoluble drugs may be absorbed by a mechanism involving preliminary solubilization of the drug by the bile salts which are normally present in the intestine. Hexoestrol and glutethimide were also studied; solubilization was found to increase in the order griseofulvin < glutethimide < hexoestrol.

Lysolecithin is also capable of solubilizing griseofulvin [120]. Solubilization in a range of non-ionic surfactants [121, 122] failed to achieve realistic levels of griseofulvin in an isotropic solution. Uptake increased in a homologous series with increasing oxyethylene chain length and in individual surfactants with increasing temperature but neither effect was dramatic [121]. Recent results [122] with surfactants based on erucyl and behexyl (C_{22}) alcohols (ErE_{24} and BE_{21}) indicated uptake of griseofulvin to the extent of $0.83 \times 10^{-2}\ g\,g^{-1}$ and $0.62 \times 10^{-2}\ g\,g^{-1}$ surfactant, respectively, compared with $0.95 \times 10^{-2}\ g\,g^{-1}$ of $C_{16}E_{20}$. Synthetic non-ionic surfactants with long-chain hydrocarbons (C_{32-35}) or long polyoxyethylene chains have been found by Arnarson and Elworthy [123] to solubilize less efficiently than $C_{16}E_{20}$. This perhaps suggests that manipulation of surfactant structure is not going to lead to systems with visibly increased solubilizing capacity. It may be that the subsidiary effects of surfactants such as their influence on dissolution rate may, for some drugs at any rate, be the sole advantage of inclusion in a formulation. The dissolution rate of griseofulvin is increased by a wide range of surfactants [119, 120, 124]. 1% of non-ionic surfactant can increase the rate of solution of griseofulvin by 2.5 to 3 times; higher surfactant concentrations increase this to up to 8 times. Further increase in

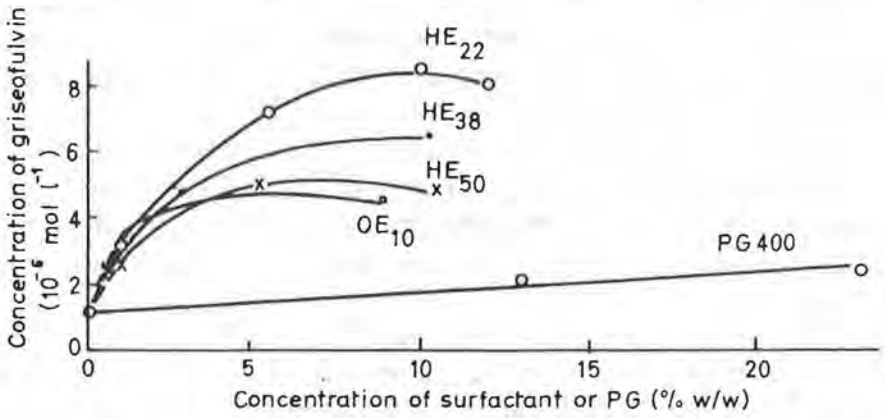


Figure 6.17 The amount of griseofulvin dissolved after 100 min in contact with various surfactant and polyoxyethylene glycol solutions, showing the decrease in rates of dissolution at higher surfactant concentrations. $H = C_{16}H_{33}$, from Elworthy and Lipscomb [124] with permission.

surfactant concentration is frequently not beneficial as the increased viscosity of the solution media will reduce solution rate giving the solution rate profile as shown in Fig. 6.17 an effect also noted in other work [125].

(D) PENICILLIN

Most of the penicillins are available as soluble salts and the need for solubilization is not great. Some of the less soluble derivatives, e.g. the *N*-benzylphenylethylamine salt of benzyl-penicillin, are used purposely, and this is the basis of their prolonged activity.

In aqueous solutions macrogols inactivate penicillin [126], as do many non-ionic and ionic surfactants [127]. However, aqueous solutions of benzalkonium chloride and dioctylsulphosuccinate have been used as solvents for penicillin for topical instillation therapy of the sinus tract [128].

(E) STREPTOMYCIN

The solubility of dihydrostreptomycin sulphate, which is water soluble, is decreased in concentrated solutions of sorbitan monolaurate (E = 12) [129]. Streptomycin sulphate is also very soluble in water and is incompatible with sodium lauryl sulphate. Combination of streptomycin with polysorbate 20 produces a strong bacteriostatic effect against antibiotic resistant bacteria. Intrapleural injection of 0.5 g dihydrostreptomycin with 'one drop' of polysorbate 20 in 4 ml has been reported to result in a sterile pleural sample 1 week after injection [130].

(F) AMPHOTERICIN B

The polyene antibiotic amphotericin B is poorly soluble in water at neutral pH. Suspensions of the antibiotic when injected by subcutaneous or intramuscular routes cause pain and are poorly adsorbed. Solubilized preparations of amphotericin B, which are more active than the crystalline form are available [Fungizone Intravenous (Squibb), Amphotericin B for Injection USP; Amphotericin Injection BNF] employing sodium deoxycholate as solubilizer. However, intravenous injection of the colloidal preparation is likely to cause a greater incidence of nephrotoxicity and nausea, probably because of the ability of the solubilized antibiotic to persist in the circulation; this is offset by its greater activity and ease of handling [131]. The solubilized systems may be diluted with Dextrose Injection but precipitation has been reported within 6 hours of its addition. Procaine hydrochloride, lignocaine hydrochloride and chlorpromazine hydrochloride cause the precipitation of amphotericin [132, 133] possibly by complexing with the solubilizing agent. The solubilized preparation is also precipitated by addition to sodium chloride injection [134].

An intravenous solution of another antifungal agent, miconazole, is available as a 200 mg solution in 10% Cremophor EL (Daktarin, Janssen) some of whose properties as an intravenous solubilizer are discussed in the next chapter.

(G) SULPHONAMIDES

The less-soluble sulphonamides are liable to be deposited in the renal tubules or ureters after oral administration. The consequent renal damage may be prevented by maintaining an alkaline urine and a high liquid intake. The use of surfactants to prepare solubilized preparations or prevent the precipitation of excess compound in the tubules is a possibility that does not seem to have been investigated. Other potential sulphonamide–surfactant interactions possibly need investigation as phthalylsulphathiazole is almost insoluble in water and is used to treat infections of the intestine, from which it is only sparingly absorbed. The presence of surfactants, whether natural or ingested, could interfere with the absorption of this sulphonamide. Similarly, since sulphonamides when used on wounds penetrate the skin with difficulty, Hadgraft [135] states that the use of aqueous vehicles containing alkylbenzene sulphonates promotes the absorption of sulphonamides through the hair follicles. This could lead to toxic systemic effects. Absorption of insoluble drugs designed to act in the intestine has been suggested before, in the case of clioquinol. The occurrence of neurotoxic reactions following oral administration of halogenated hydroxyquinolines has been reported. Whether the toxic symptoms were due to genetic factors, duration of administration or formulation effects remain to be established. Clioquinol and di-iodohydroxyquinoline tablets may contain dispersing agents to aid wetting of the hydrophobic drugs. A brand of clioquinol tablets (Entero-Vioform tablets) contains a synthetic surfactant (sapamine) as a wetting agent. The systemic absorption in man of clioquinol, administered as a powder with 7% sapamine, has been confirmed [136]; Khalil and El-Gholmy [137] have shown the effectiveness of sapamine in increasing the dissolution rate of both clioquinol and di-iodohydroxyquinoline *in vitro*; a 0.2% NaLS solution causes an 18-fold increase in rate of clioquinol solution. While this does not necessarily imply a biological effect, the possible implications are clear.

Khawam *et al.* [138, 139] studied the solubilization of sulphanilamide in polysorbate 20, 60, and 80 solutions. The effect is not striking: a 4% solution of polysorbate 20 increases the solubility of the drug at 24° C from 7.17 g l^{-1} to only 9.81 g l^{-1}, and there are no great differences between the three detergents. It is doubtful if this is a micellar effect, as the solubility is also increased by 10% aqueous solutions of PEG 400, 4000, and 6000.

The behaviour of sulphisoxazole in surfactant and glycol solutions has been studied in a series of papers [140, 141]. In order to clarify the mechanism of the reduction in rectal absorption of this sulphonamide in the presence of PEG 4000 the effect of this compound on its physicochemical properties was examined. There is a linear relationship between the solubilities of sulphathiazole, sulphapyridine, and sulphisoxazole and the concentration of PEG 4000. The drugs apparently do not form complexes with the glycols; it is thought that the reduction in activity is due to a depression of the concentration of the drug in rectal lipid. The effect of non-ionic surfactants is to reduce the absorption of the sulphonamides through solubilization in micelles [141]. Fig. 6.18 indicates the extent of solubilization in polysorbate 80 solutions. Values of apparent distri-

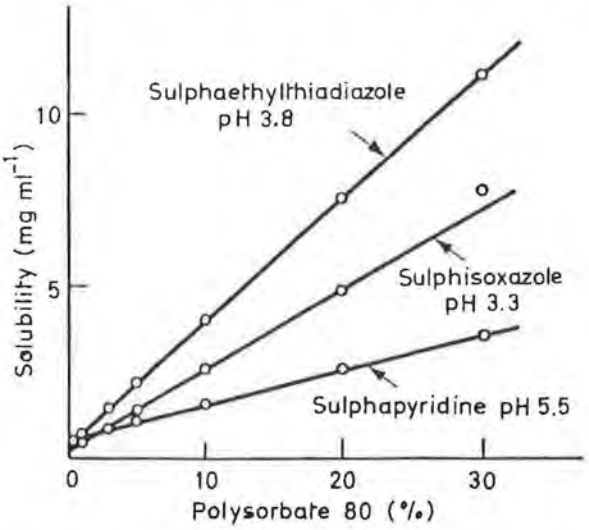


Figure 6.18 The solubility of sulphaethylthiadiazole, sulphisoxazole, and sulphapyridine in buffered solutions of polysorbate 80. From Kakemi *et al.* [141] with permission.

bution coefficients were obtained (K_m is the apparent distribution coefficient of the unionized drug between micelle and aqueous solution – the higher its value, the greater is the possibility of finding the drug in the micellar 'phase') in solutions of polyoxyethylene surfactants. Table 6.12 shows that the more hydrophobic the detergent, the greater the tendency of the sulphonamide to partition in favour of the micelle. Ionized sulphonamides are poorly solubilized in the micelles, but it is the unionized form which is biologically active. A correlation between K_m and the reduction in rectal absorption can be seen by comparing the values in Table 6.12 with the effect on absorption shown in Fig. 6.19a and b. The higher the K_m value, the greater is the reduction in absorption.

The diffusion of sulphanilamide from ointments has been increased by addition of either Tweens or Spans [142]. This, then, is another mechanism whereby surfactants can influence the effectiveness of formulation. For example, Sulphanilamide (5%) in petrolatum does not inhibit sensitive *Staph. aureus*, yet in

Table 6.12 Values of the apparent distribution constant of unionized sulphisoxazole in presence of non-ionic surfactant

Non-ionic surfactant	K_m
Polyoxyethylene sorbitan monolaurate	0.90
Polyoxyethylene sorbitan monopalmitate	0.95
Polyoxyethylene sorbitan monostearate	1.20
Polyoxyethylene (30) – stearate	1.00
Polyoxyethylene (45) – stearate	0.70
Polyoxyethylene (10) – lauryl ether	1.50
Polyoxyethylene (15) – lauryl ether	1.00

From [141].

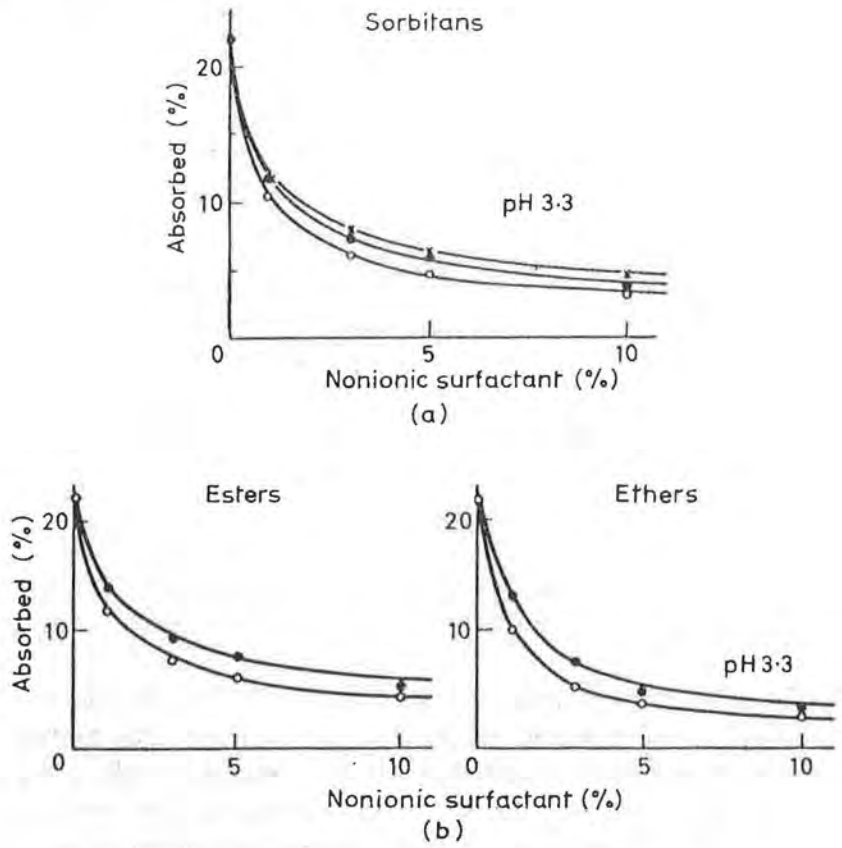


Figure 6.19(a) The effect of polyoxyethylene sorbitan alkyl esters on the rectal absorption of non-ionized sulphisoxazole.

×—× polyoxyethylene sorbitan monolaurate
●—● polyoxyethylene sorbitan monopalmitate
○—○ polyoxyethylene sorbitan monostearate

(b) The effect of polyoxyethylene alkyl esters and ethers on the rectal absorption of non-ionized sulphisoxazole at pH 3.3.

LH diagram
○—○ polyoxyethylene stearate-45
●—● polyoxyethylene stearate-30
RH diagram
○—○ polyoxyethylene lauryl ether-10
●—● polyoxyethylene lauryl ether-15

From Kakemi *et al.* [141].

the presence of polysorbate 20 (15%) some inhibition is observed; in the presence of the same concentration of PEG 400 large inhibition zones have been noted [143]. These results should be considered in the light of the previous remarks and the finding that at 1% concentration levels polysorbates 20, 40, 60, and 80 markedly reduce the activity of sulphanilamide and it is likely that the surfactant increases release rate but decreases the activity of the drug.

Span 60 (sorbitan monostearate) and Atlas G-2164 (Polyoxyethylene propylene glycol monostearate) increase the absorption of sulphathiazole from a

Table 6.13 Solubility of sulphacetamide sodium and sulphathiazole sodium in liquid petrolatum and cottonseed oil bases

Base	Surfactant	Sulphacetamide sodium solubility (mg %)	Sulphathiazole sodium solubility (mg %)
Liquid petrolatum	None	Negligible	Negligible
	1% Arlacel 83	2.18	1.83
	5% Arlacel 83	9.27	0.84
	10% Arlacel 83	17.14	1.52
Cottonseed oil	None	0.86	1.48
	1% Arlacel 83	0.79	0.92
	5% Arlacel 83	8.09	2.13
	10% Arlacel 83	19.95	2.04

From [145].

lanolin–petrolatum base [144]. It is not possible to decide whether this is due to a solubilization effect or a simple miscibility effect. However, it is known that surfactants increase the solubility of soluble sulphonamides in ointment bases. Whitworth and Becker's results [145] are shown in Table 6.13. Arlacel 83 increased the diffusion of both drugs from the cottonseed oil; the highest concentration of surfactant decreased the diffusion process from the petrolatum base. It is evident that the solubility of a drug in the vehicle is an important factor in the process. Solubilization will increase the saturation levels of the drug and will tend to promote its diffusion from the vehicle.

An ultracentrifugal study of polysorbate–drug interaction [146] has given values of apparent micellar partition coefficients for sulphapyridine and sulphisoxazole quite different from those quoted in Table 6.12 for sulphisoxazole, although no reference is made to this. A P_m of 79 ± 2 is quoted for sulphisoxazole in 1 to 4% polysorbate 80 at 0.001 and 0.01% solute levels.

(H) TETRACYCLINES

Naggar *et al.* [147] investigated the solubilization of the zwitterionic antibiotics tetracycline and oxytetracycline by polysorbate 20 and 80 at pH 5 and assumed that the interactions were due to some form of 'complexation' which seems unlikely. A wider range of tetracyclines and their interactions with a non-ionic, anionic and cationic surfactant were studied by Ikeda *et al.* [148] over a pH range of 2.1 to 5.6. It is unlikely that surfactant solutions of tetracycline are required, but the results are relevant in discussing tetracycline–surfactant interactions that could influence the activity of the antibiotic. Apparent partition coefficients of four tetracyclines in a polyoxyethylene (Brij 35) are shown in Table 6.14 obtained from dynamic dialysis measurements; the interactions with ionic surfactants (Table 6.15) appear more complex.

The tetracyclines have three macroscopic dissociation constants and thus their ionic behaviour is a complex function of pH. In the pH range of the solubilization

Table 6.14 Apparent partition coefficients of tetracyclines in Brij 35 solution at various pHs (25° C)

Substance	pH 2.1	3.0	3.9	5.6
Tetracycline	8.05	8.64	6.31	5.80
Oxytetracycline	8.01	7.61	6.54	5.68
Chlortetracycline	19.0	17.9	13.3	10.0
Minocycline	2.1	4.1	3.8	17.0

From [148].

Table 6.15 Apparent partition coefficients of tetracycline in sodium lauryl sulphate and dodecyltrimethylammonium chloride solutions at various pHs (25° C)

Solution	pH 2.1	3.0	3.9	5.4
Sodium lauryl sulphate	2860	2690	1130	390
Dodecyltrimethylammonium chloride	0	13	15	18

From [148].

study (2.1 to 5.6) the tetracycline molecules convert from cationic species to zwitterionic species. The zwitterionic form partitions most into a lypophilic phase and is the most active form biologically. The micellar partitioning results indicate that the cationic form is preferred for interaction with the micelle, perhaps because some of the tetracyclines are surface active, there having been a report that oxytetracycline aggregates in solution [149]. Minocycline shows the opposite trend to that displayed by tetracycline, oxytetracycline and chlortetracycline in Table 6.14. Minocycline has two $-N(CH_3)_2$ groups at position R_1 (IV) and III. At pH 2 the molecule will thus have little surface activity and would have difficulty orienting itself in a surfactant micelle. As the pH is increased, the protonation of the dimethylamino groups decreases and the molecule perhaps regains its amphipathic nature so allowing increased interaction with the surfactant. These results emphasize that many drugs do not obey the simple rules of micellar partitioning discovered with smaller and perhaps simpler molecules, and, indeed, that molecules within a given series do not always behave in the same manner.

Ikeda *et al.* [148] have analysed their results to obtain the partition coefficients for the cationic (P_c) and zwitterionic (P_z) tetracycline species. Fig. 6.20 should be consulted for the structures. The cationic form may be represented thus (I°, II°, III^+) and the zwitterionic (I^-, II°, III^+) or more simply (0 0 +) and (− 0 +), respectively.

If the apparent partition coefficient, P_m, is defined as

$$P_m = \frac{[D_m]/\phi}{[D_w]/(1-\phi)} = \frac{[D_m](1-\phi)}{[D_w]\phi} \tag{6.13}$$

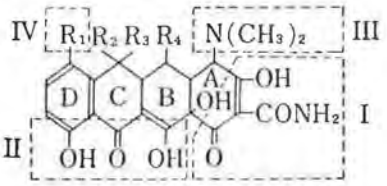


Figure 6.20 Three or four functional groups associated with macroscopic dissociation constants of tetracycline derivatives
tetracycline:
$R_1 = H$, $R_2 = CH_3$, $R_3 = OH$, $R_4 = H$
oxytetracycline:
$R_1 = H$, $R_2 = CH_3$, $R_3 = OH$, $R_4 = OH$
chlortetracycline:
$R_1 = Cl$, $R_2 = CH_3$, $R_3 = OH$, $R_4 = H$
minocycline:
$R_1 = N(CH_3)_2$, $R_2 = H$, $R_3 = H$, $R_4 = H$

where ϕ is the volume fraction of the micellar phase,

$$P_c = \frac{[(0,0,+)_m]}{[(0,0,+)_w]} \tag{6.14}$$

$$P_z = \frac{[(-0+)_m]}{[(-0+)_w]}. \tag{6.15}$$

If K_1 is the dissociation constant of the tetracycline, i.e.

$$K_1 = \frac{[(-0+)_w][H^+]}{[(00+)_w]} \tag{6.16}$$

$$P_m = \frac{[(0,0,+)_m] + [(-0+)_m](1-\phi)}{[(00+)_w] + [(-0+)_w]\phi}. \tag{6.17}$$

Substituting Equations 6.14, 6.15 and 6.16 into Equation 6.17 yields

$$P_m\{[H^+] + K_1\} = P_c[H^+] + K_1 P_z. \tag{6.18}$$

P_c and P_z can be estimated from a plot of $P_m\{[H^+] + K_1\}$ versus $[H^+]$.

The interaction between the tetracyclines and the ionic surfactants (Table 6.15) is of a different nature: a relatively small P_m being observed for tetracycline in DTAC and a large, presumably electrostatic interaction with NaLS at pH 2.1. The anionic–cation interaction would sufficiently alter transport properties so that dialysis rates would be altered; it is perhaps wrong to ascribe the notation K_m to the values obtained.

6.2.3 Steroids

The steroids have wide pharmacological applications, and there is a need for solutions of these compounds for topical and parenteral uses. Many of the steroid

hormones are of low aqueous solubility. Various authors have reported the use of surface-active agents, proteins, and bile acids to solubilize these hormones.

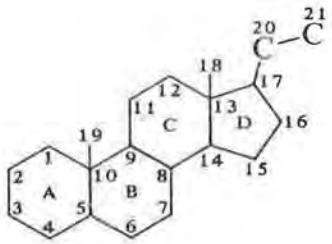
(A) EFFECT OF STEROID STRUCTURE ON SOLUBILIZATION

The effect of steroid structure on solubilization has been briefly discussed in Section 5.3.2. Sjöblöm [150] has compared the maximum solubilizing powers of association colloids for a wide range of steroids (Table 6.16).

Table 6.16 Maximum solubilization of steroids in association colloid solutions

Steroid	Mol steroid/mol micelle		
	NaDS (40° C)	C_{14}TAB (20° C)	Polysorbate 20 (20° C)
Oestrone	0.014		0.0068
Oestradiol-17β	0.025		0.013
Oestradiol-17α	0.029		0.017
Oestriol	0.031		0.024
17α-ethynyloestradiol-17β	0.13		0.18
Oestrone-3-acetate	0.15		0.046
Oestradiol-3-benzoate	0.018		0.010
Oestradiol-3,17-dipropionate	0.051		0.013
Testosterone	0.18		0.027
17α-methyl testosterone	0.24	0.17	0.046
17α-ethynyl testosterone	0.0074	0.0044	0.0007
19-nortestosterone	0.27		0.13
Testosterone acetate	0.24		0.03
Testosterone propionate	0.22	0.094	0.044
Progesterone	0.24		0.037
11-hydroxy progesterone	0.30		0.026
17-hydroxy progesterone	0.090		0.0064
21-hydroxy progesterone (= desoxycorticosterone)	0.38		0.10
11,21-dihydroxy progesterone (= corticosterone)	0.42		0.14
17,21-dihydroxy progesterone	0.15		0.022
11,17,21-trihydroxy progesterone (= hydrocortisone)	0.30		0.057
11-desoxycorticosterone	0.38		0.11
11-desoxycorticosterone-21-acetate	0.16	0.070	0.013
Cortisone	0.20	0.14	0.023
Cortisone-21-acetate	0.071	0.050	0.009
Prednisone acetate	0.23	0.27	0.036
	0.087		0.012
Hydrocortisone	0.30	0.32	0.057
Hydrocortisone-21-acetate	0.026	0.025	0.0043
Prednisolone	0.22	0.21	0.047
Dexamethasone	0.16	0.27	0.041

From [150]. See also [151, 152–157].
NaDS = sodium dodecyl sulphate, C_{14}TAB = tetradecyltrimethylammonium bromide.



(II)

Uptake ranges from 7×10^{-4} mol steroid/mol polysorbate 20, for example, to 0.18 mol mol^{-1}. If we consider two closely related structures, oestrone and oestradiol-17β, differing only in position 17; the marked difference this structural change induces is seen in Table 6.17. The oestradiol-17β is more hydrophilic with a hydroxyl group replacing the keto group of the oestrone. The results of Ekwall *et al.* [151] that in aqueous solutions of sodium lauryl sulphate the order of increasing solubilization follows the trend testosterone < progesterone < desoxycorticosterone confirms the findings that the substituent in position 17 determines the degree of solubilization. Progesterone has, in position 17, a $-CO.CH_3$ group, testosterone an $-OH$ group, and desoxycorticosterone a $-CO.CH_2OH$ group. A fair degree of correlation of solubilization parameters and the partition coefficients of a range of 19 steroids is displayed in Table 6.18 taken from the work of Tomida *et al.* [158].

When the data are plotted, two almost parallel lines are obtained which can be expressed by the following equations derived by least-squares:

$$\log P_m = 0.494 \log P_{octanol} + 1.24 (n = 12, r = 0.986, s = 0.066) \quad (6.19)$$

$$\log P_m = 0.523 \log P_{octanol} + 1.46 (n = 7, r = 0.995, s = 0.044). \quad (6.20)$$

The main selective structural feature is whether or not the steroid possesses a fluorine atom at carbon 9.

Those with fluorine are solubilized to a greater extent than would be predicted, this also being the conclusion of Barry and El Eini [160] who found that

Table 6.17 Maximum solubilizing power of surfactants for oestrone and oestradiol-17β

Surfactant	Conc. range (mol l^{-1})	Temp. (°C)	Mol micellar substance mol hormone^{-1}	
			Oestrone	Oestradiol-17β
Sodium caprate	0.1–0.5	20	202	99
Sodium lauryl sulphate	0.01–0.15	40	72.5	58.1
Tetradecyltrimethyl-ammonium bromide	0.005–0.08	20	44.6	13.3
			g mol^{-1}	
Polysorbate 20	1–20%	20	179×10^3	95.5×10^3

From [150].

Table 6.18 Solubilization parameters for the steroids in polyoxyethylene (23) dodecyl ether ($C_{12}E_{23}$) and partition coefficients between water and *n*-octanol, $P_{octanol}$, and water and ether, P_{ether} at 25 ± 1°C (from [158])

No.	Compound	Aqueous solubility (M)	R^*	P^m_{app}	$P_{octanol}$	P_{ether}†
1	Hydrocortisone (XVIII)	1.08×10^{-3}	0.115	97.9	35.7	1.60
2	Corticosterone	5.79×10^{-4}	0.131	187	86.5	4.52
3	Deoxycorticosterone	3.55×10^{-4}	0.157	399	798	52.0
4	Cortisone	5.32×10^{-4}	0.0388	66.7	26.2	1.40
5	Hydrocortisone acetate (VII)	4.58×10^{-5}	0.0116	229	154	26.0
6	Cortisone acetate	6.18×10^{-5}	0.0140	205	126	25.1
7	Deoxycorticosterone acetate	2.35×10^{-5}	0.0187	718	1190	95.5‡
8	11-Hydroxy progesterone	1.53×10^{-4}	0.0459	271	227	35.5‡
9	Progesterone (XIX)	3.79×10^{-5}	0.0559	1330	7410	604
10	Testosterone (VI)	8.26×10^{-5}	0.0579	633	1960	87.3
11	Prednisolone	6.54×10^{-4}	0.0794	110	41.4	1.13
12	Prednisolone acetate	4.22×10^{-5}	0.0131	281	250	21.1
13	Triamcinolone	2.07×10^{-4}	0.0219	96.3	10.8	0.757
14	Triamcinolone acetonide (VIII)	4.95×10^{-5}	0.0312	569	205	14.6
15	Triamcinolone diacetate (XVII)	7.41×10^{-5}	0.0245	299	83.7	—
16	Dexamethasone	2.58×10^{-4}	0.0721	253	67.8	3.87
17	Betamethasone	1.71×10^{-4}	0.0535	283	87.7	4.76
18	Dexamethasone acetate	1.25×10^{-5}	0.0134	967	806	70.8†
19	Betamethasone 17-valerate	1.95×10^{-5}	0.0387	1790	3070	509

* The slope of the solubility versus surfactant concentration (M) plot. † Data taken from [159]. The experiment was carried out at 23 ± 1° C. ‡ Value estimated from the data in [159].

dexamethasone was solubilized to a greater degree than would be expected from the R_m value obtained by chromatography. This is probably due to the different sites of solubilization for the two groups of steroids. The R_m value, defined as

$$R_m = \log\left(\frac{1}{R_f} - 1\right) \tag{6.21}$$

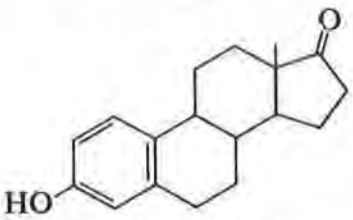
is a useful quantitative expression of a molecule's polarity.

While general trends, e.g. between hydrophilicity or solubility in water and uptake into micelles of a given surfactant, have been demonstrated the other factors which specifically influence packing into a structured micelle are more difficult to quantitate. Perusal of the results in Tables 6.16 and 6.18 indicates some of the structural features of the steroids which increase or decrease solubilization. Introduction of an ethynyl group at C_{17} as in ethynyloestradiol enhances the solubility in ionic and non-ionic micelles. However, introduction of a 17-ethynyl group into the testosterone molecule results in decreased solubility. Steroids of the testosterone group are generally solubilized in much greater amounts than the oestrogens in ionic micellar solutions. According to Sjöblöm, this indicates that the solubilization of steroids is not uniformly influenced by a certain substituent, but that the whole of the steroid molecule determines its micellar solubility.

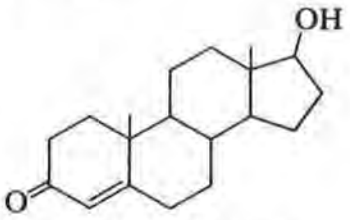
Sjöblöm concludes that: (i) hydrophilic substituents do not unconditionally increase the micellar solubility of the steroids, possibly because of the orientation of the steroids in the micelle, which might depend on the balance of hydrophilicity between rings AB and CD; (ii) the position of the hydrophilic substituents is of great importance; and (iii) suitable hydrocarbon substituents increase the solubility in the micelle [152].

A short side chain at C_{17} enhances the solubilization of steroids, especially when it contains a free hydroxyl group. A greater number of non-ionic molecules are required to solubilize one steroid molecule than is required by ionic micelles. In the oestrogens this difference is small, but in most of the other cases the difference is nearly 10-fold (see Table 6.16). This would indicate a different mechanism of solubilization; the shift of the absorption maximum and the depression of the molar extinction for all the steroids except the oestrogens are much more pronounced in Tween solutions than in ionic colloid solutions. This would suggest a unique mode of solubilization for the oestrogens, most of which are indeed poorly solubilized, only the 21-acetoxy steroid occupying an intermediate position.

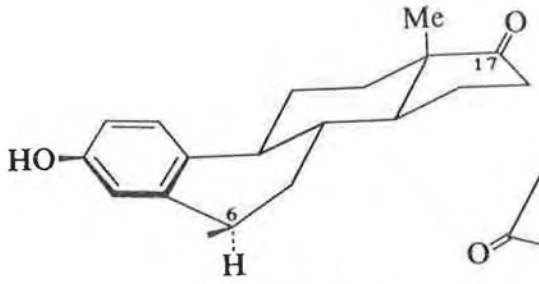
Compare oestrone and testosterone in the diagram below:



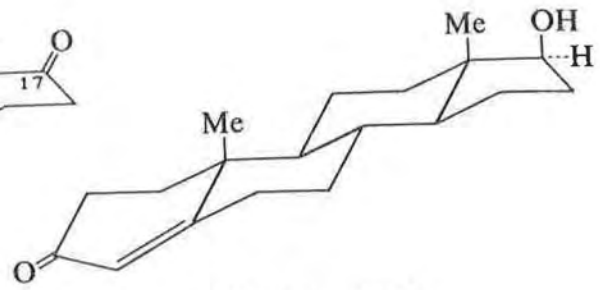
(III) Oestrone



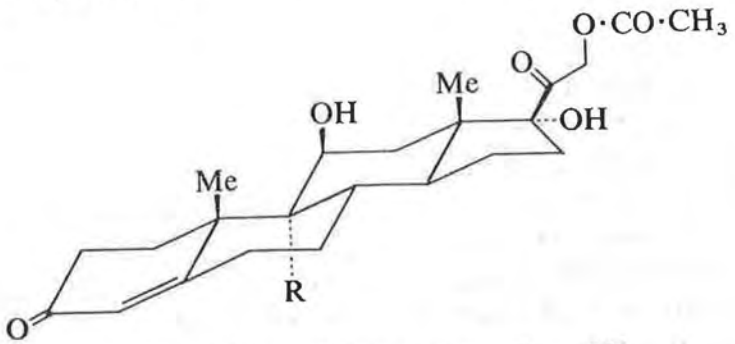
(IV) Testosterone



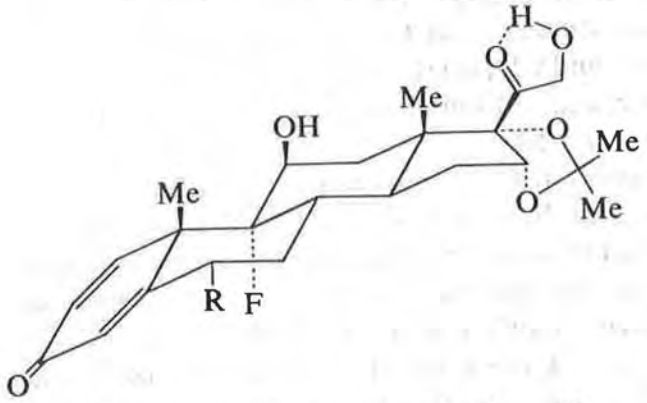
(V) Oestrone



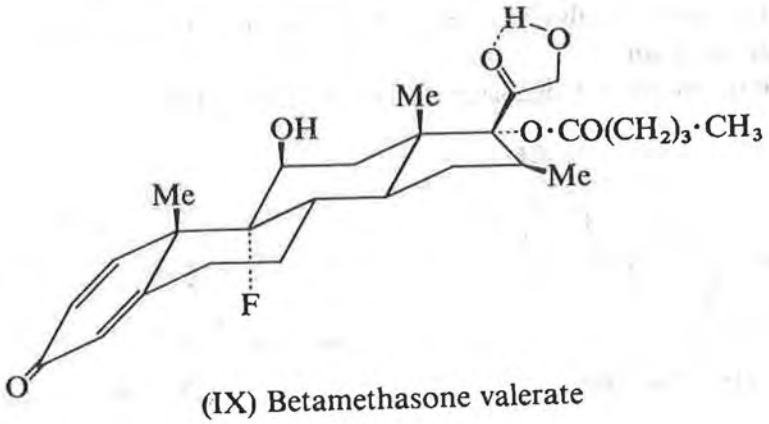
(VI) Testosterone



(VII) Hydrocortisone acetate (R = H)
Fludrocortisone acetate (R = F)



(VIII) Triamcinolone acetonide (R = H)
Fluocinolone acetonide (R = F)



(IX) Betamethasone valerate

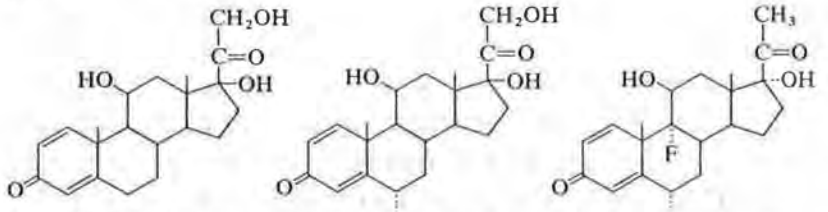
In both compounds rings B, C, and D have the same rigid configuration. In oestrone (V) ring A is rigid and planar, although in testosterone (VI) ring A is flexible. In the latter case this might have some influence on the packing of the testosterone molecule into the micelle. Ring A in oestrone has an ionizable group, while the keto group in testosterone on ring A is non-ionizable. The differences between these two rings may influence to some extent the orientation of the molecule in the micelle. The differences between the molecules and their derivatives would require a more critical examination before any conclusive results could be obtained.

Triton WR 1339 and Tween 80 have both been used in formulations of adrenal cortical hormone preparations for the eye [161, 162]. It was found that the solubility of prednisolone, methylprednisolone, and fluoromethalone in aqueous solutions of Triton WR 1339 was linearly dependent on the detergent concentration. The structures of the compounds are given below their solubility behaviour in Table 6.19. From this it can be seen that there are striking differences in the amounts solubilized, and it is obvious that the fluoro-derivative is more difficult to solubilize than the others mentioned.

Table 6.19 Solubilizing power of Triton WR 1339 for steroids

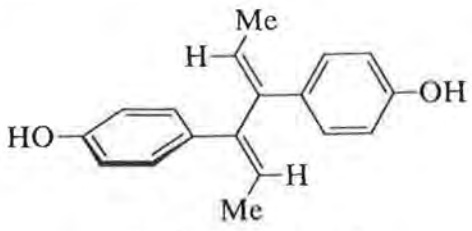
Steroid	Solubility in water (mg ml^{-1})	Steroid mg ml^{-1}/% w/w Triton WR 1339	Mol steroid mol^{-1} Triton WR 1339	Mol Triton mol^{-1} steroid
Prednisolone (X)	0.223	0.249	0.0486	20.6
Methylprednisolone (XI)	0.095	0.114	0.0214	46.7
Fluorometholone (XII)	0.003	0.00927	0.00173	578.0

From [161, 162].

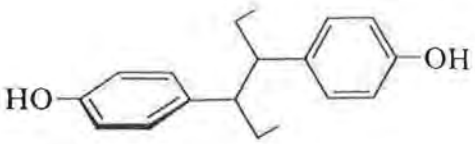


(X) Prednisolone (XI) Methylprednisolone (XII) Fluorometholone

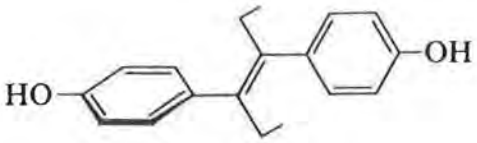
The solubility of non-steroidal oestrogens in ionic and non-ionic surfactant solutions has been investigated by Nakagawa [163, 164]. The compounds included dienoestrol, hexoestrol, diethylstilboestrol, and chlorotrianisene: the structures of which may be compared below. In both polysorbate 20 and 80 the order of increasing solubility (gram for gram) is dienoestrol, hexoestrol, and diethylstilboestrol. Chlorotrianisene, a bulkier molecule, is much less soluble, being approximately 1/20 as soluble in polysorbate 80 at 30° C than the others in this series and less soluble than many of the steroidal hormones. It has been



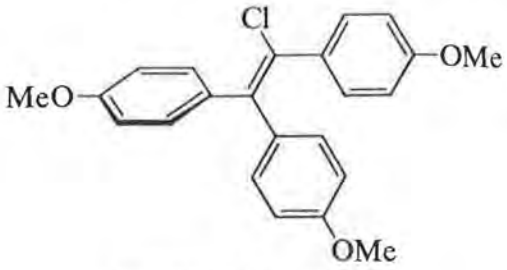
(XIII) Dienoestrol



(XIV) *meso*-Hexoestrol



(XV) Stilboestrol



(XVI) Chlortrianisene

shown that the steroid hormones have 100 to 500 times the solubility of methylcholanthrene, a polycyclic aromatic hydrocarbon which resembles the steroids in structure. It is possible that in the solubilization process there is some interaction between the hydrophilic groups of these hormones and some portion of the surfactant.

(B) EFFECT OF SURFACTANT STRUCTURE ON UPTAKE OF STEROIDS

The solubilizing efficiency of a series of cetyl polyoxyethylene esters decreased as the polyoxyethylene chain length was increased [160] when surfactants were compared on a weight basis. Partition coefficients obtained by dialysis and solubility methods are shown in Table 6.20. P decreases with increasing polyoxyethylene chain length. As discussed in Section 5.3.1, although the number of steroid molecules per micelle is smaller for more hydrophilic surfactants, the total amount of steroid per mole of surfactant is greater, hence the observed increase in solubilizing efficiency with increased hydrophilic chain length when molar concentrations are compared. In practical terms comparison on a weight basis is more realistic and the results are clearly shown in Fig. 6.21.

(C) EFFECT OF TEMPERATURE

Increasing temperature decreases the solubilization capacity of non-ionics even though the micelles grow in size [160], but if the molar ratio of steroid to surfactant (and not micelle) is calculated this value increases for steroids in polysorbate 40 and tetradecylammonium bromide (TDABr) [165] (see Table 6.21). This topic is further discussed in Section 5.3.3.

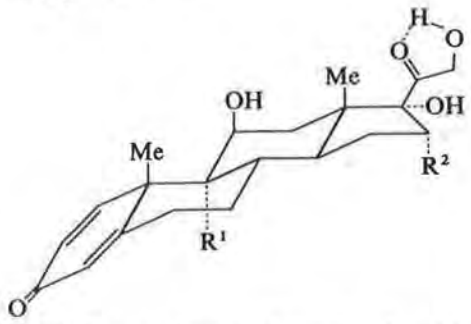
(D) EFFECT OF ELECTROLYTE ADDITION

Very little work has been published on the effect of additives on steroid solubilization. Lundberg *et al.* [166] have, however, measured the uptake of three

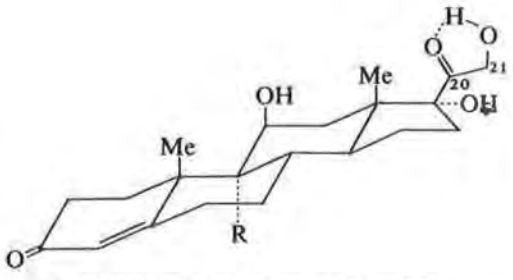
Table 6.20 Partition coefficients of steroids between water and ether, P, and aqueous and micellar phases from solubility, P_s, and dialysis, P_d, at 25° C

Steroid	Surfactant $C_{16}E_{17}$ $n = 99$		$C_{16}E_{32}$ $n = 56$		$C_{16}E_{44}$ $n = 39$		$C_{16}E_{63}$ $n = 25$			
	R_s	R_d	R_s	R_d	R_s	R_d	R_s	R_d	R	R_m
Hydrocortisone (XVIII)	110	110	101	103	86	87	68	66	1.63	0.27
Dexamethasone (XVII)	314	295	273	269	244	240	199	208	3.89	0.48
Testosterone (VI)	786	807	661	654	570	588	452	442	56.9	1.04
Progesterone (XIX)	2160	2230	1790	1730	1550	1400	1250	1000	613	1.46

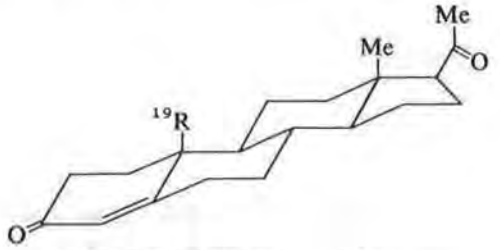
From [160]. n = aggregation number of the surfactant and R_m is calculated from $\log\left(\frac{1}{R_f} - 1\right) = R_m$.



(XVII) Dexamethasone (R^1 = F; R^2 = Me)
Triamcinolone (R^1 = F; R^2 = OH)
Prednisolone (R^1 = R^2 = H)



(XVIII) Hydrocortisone (R = H)

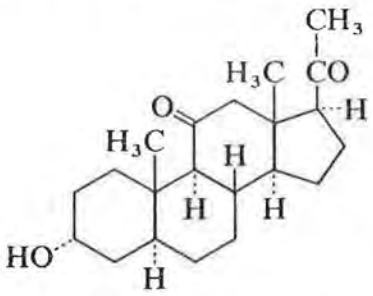


(XIX) Progesterone (R = Me)

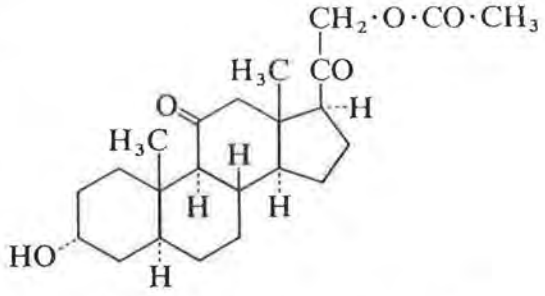
steroids in TDABr. 0.2 M NaCl decreased the solubilization of testosterone and progesterone and increased that of oestrone confirming the notion that the first two steroids are solubilized in the polyoxyethylene layer of the micelle and that oestrone is solubilized in the hydrocarbon core. 0.1 M NaCl decreased the solubilizing capacity of sodium glycocholate for testosterone [167] by about 10%.

(E) SOLUBILIZATION OF STEROID MIXTURES

Of the two widely known solubilized preparations of intravenous anaesthetics on the market, one, Althesin (Glaxo, UK) contains a mixture of steroids. The more active anaesthetic is alphaxolone (9 mg ml^{-1}) (XX) and a less active alphadalone acetate (3 mg ml^{-1}) (XXI) has been added to improve the solubility of the alphaxolone in the Cremophor EL vehicle (20%).



(XX) Alphaxolone



(XXI) Alphadalone acetate

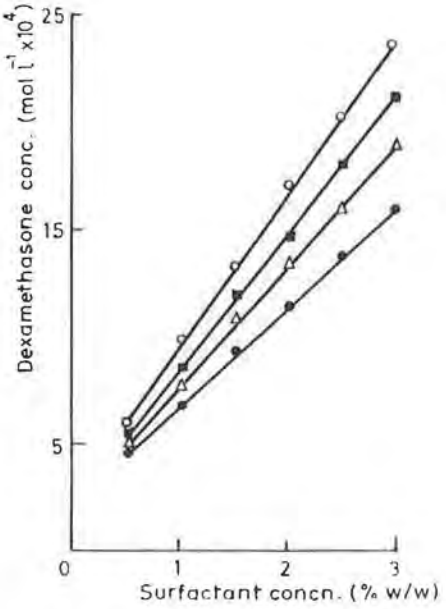


Figure 6.21 Solubility of dexamethasone in water (mol $l^{-1} \times 10^4$), ▲, and as a function of % w/w aqueous concentrations of $C_{16}E_{17}$, ○, $C_{16}E_{32}$, ■, $C_{16}E_{44}$, △, and $C_{16}E_{63}$, ●. From Barry and El Eini [160] with permission.

The effect of alphadalone acetate on the solubility of alphaxolone is a phenomenon that remains to be explained. Simultaneous solubilization of steroid hormones has only been studied by Lövgren and co-workers [168, 169]. Oestradiol was solubilized independently of the C_{21} steroids and testosterone studied, i.e. the capacity for oestradiol was unaffected by the solubilization of the latter. However, the solubilization of ethinyl oestradiol with progesterone and with testosterone was dependent on the presence of the other. The solubility of 11 α-hydroxyprogesterone was enhanced by ethinyl oestradiol – an effect akin to that of alphaxolone and alphadalone acetate. In several other pairs of steroids solubilization was reduced. When a progesterone-saturated solution of polysorbate 40 was equilibrated with an excess of ethinyl oestradiol, 96% of the solubilized progesterone precipitated while the oestrogen component was

Table 6.21 Solubilization capacities of surfactants for hormonal steroids as a function of temperature (K)

Surfactant	Steroid	Mol steroid/mol surfactant				
		293	300.5	308	315.5	323
Polysorbate 40	Oestradiol	0.013	0.016	0.019	0.022	0.026
	Ethinyl oestradiol	0.18	0.23	0.27	0.32	0.37
	Testosterone	0.027	0.039	0.052	0.065	0.076
	Ethisterone	0.0007	0.0009	0.0012	0.0016	0.0018
	Progesterone	0.037	0.049	0.063	0.073	0.084
	17α-Hydroxyprogesterone	0.0072	0.0079	0.0085	0.0091	0.0091
Tetradecyltrimethyl-ammonium bromide	Oestradiol	0.068	0.080	0.092	0.105	0.118
	Ethinyl oestradiol	0.27	0.34	0.43	0.51	0.57
	Testosterone	0.13	0.19	0.25	0.29	0.35
	Ethisterone	0.0046	0.0055	0.0066	0.0074	0.0083
	Progesterone	0.16	0.15	0.16	0.16	0.16
	17α-Hydroxyprogesterone	0.043	0.060	0.082	0.098	0.114

From [165].

solubilized maximally. When the saturation was carried out in the opposite way, 81% of the ethinyl oestradiol precipitated and progesterone was solubilized maximally. If an excess of both steroids was added at the same time, progesterone was solubilized to its maximum extent, while the solubility of the ethinyl oestradiol dropped to 19% of its maximal value in agreement with the result

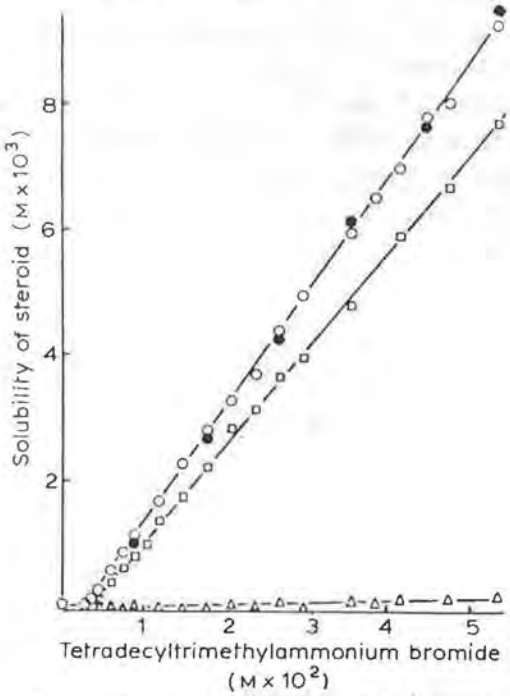


Figure 6.22 Solubility of progesterone in aqueous solutions of tetradecyltrimethylammonium bromide. ○, progesterone only; △, progesterone first and ethinyl oestradiol second; □, ethinyl oestradiol first and progesterone second; and ●, progesterone and ethinyl oestradiol at the same time. From Lövgren *et al.* [168].

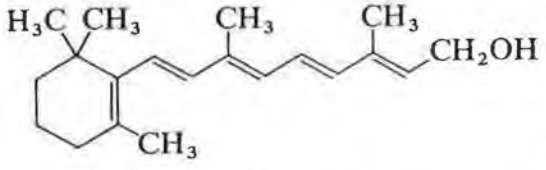
obtained when it was added as the first component [168]. When solubilization occurs in different sites, if micellar structure is unaltered, solubilization of solute pairs should be independent and unaffected by mode of addition. No relationship between thermodynamic parameters and simultaneous solubilization behaviour has been found [165] and one is left with only the notion that there is independent solubilization if the sites of solubilization are different and if the same or adjacent, the solutes interfere with the others' accommodation in the micelle.

Some results of the solubility of progesterone in aqueous TDTMABr are shown in Fig. 6.22 in which differences in the order of addition of ethinyl oestradiol and progesterone are reflected in large differences in the solubility of one of the species.

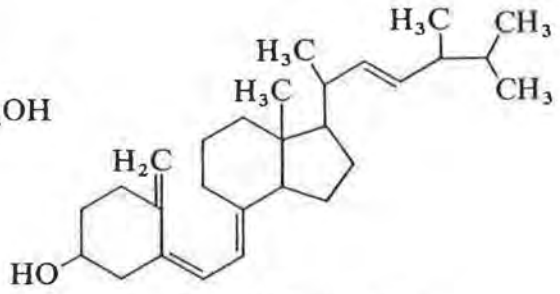
Probably more work has been carried out on steroid solubilization than on most other classes of drug. In spite of the mass of data the behaviour of some steroid–surfactant systems, especially those containing two steroids, is by no means understood. The use of oil–water partition coefficients allows us to predict with a reasonable degree of precision the rank order solubility of a given steroid of a series in a surfactant, but not yet to relate surfactant properties to micellar capacity.

6.2.4 Fat-soluble vitamins

Of the six vitamins regarded as essential accessory food factors (vitamins A, B_1, B_2, nicotinamide, C and D), only vitamins A and D are insoluble in water. Presentation of fish-liver oils, rich in these two vitamins, as emulsions enhances the absorption of the vitamins, but such preparations are not always palatable. However, half a century ago Lester-Smith [170–172] observed the solubilization of vitamins A and D in soap solutions formed by the saponification of vitamin-containing oils. Vitamins E and K are also insoluble in water; vitamin E is used in the treatment of habitual abortion, and vitamin K is employed to combat hypoprothrombinaemia.



(XXII) Vitamin A



(XXIII) Vitamin D_2

Using sucrose mono-esters of fatty acids prepared according to Osipow *et al.* [173], Mima [174] solubilized vitamins A, D_2, and vitamin E acetate. The sucrose esters were employed in an attempt to overcome the problems encountered when polyoxyethylene glycol ethers are used, such as the sensitivity

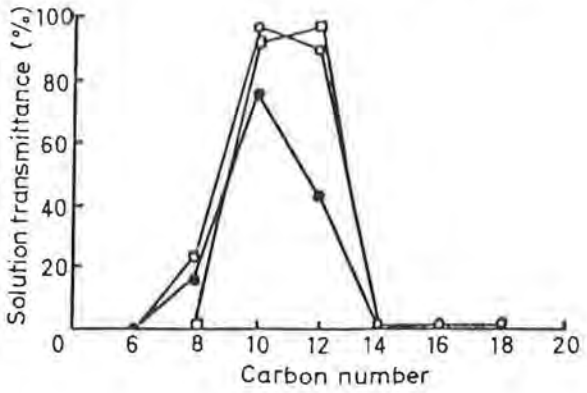


Figure 6.23 The solubility of vitamins in solutions of sucrose esters of varying alkyl chain length as shown by transmittance data, illustrating maximum solubilization at C_{10} and C_{12}. ○—○ vitamin A alcohol; ●—● vitamin D_2; □—□ vitamin A acetate. Ratio of vitamin : ester : water : 1 : 6 : 200. Drawn from the data of Mima [174].

of such systems to clouding (especially in the presence of non-polar materials) and their potential toxicity. Aqueous solutions of the vitamins prepared with the sucrose esters do not cloud and are very stable. Of sucrose mono-caprylate, caprate, laurate, myristate, palmitate, and linolenate, the caprate (C_{10}) ester was found to be most efficient for solubilizing vitamin D_2 and vitamin A alcohol [175] (Fig. 6.23). The haemolytic activity of some of these esters is unfortunately higher than for the established non-ionic detergents, and they must, therefore, be used with caution in injections. A Japanese patent [176] describes the use of 6-L-ascorbyl caprylate to solubilize the fat-soluble vitamins.

Aqueous injections of vitamins A, D, E, and K have been prepared in polysorbate 20, 40, 60, and 80 solutions [177]. Table 6.22 shows the solubility of these vitamins in 10% polysorbate solutions, polysorbate 20 and 80 being the best two solubilizers.

It has been reported that the absorption of carotene (a precursor of vitamin A) is more rapid when presented solubilized in solutions of polysorbate 80 than when administered orally or intramuscularly in oil [178]. Sobel [179] has revealed improved absorption of vitamin A itself when in solubilized form; the transfer of the vitamin to the milk of nursing mothers is superior in such aqueous solutions [180].

Table 6.22 Solubility of fat-soluble vitamins in 10% polysorbate solutions

Polysorbate	Vitamin D_2 (I.U. ml^{-1})	Vitamin E (mg ml^{-1})	Vitamin K_3 (mg ml^{-1})	Vitamin A alcohol (I.U. ml^{-1})
20	20000	5.7	4.7	80000
40	16000	3.8	4.0	60000
60	15000	3.2	3.7	60000
80	20000	4.5	4.5	80000

From [177].

The stability of vitamin A alcohol in neutral aqueous solution is enhanced by polysorbate 20, but not by polysorbates 40 and 60 [177] its stability in 20% polysorbate 20 is greater than its stability in cottonseed oil or in pure surfactant [181].

Many of these non-ionic substances are bitter and to minimize the amounts required, some solubilization studies have been undertaken in systems containing polygols. Coles and Thomas [182] observed that the addition of 30% glycerol makes it possible to halve the amount of surface-active agent required in the solubilization of vitamin A alcohol. More detailed studies have been made [183, 184] and the results are presented in the form of phase diagrams. The more comprehensive diagram (Fig. 6.24) illustrates the variety of phases possible in the system and the comparatively small region of isotropic liquid phase. The concentration of vitamin A palmitate is 6.6%. Increasing the concentration of glycerin reduces the amount of polysorbate required to form an isotropic phase.

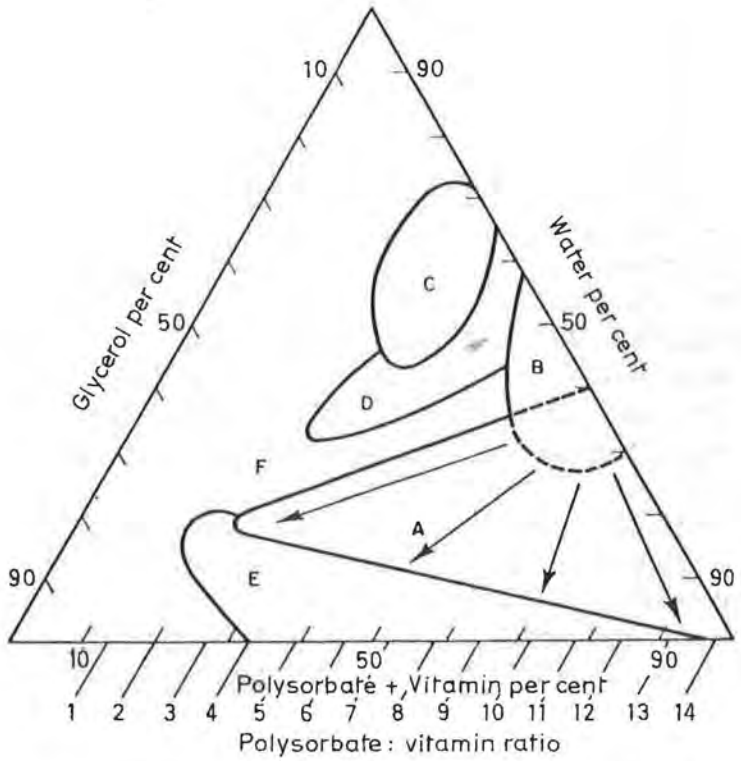


Figure 6.24 The vitamin A: polysorbate 80: glycerol: water system.

Zone	*Description*
A	Transparent, single phase
B	Semi-solid
C	Faintly opalescent
D	Markedly opalescent
E	Two transparent phases
F	Emulsions

From Boon *et al.* [183].

Hüttenrauch and Klotz [184] found the order of decreasing 'co-solubilization' saccharose > sorbitol > glycerin in the preparation of clear aqueous solutions of vitamin A with 15% polyoxyethylene sorbitan oleate. The polygol is thought to increase the proportion of hydrophile in the micelle, reducing the hydration of the oxyethylene chains, producing areas which would approximate to 100% glycol. If polygols increase the solubilization of vitamin A then it would be expected that the extent of solubilization would vary with the HLB of the surfactant. A relationship has been found between the HLB values of commercial polyoxyethylene glycol sorbitan mono-oleates and their solubilizing capacity for vitamin A palmitate [185, 186].

Table 6.23 shows that the solubility of vitamin A palmitate increases the larger the lyophobic chain and the smaller the polyoxyethylene radical, which is opposite

Table 6.23(a) Solubilizable amounts of vitamin A palmitate per mole of surface-active agent in 20% aqueous solution

Surfactant	E*	Mean molecular weight	MAC (mol vitamin/mol surfactant)
Polysorbate 20	23.5	1,385	0.15
Polysorbate 40	20.1	1,286	0.54
Polysorbate 60	18.7	1,251	0.67
Polysorbate 80	19.1	1,270	0.68
PEG monolaurate	12.8	764	0.12
PEG monomyristate	13.4	851	0.31
PEG mono-oleate	13.3	867	0.67
PEG mono-oleate	8.7	586	0.16
PEG monolaurate	12.8	764	0.12
PEG monolaurate	23.2	1,223	0.08
PEG monolaurate	30.8	1,551	0.04

* E = mean number of ethylene oxide units per monomer (assay figure).

(b) Solubility of vitamin K_3 (2-methyl-1,4-naphthoquinone) in surfactant (20%) solutions

Surface-active agent	E^1*	MAC (mg ml^{-1})	MAC (mol/mol surfactant)
Polyoxyethylene sorbitan monolaurate	8.5	3.58	7.5×10^{-2}
	8.8	3.22	6.9×10^{-2}
	13.3	2.94	8.0×10^{-2}
	17.4	2.24	7.2×10^{-2}
Polyoxyethylene monolauryl ether	7.5	4.06	6.1×10^{-2}
	6.9	3.52	5.0×10^{-2}
	10.1	3.04	5.6×10^{-2}
	18.0	2.82	4.4×10^{-2}

* E^1: number of ethylene oxide units from assay.
From [186, 189].

to the expected findings derived from the co-solvent effects yet expected from predictions of micelle size. Some results showing similar effects are included in Table 6.23 for vitamin K_3. Indeed, Nakagawa [187] finds that the solubility of the fat-soluble vitamins in liquid paraffin is very much greater than in an 80% w/v PEG 300 solution, except for acetonaphthone, vitamin K_4, and vitamin K_3 (2-methyl-1,4-naphthoquinone). There are, however, optimum HLB values for the solubilization of vitamins A and D. Using transmittance data, as for the sucrose esters, Mima [188] determined these HLB values for vitamin A palmitate, vitamin A acetate, vitamin A alcohol, and vitamin D_2, these being, respectively 14.5 to 15.5, 15.8 to 16.2, and above 17.9 for the latter two. Vitamins obtained by purification (those with a greater number of international units of activity per gram) have a wider range of optimum HLBs, but the optimal HLB tends to be higher. Thus not only do we have to contend with variations in the properties of commercial surface-active agents but also with the degree of purity of the vitamin. Ito *et al.* [189] found that the range of HLB for solubilization of vitamin A palmitate was 15 to 17.

Considerable batch variation in the solubilizing properties of polysorbate 80, and a correlation between the assay for ethylene oxide content and solubilizing capacity has been found [183]. This emphasizes the need for careful analytical control of materials when experimental work is in progress. The areas of the phase diagram which gave clear solutions with all the surfactant samples represent about half the area shown in Fig. 6.24 obtained with one sample.

Formulae have been assembled for multi-vitamin syrup and multi-vitamin drops [190, 191] using polysorbate 80 to solubilize vitamin A palmitate and vitamin D with glycerin as co-solubilizer, enabling a high concentration of drug to be given per dose. The solubilizer serves the extra purpose of allowing the preparations to be diluted into water or milk for paediatric administration. The sorbitol, primarily added to enhance the taste of the preparation, but which increases the absorption of vitamin B_{12}, obviously also acts as a co-solubilizer [192]. A similar preparation is described by Whittet and Cummins [193].

Non-ionic surfactant solutions have, however, a tendency to cloud, and many substances lower the cloud point of the detergent solutions. The polarity of the solubilized substance affects the turbidity formation: vitamin A alcohol and vitamin D cause clouding, but vitamin A palmitate has practically no effect. With severe clouding, separation into two layers or precipitation may occur [190, 191], the preparation returning to the crystal state on cooling or on remixing the separated layers. The cloud point must be sufficiently high to prevent such separation through variation in storage temperatures, as such fluctuations must adversely affect the stability of the vitamins.

The solubility of vitamin A in surfactant solutions is utilized in an assay procedure for the estimation of naturally occurring vitamin A in chicken livers, synthetic vitamin A in powdered formulations for infants, and vitamin A in stabilized animal-feed supplements [192, 193]. The vitamin is solubilized by Triton X-100 and extracted with a mixed solvent.

6.2.5 Barbiturates

The search for suitable solubilizers is made necessary in the case of the barbiturates by the fact that the soluble sodium salts are unstable and less-soluble forms have therefore to be used. The increases in solubility brought about by 1 to 2% solutions of polysorbates 20–80 are not startling; more water-soluble derivatives show a smaller increment in solubility in surfactant solutions (see Table 5.7, Chapter 5).

The degradation of barbiturates in alkaline solution is well known. Stability may be increased by selection of a suitable co-solvent or solubilizing agent such as ethanol, propylene glycol or polysorbate 80 [194]. A polysorbate 80 solution was used to solubilize 0.4 g phenobarbitone but polysorbate 80 used alone in preparations of this type tends to impart an obnoxious taste to the product, and sweetening agents are required. The device of lowering pH to increase stability resulted in the precipitation of the free acid at pHs in the region of 7 to 8 and led to the investigation of methods to increase the solubility of the acidic form of the barbiturates [195, 196].

Uptake of phenobarbitone in a sodium paraffin sulphonate is not a linear function of surfactant concentration [197]. Above the critical micelle concentration there is an inflection, around 1%, which might result in problems in the dilution of the system.

6.2.6 Salicylates and related compounds

The insolubility of acetylsalicylic acid is a contributing factor to its irritant action on the gastric mucosa; it is hydrolysed in aqueous solution. It has, however, been incorporated in a suppository base with macrogols 1540 and 6000 which increase its solubility and appear to improve the absorption of the drug [198].

Representative classes of surfactants have been considered as solubilizers for aspirin [199]. Ranked in order of decreasing effectiveness were cetylpyridium chloride > polysorbate 20 > benzalkonium chloride > polysorbate 80 > di-octylsulphosuccinate, DOSS.

In a detailed study of the influence of non-ionic surfactant structures on the solubilization of salicylic acid it was found that as the alkyl chain length of polysorbate increases the molar ratio of solubilizate to surfactant increases [200]. As the oxyethylene chain length of a series of Myrj surfactants is increased this molar ratio also increases. A series of monohydric alcohols of decreasing dielectric constant, a group of polyhydroxy alcohols, PEG 400, and polysorbate 20 were investigated for their effect on the solubilizing power of the non-ionic surfactant polysorbate 80 [201]. Monohydroxy alcohols increased or decreased the solubilizing power of the detergent in order of their polarity while the polyglycol and the polyhydroxy alcohols had little effect. A surprising finding was that polysorbate 20 decreased the solubilizing power of polysorbate 80 for salicylic acid in a linear fashion; the results are given in Table 6.24. It might have been expected that the addition of another micelle-forming compound, especially

Table 6.24 Effect of polysorbate 20 on the solubilizing power of polysorbate 80 on salicylic acid

Polysorbate 80		Critical miscibility ratio: salicylic acid/polysorbate 80
No additive		0.150
Polysorbate 20	20%	0.145
	40%	0.140
	60%	0.135
	80%	0.130

From [201, 202].

one of a similar structure, would have increased the solubility of the salicylic acid in the solution but this is too simplistic a view.

Evidence of decreased solubility of both chlorhexidine diacetate and chlorhexidine dihydrochloride in Brij surfactant mixtures has been adduced [203] though this is only clear in the case of the dihydrochloride at concentrations higher than 5% when uptake is some 30% higher in Brij 96 than in Brij 92–96 mixtures if HLB = 11.

Nishikido has analysed uptake of a dye into mixed non-ionic surfactants [204] in terms of the solubilizing powers of the simple surfactants and the mixtures. Defining S_m^{ad} as the solubilizing power in the ideal state if each component forming mixed micelles contributes separately to the total solubilization, one can write

$$S_m^{ad} = \alpha_1 x_1^m + \alpha_2 x_2^m \tag{6.22}$$

where α_1 and α_2 are the solubilizing power of components 1 and 2 and x_1 and x_2 their mole fractions in the micelle. In an ideal system the ratio S_m/S_m^{ad}, where S_m is the actual solubilizing power of the system, would be equal to unity. In the alkyl polyether systems studied all expect the $C_{10}E_6$–$C_{12}E_6$ system, which is nearly ideal, showed negative deviation from ideality, thus solubilization is generally less than expected in mixed micelles because of the nature of the mixed micelle. A positive deviation in S_m/S_m^{ad} is expected in anionic–non-ionic polyether systems from which it is concluded that some interaction between polyoxyethylene chains and anionic surfactants contributes favourably to solubilization. Such beneficial effects have been measured in sodium lauryl ether sulphate–non-ionic systems in solubilizing perfume oils [205]. A range of glycols (hexylene, butylene, dipropylene and diethylene glycol) was measured: all had little solubilizing effect in the presence of sodium lauryl ether sulphate, except hexylene glycol which was as effective as polyoxyethylene (9) nonyl phenol, which was the most effective of the nonyl phenyl surfactants chosen as co-solubilizer.

6.2.7 Oils

For most pharmaceutical oils three to five parts of surfactant are sufficient to solubilize one part of oil in water; surfactants with an HLB in the region of 15 to

18 are ideal as solubilizers for this purpose, polysorbate 60 and polysorbate 80 being widely used in liquid oral preparations. The fish-liver oils, such as those of cod, halibut, and shark, can be made water miscible so that preparations can be diluted with flavoured vehicles for administration. Polysorbate 80, used to solubilize vitamins A and D in an aqueous vehicle of sorbitol and water [206], also acts as a carrier for flavouring oils.

Table 6.25 gives the amounts of cetomacrogol 1000 or polysorbate 20 required to solubilize 1% v/v of various oils used in flavouring. Polysorbate 20 has been used to prepare peppermint oil concentrates [208] and the phase diagram of a peppermint oil–water–polysorbate 20 system has been studied [209] (Fig. 6.25). A concentrate of 7.5% oil, 42.5% polysorbate 20, 50.0% water (represented by

Table 6.25 Amount of surfactants (cetomacrogol and polysorbate 20) required to solubilize 1% flavouring oils in water

Oil	Cetomacrogol, % w/v	Polysorbate 20, % v/v
Peppermint oil	4.5	5.0
Anise oil	7.0	9.0
Caraway oil	5.0	—
Dill oil	4.0	—
Cinnamon oil	7.0	12.0
Clove oil	—	6.0

From [207, 208].

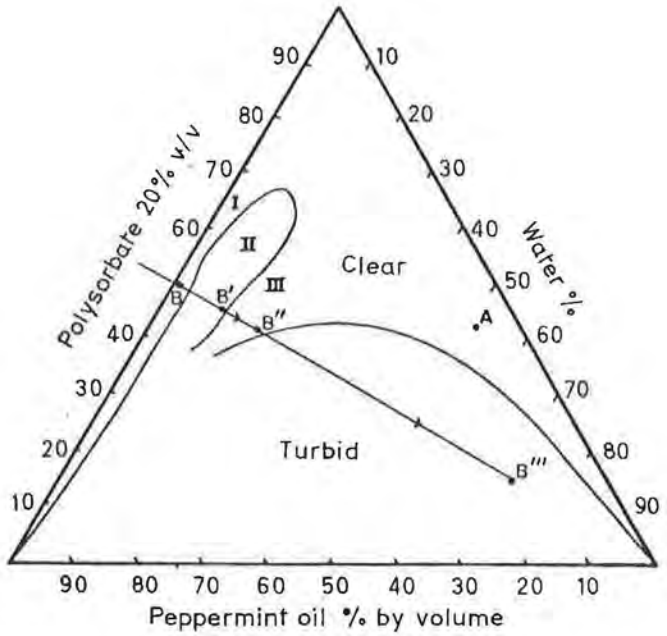


Figure 6.25 Partial phase diagram of polysorbate 20-peppermint oil–water system from O'Malley *et al.* [209]. Phases with compositions represented by the upper parts of the diagram are clear, those below, turbid. Point A represents 7.5% oil, 42.5% polysorbate 20, and 50.0% water.

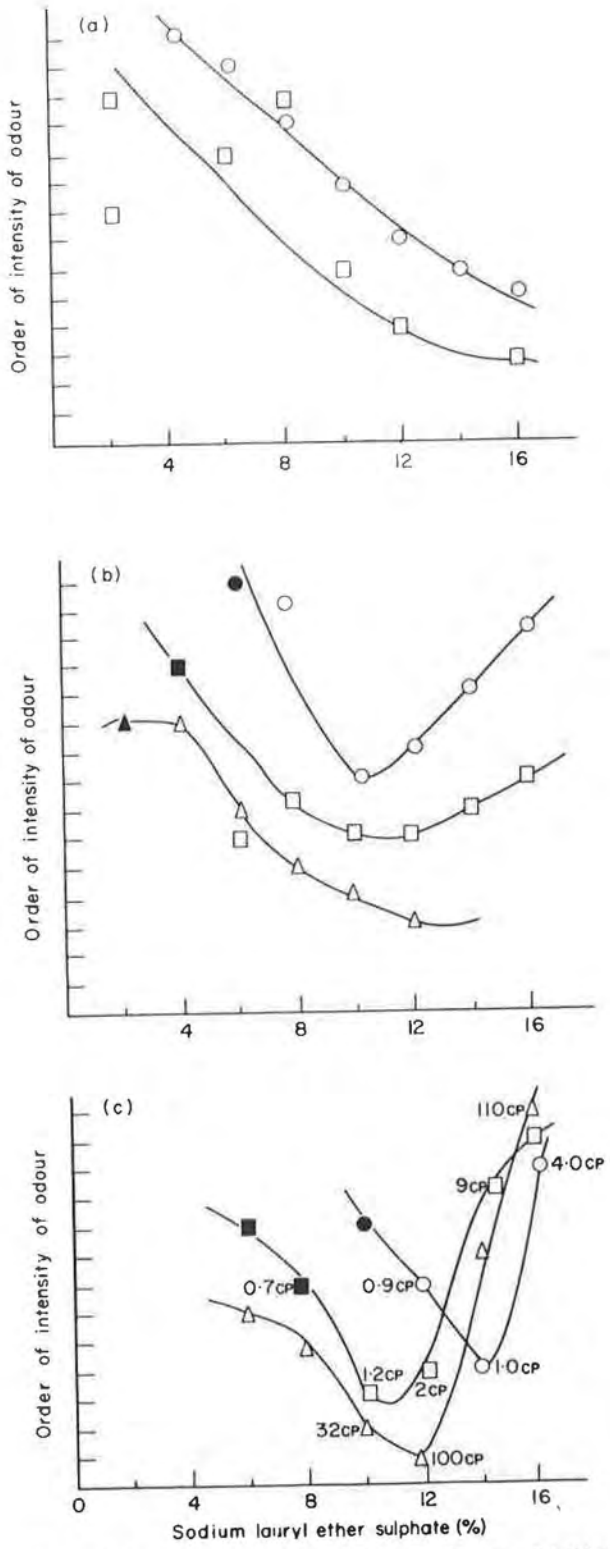


Figure 6.26 Comparison of the orders of intensity of odours of (a) 0.5%, (b) 1% and (c) 2% of perfume W 100 in sodium lauryl ether sulphate solutions with 0% (○), 2% (□) and 4% (△) added coconut diethanolamide (CDE). Solid points indicate opalescent solutions. From Blakeway *et al.* [205].

point A in Fig. 6.25) can be diluted ten times with water to give a satisfactory preparation of peppermint water, but care must be taken in choosing concentrates. Point B, for example, represents 49% oil, 50% polysorbate 20, and 1.0% water (clear solution). Dilution of 10 ml with 1.0 ml distilled water produces a cloudy solution. Addition of a further 1 ml causes the solution to become clear (B^{11}) and diluting the original solution three times with water produces a turbid mixture (B^{111}). Moderate changes in temperature (20, 30, 40° C) have little effect on the phase diagram.

Similar phase diagrams have been obtained for lavender, anise, clove and peppermint oils when the surfactant is a polyoxyethylene glyceryl fatty acid [210]; Ello [211] has solubilized a number of essential oils in polysorbate 20, 40, 60 and 80.

Many essential oils are subject to atmospheric oxidation. There is some evidence that solubilized benzaldehyde is more resistant to atmospheric oxidation than emulsified benzaldehyde [212, 213]. Suspensions of methyl linoleate in water in the absence of surface-active agents are oxidized at a very low rate; the presence of soap in all cases increases the rate of oxidation [212, 213], yet emulsions of the oil are oxidized more quickly than solubilized solutions. One may conclude from this evidence that if an insoluble oxidizable substance has to be formulated in an aqueous vehicle it is better solubilized rather than emulsified.

Solubilization of essential oils is unlikely to alter the perception of flavour; however, the intensity of odour perceived when perfumery oils are solubilized in aqueous surfactant systems can be a complex function of the solubilizer system [205]. The intensity of odour is proportional to the concentration of the perfume in the aqueous phase rather than to its concentration in the micelles. Increasing

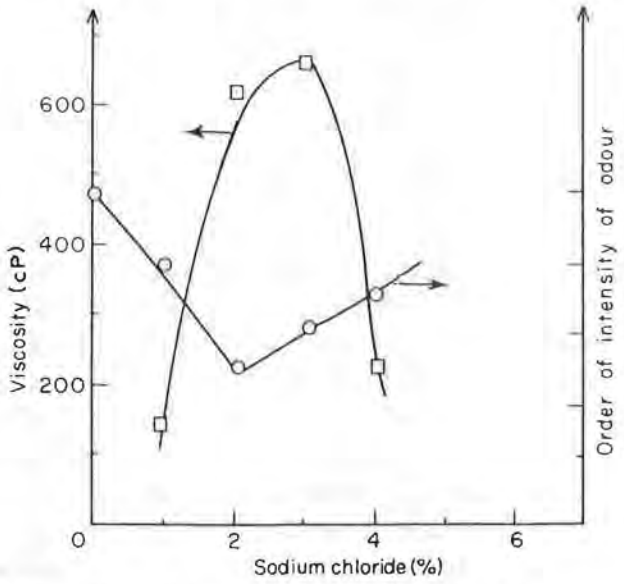


Figure 6.27 Effect of increasing NaCl content on viscosity (□) and rank order of odour intensity (○) of a solution of 2% perfume W 100 in 12% sodium lauryl ether sulphate and 2% coconut diethanolamide. From Blakeway *et al.* [205].

the concentration of surfactant decreases the odour intensity. This is seen clearly in Fig. 6.26 at low (0.5%) concentrations of perfume W100 in sodium lauryl ether sulphate solution. With higher concentrations of perfume up to 2%, the intensity profile takes on a biphasic aspect. One aspect of the system which influences the perfume intensity is its viscosity which when altered by the addition of NaCl causes the changes seen in Fig. 6.27. Non-polar oils such as liquid paraffin (mineral oil) have been used as model substances in investigation of solubilization [214–216]. The influence of the nature (e.g. polarity) of the oil on its solubilization has been studied by Lo *et al.* [216]; this work is discussed in more detail in Chapter 2. The kinetics of solubilization of non-polar oils by non-ionic surfactants has been the subject of a recent study [216a].

6.2.8 Miscellaneous drugs

It has been impossible to deal with all reports of solubilization of drug substances. Those chosen have tended to illustrate certain trends, such as the influence of drug structure or surfactant HLB on drug solubility. Some systems not considered above, perhaps because they deal with only one drug substance and one surfactant, will be referred to in Chapter 7 which considers the influence of surfactants on the bioavailability of solubilized drugs and other consequences of the addition of surfactants to pharmaceutical products. We consider below reports on the solubilization of a miscellaneous selection of drugs.

Some interest has been shown in solubilization of diuretics cyclopenthiazide, hydrochlorothiazide, hydroflumethazide and bendrofluazide [217] and frusemide [218, 219]. The solubilities of the thiazide diuretics in water were not quoted. Micellar partition coefficients and the slopes of solubility–surfactant concentration plots were tabulated. At 35° C in polysorbate 80 the order of P_m values was hydrochlorothiazide (50) < hydroflumethazide (106) < bendrofluazide (186) < cyclopenthiazide (195). For these and for frusemide, polysorbate 80 was the most efficient solubilizer. The solubility of frusemide in water is 65 $\mu g\,ml^{-1}$ at $35 \pm 0.5°$ C [218]. Its normal dose is 10 to 40 mg which must be accommodated in a liquid dose of 5 ml. As 20% w/v of polysorbate 80 solubilizes only 7.2 mg frusemide per ml, attempts were made to reduce the surfactant concentration by using co-solvents propylene glycol, ethyl alcohol and dimethylacetamide (DMA), but DMA at a concentration of 50% in water can dissolve only 8.3 mg frusemide per ml. Polysorbate 80–DMA mixtures are compared with the co-solvent–water mixtures in Fig. 6.28. If the desired drug concentration is $10\,mg\,ml^{-1}$, 10% polysorbate 80, 40% DMA must be used. Shihab *et al.* [219] manipulate the solubility of frusemide in polysorbate 80 with electrolytes, addition of 0.2 M potassium sulphate increasing solubility from $1.26\,mg\,ml^{-1}$ to $1.61\,mg\,ml^{-1}$. NaCl, KCl, $MgCl_2$ and Na_2SO_4 were also used (Table 6.26).

The practicality of both approaches is open to question in view of the potential toxicity of the co-solvents and electrolytes. The order of interaction of prostaglandins with the non-ionic surfactant $C_{12}E_{23}$ was $PGE_1 > PGE_2 > PGF_{2\alpha}$ [220] which corresponds to the order of their cyclohexane/water partition coefficients.

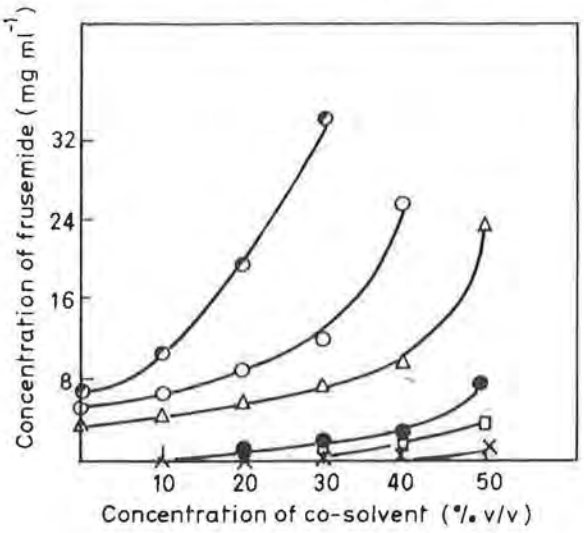


Figure 6.28 Effect of co-solvents and surfactants on the solubilization of frusemide at 35 ± 0.5° C.
◒—◒: polysorbate 80 (20% w/v) + DMA, ○—○: polysorbate 80 (15% w/v) + DMA
△—△: polysorbate 80 (10% w/v) + DMA, ●—●: DMA, □—□: ethyl alcohol
×—×: propylene glycol.
From Sivakumar and Mithal [218] with permission.

Table 6.26 Effect of electrolytes on the solubility of frusemide in 5% w/v polysorbate-80

Molar conc. of electrolyte	Solubility of frusemide (mg/100 ml)				
	NaCl	KCl	$MgCl_2$	Na_2SO_4	K_2SO_4
0.00	125.6	125.6	125.6	125.6	125.6
0.01	130.2	127.0	128.2	129.9	131.0
0.02	131.9	129.8	131.4	133.7	134.4
0.05	132.3	131.9	135.5	139.6	144.6
0.10	133.2	132.5	136.4	149.9	147.5
0.20	134.1	134.1	141.4	157.8	160.9

From [219].

Stable aqueous solutions of narcotic phenoxyacetamides for intravenous administration have been prepared with non-ionic solubilizing agents. The solutions are clear, can be sterilized, and show 'venous compatibility' [221]. Sucrose laurate is among the surfactants described in a similar patent for solubilizing narcotic amides [222]. Various formulations of tetrahydrocannabinol for intravenous administration have been suggested [223, 224].

Studies on the effect of solubilizer concentration on the biological activity of propanidid [225] and tetrahydrocannabinol [226] have been published and are discussed at length in Chapter 7.

Many active ingredients of ointments and lotions are not readily dispersible because of their insolubility. Coal-tar products are an example which have been successfully blended into ointment bases by the use of surfactants [227]. A 1% crude coal-tar ointment in which the tar is dispersed by the addition of 0.5% polysorbate 20 prior to its incorporation in the base, produces fewer adverse skin reactions than the normal preparations without surfactant [228]. Such preparations are also more readily removed from the skin with water. It has been stated, however, that incorporation of coal-tar into hydrophilic ointment bases allows the penetration of carcinogenic components which may be present in the tar. A clear transparent solution of the US Formulary Coal-Tar Solution can be made, provided that 10% polysorbate 20 remains in the final dilution [229].

Spans and Tweens have been used to overcome similar problems in the formulation of medicines for internal use. The solubilization of resinous components of tinctures such as benzoin and myrrh in aqueous vehicles and the incorporation of water-soluble ingredients into oily vehicles has been discussed by Stoklosa and Ohmart [230]. Gerding and Sperandio [229] give examples of mixtures of tinctures and fluid extracts which, on addition of polysorbate 20, will not precipitate on dilution. Cetomacrogol 1000 added in small amounts to opiate linctus of squill, syrup of ginger, compound mixtures of camphor, and of lobelia and stramonium has a similar clearing action [207].

Cetomacrogol also prevents the precipitation of chlorophyll in mixtures containing tinctures of solanaceous drugs. Addition of non-ionics to preparations containing balsamic compounds, such as Gee's Linctus, renders the preparation clear.

6.3 Pharmaceutical aspects of solubilization in non-aqueous systems

Comparatively little material on solubilization of drugs in non-aqueous systems is available, yet the amount of water or aqueous solution which can be incorporated in organic solvents containing surfactants which form inverse micelles can be considerable. One of the limitations has, of course, been the availability of surfactants sufficiently soluble in non-aqueous solvents to reach a critical micelle concentration. Frank and Zografi [231] observed that 20 mol H_2O was solubilized by Aerosol OT (di(2-ethylhexyl) sodium sulphosuccinate) in octane. Most work has been carried out on systems such as these which are totally unsuitable for most pharmaceutical purposes. Some measurements on more "acceptable" non-aqueous solvents have been made [232] using a range of vegetable oils such as almond oil and olive oil as the non-aqueous phases. In this work the L_2 (isotropic non-aqueous phase) was identified along with the regions for L_1, M_1, G and related mesophases. The solubility of the non-ionic surfactants (Brij 92 and 96) in many of these oils is low thus limiting the formation of inverse micelles. Some preliminary work was carried out using Span 80 and Tween 80 mixtures and almond oil. Limited areas of L_2 phase formation occur (Fig. 6.29). Results [216] suggest that the nature of the surfactant aggregates is of

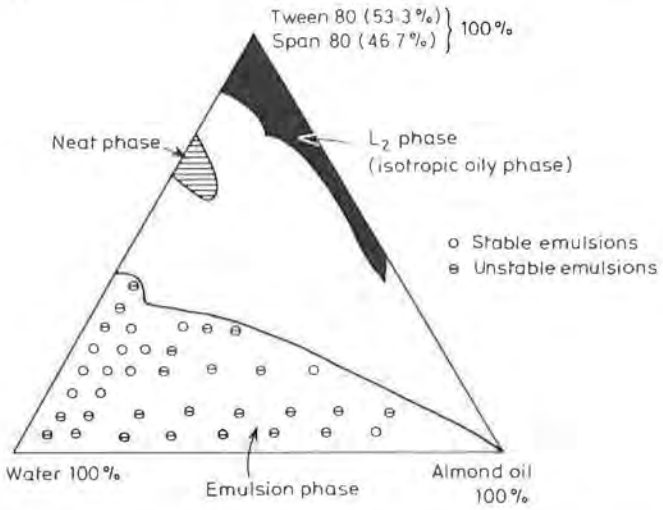


Figure 6.29 Partial phase diagram for a water–almond oil–surfactant system showing the absence of significant L_1 phase and the limited range of the L_2, neat and emulsion phases. From Kabbani *et al.* [232].

considerable importance in determining the uptake of water. While one might expect Brij 96 with the largest hydrophilic group to form the largest aggregates in a non-aqueous solvent, it might not sterically be suited to forming large aggregates except in the presence of the smaller Brij 92 molecules. An attempt to depict this is shown in Fig. 6.30. Palit *et al.* [233, 234] have found that, in general, solubilization in non-aqueous solvents is enhanced when mixtures of the two surfactants are present provided that one surfactant is hydrophobic and the other hydrophilic. The two surfactants in this study satisfy this requirement.

The considerable influence of the oil phase on L_2 phase formation has been noted.

Considerable data have been gathered on solubilization of water in non-aqueous liquids by Lin *et al.* in the course of work on emulsification [236] thus elucidating some of the factors influencing solubilization: optional ethylene oxide chain length, ratios of surfactants, the nature of the oil phase. Fig. 6.31 shows that

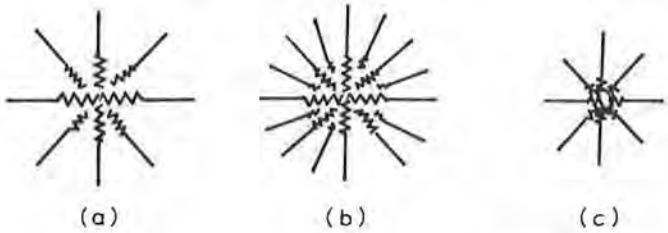


Figure 6.30 Diagrammatic representation of maximal micelle size and water uptake in non-aqueous solvents when the Brij 96 and Brij 92 are mixed to provide micelles as in (b). (a) Pure Brij 96, (c) pure Brij 92 micelle. In (b) better packing and exclusion of the polyoxyethylene core from non-aqueous solvent is made possible by alternating short and long polyoxyethylene chain components. From Lo *et al.* [235] with permission.

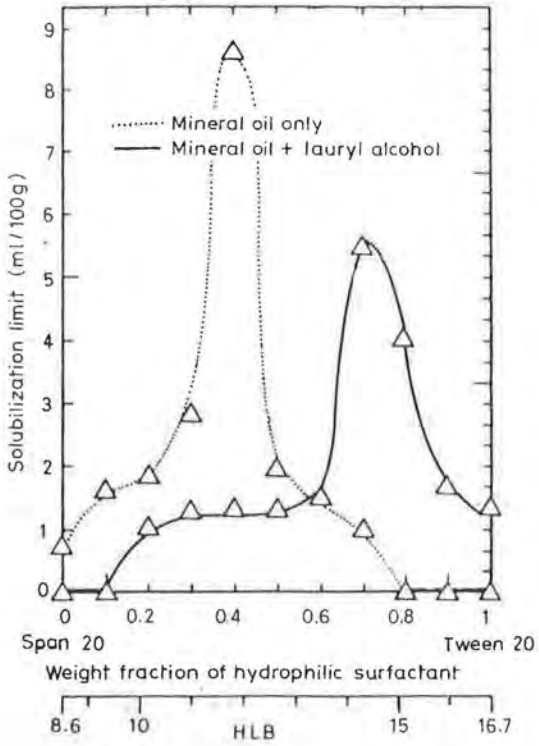


Figure 6.31 Shifting of optimum water solubilization by addition of lauryl alcohol. (Emulsions contain 30% oil phase, 65% deionized water, and 5% surfactant mixtures. Surfactant mixtures consist of hydrophilic Tween 20 and lipophilic Span 20 at ratios and corresponding HLB values indicated by abscissa. Dotted lines represent data for pure mineral oil systems. Solid lines represent data for oil mixture consisting of 8 parts mineral oil and 2 parts lauryl alcohol). From Lin *et al.* [236].

in mixtures of Span 20 and Tween 20 in mineral oil, the optimal ratio for water uptake is shifted to a higher HLB on addition of lauryl alcohol to the oil phase, and the uptake of water considerably reduced. The addition of the polar oil has marked effect on the capacity of the system. Very little work has been published on the effects of drugs added to the solubilizate phase on the properties of the system although it is likely to be considerable [237].

Water-in-oil solubilized adjuvant formulations of vaccines containing *Clostridium welchii* type D toxoid as antigen were prepared first in 1968 and tested in laboratory animals by Coles *et al.* [238]. The adjuvant action of oil-in-water emulsions, multiple emulsions and water in gelled oil emulsions is well known but these varied systems have the disadvantages of high viscosity which makes injection physically difficult. Lin [236] quotes an HLB of 9.7 as the optimum value for water solubilization in mineral oil. Coles *et al.* [238] found a value of 10. While the addition of a small quantity of the lipophilic surfactant Arlacel 80 (sorbitan mono-oleate) to a system of Tween 81 (polyoxyethylene (5)-sorbiton mono-oleate) allowed increasing amounts of water to be solubilized, when toxoid solution was substituted for water the Arlacel decreased the amount which could

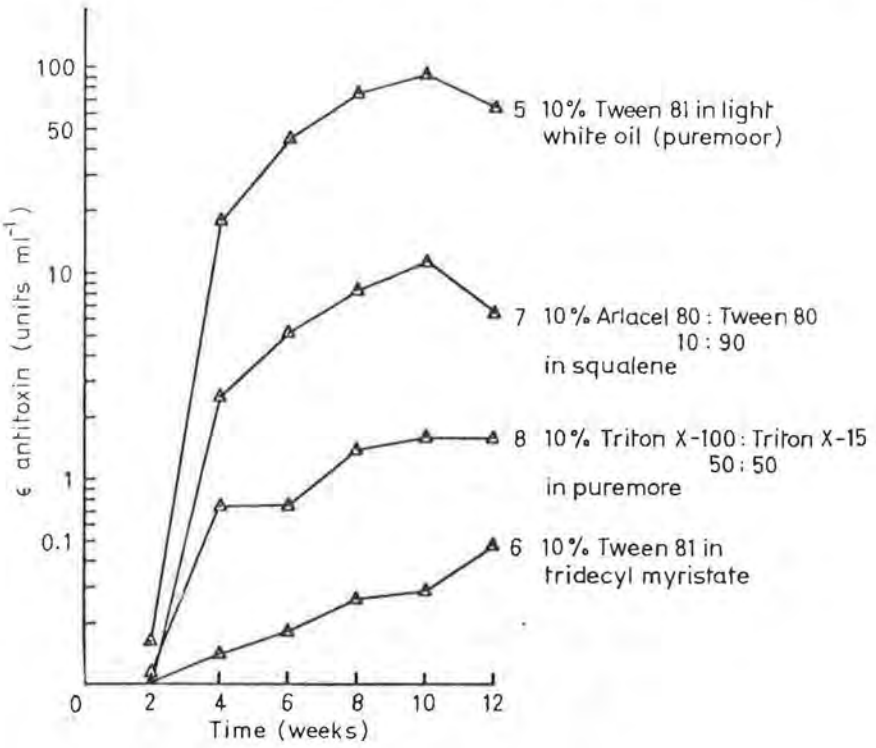


Figure 6.32 ε-Antitoxin titres in guinea-pig serum ($n = 6$) after 1 ml subcutaneous doses of vaccines 5–7 and a 0.2 ml dose of vaccine 8. From Coles *et al.* [238].

be solubilized. They also found that water was solubilized in paraffin oil and pure hydrocarbons, straight or branched, at lower concentrations in fatty alcohols and fatty acid esters and at extremely low concentrations in vegetable oils, pure triglycerides and fatty alcohol esters. This then limits non-aqueous solubilization for medicinal products. Vaccines in tridecyl myristate and squalene as well as mineral oil were examined and in one system (8) a Triton X-100/Triton X-15 mixture was used (unsuccessfully) as the solubilizer. ε-Antitoxin titres produced in rabbit serum on administration of four of these vaccine formulations are shown in Fig. 6.32. The tridecyl myristate system was unstable at 37° C with Arlacel and Tween mixtures but the solubilized systems are generally more stable than their emulsified counterparts, although not of course immune to destabilization in a biological environment. They are now more readily prepared than emulsions and have a lower viscosity.

6.4 Solubilization with block co-polymeric surfactants

So far in this chapter we have attempted to survey solubilization of pharmaceutical products by drug class. Here we diverge to discuss solubilization by a class of surfactant. For reasons of toxicity many ionic surfactants are excluded from serious contention as solubilizing agents for use in medicines. Not all non-

ionic surfactants are without blemish in this regard, as we will see in Chapter 9, and there must still be scope for the investigation of new surfactants which can be used with impunity.

An interesting class of non-ionic surface-active agents are polyoxyethylene–polyoxypropylene–polyoxyethylene block co-polymeric surfactants, sold under the trade name Pluronic and also known by their generic name as poloxamers [239]. Of the available block co-polymeric surfactants, the poloxamers have been most widely studied to date, yet there has been considerable confusion in the literature over the exact nature of their colloidal behaviour, in particular whether or not micelles are formed [240]. Recently, surface-tension measurements on a series of poloxamers in aqueous solution [241] and photon correlation spectroscopy [242] has helped to resolve some of these problems but as befits their structure their behaviour patterns tend to be complex. At low concentrations, approximating to those at which more conventional non-ionic detergents form micelles, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentrations these monomolecular micelles associate to form aggregates of varying size which have the ability to solubilize drugs [243] and to increase the stability of solubilized agents [244].

Table 6.27 lists approximate values of molecular weight and ethylene oxide and propylene oxide chain lengths for the poloxamers, and the designation of poloxamers and the commercial Pluronic surfactants.

Table 6.27 Approximate values of n, m and M for various polyoxyethylene–polyoxypropylene glycols (Pluronic or poloxamers)

Poloxamer designation	Pluronic* designation	Molecular weight of C_3H_6O- portion	m†	'Percent' C_2H_4O	Molecular weight of C_2H_4O- portion	n†	Total molecular weight, M
181	L61	1 750	23	10	194	4	1 944
182	L62	1 750	23	20	438	10	2 188
183	L63	1 750	23	30	750	17	2 500
184	L64	1 750	23	40	1 167	27	2 917
185	P65	1 750	23	50	1 750	40	3 500
188	F68	1 750	23	80	7 000	159	8 750
231	L81	2 250	30	10	250	6	2 500
234	P84	2 250	30	40	1 500	34	3 750
235	P85	2 250	30	50	2 250	51	4 500
237	F87	2 250	30	70	5 250	119	7 500
238	F88	2 250	30	80	9 000	205	11 250
331	L101	3 250	43	10	361	8	3 611
333	P103	3 250	43	30	1 393	32	4 643
335	P105	3 250	43	50	3 250	74	6 500
338	F108	3 250	43	80	13 000	296	16 250
101	L31	950	13	10	106	2	1 056
401	L121	4 000	53	10	444	10	4 444

* F denotes 'solid', P denotes 'pasty' and L denotes 'liquid' consistencies at 25° C.
† Molecular weight of C_3H_6O– is 76 and of C_2H_4O– is 44.

Some relationships between poloxamer structure and the solubilization of para-substituted acetanilides have been defined by Collett and Tobin [243]. The solubilities of the substituted acetanilides such as 4-hydroxyacetanilide, in aqueous poloxamer solutions increase with increasing oxyethylene content of the polymer although the more hydrophobic members of the series do not show this trend [243]. The results as expressed in Table 6.27 show that, for example, 4-nitroacetanilide is less soluble in the more hydrophilic poloxamers, and this is the general trend shown by the halogenated derivatives. These are apparently contradictory results. Some attempt was made to relate solubilization of the series to the π values of their functional groups. Thus in Table 6.28 we see solubilization expressed as the slope of the plot of mol drug solubilized mol^{-1} poloxamer against percentage ethylene oxide in the surfactant. Slope of the hydrophilic derivatives are thus positive and those of the more hydrophobic compounds, negative. A linear relationship is obtained for the solubilization of a hydrophobic acetanilide, 4-fluoroacetanilide and the propylene oxide–polyethylene oxide ratio of the solubilizer (Fig. 6.33a) but when the amount of drug solubilized by the hydrophobe is calculated it decreases as the hydrophobicity of the solubilizate increases, which is contrary to expectation (Fig. 6.33b). Collett and Tobin suggest some hydrophobic barrier in the micelle which seems unlikely, but there is no doubt that the micellar properties are not as predicted [241]. Apparent critical micelle concentrations determined from surface tension measurements decrease with increasing HLB. The fact that this is contrary to expectation might lead one to suspect that these are not true CMCs but are the consequence of interaction between the solubilizate and polymer. Methyl, ethyl, and propyl parahydroxybenzoate, for example, interact with poloxamer co-polymers to no greater extent than they do with polyoxyethylene glycol 6000 which does not micellize; butyl parahydroxybenzoate, on the other hand, is solubilized to a greater extent in this Pluronic than by polysorbate 80. The flexibility of the chains at the air–water

Table 6.28 The slopes for plots of mol *p*-substituted acetanilide solubilized mol^{-1} poloxamer (pH 1.0, 37° C) against percentage oxyethylene in the poloxamer molecule and the π value of the substituent (from [247])

Substituent	Slope, $K \times 10^2$	π*
H	6.30	0
4-OH	15.0	−0.36
4-OMe	2.74	−0.133
4-OEt	0.31	0.367†
4-CHO	5.20	0.091
4-NO_2	−0.32	0.499
4-F	−1.30	0.309
4-Cl	−0.78	0.714
4-Br	−1.03	1.130
4-I	−0.83	1.303

* From [245]
† From [246].

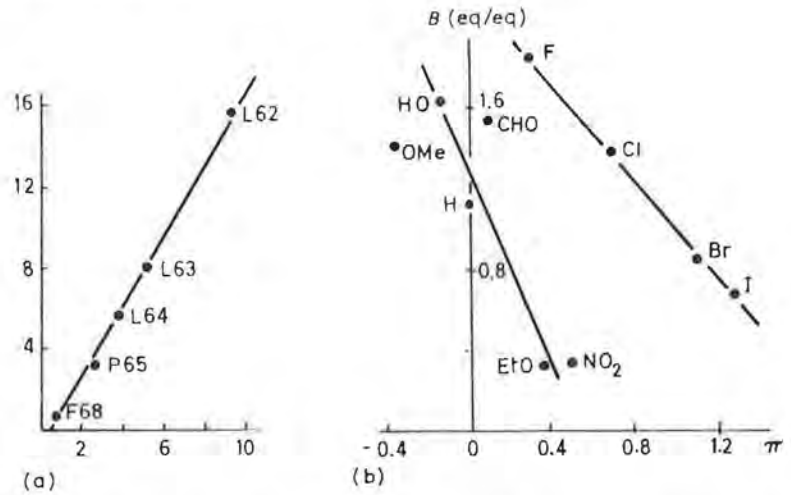


Figure 6.33(a) Solubilization of 4-fluoroacetanilide in aqueous solutions of poloxamers L62, L63, L64, P65 and F68 expressed as equivalents of drug per equivalent of ethylene oxide against the poloxamer mole ratio. Ordinate: $S/C_{EO} \times 10^2$ (equivalents of drug solubilized per equivalent of ethylene oxide). Abscissa: $C_R/C_{EO} \times 10^2$ (propylene oxide–ethylene oxide mol ratio). (b) The amount of *p*-substituted acetanilide solubilized (B) by the hydrophobe of poloxamer molecules as a function of the π value of the substituent group on the acetanilide molecule. From Collett and Tobin [247].

interface [241] suggests that the folding of the longer hydrophobic chains in bulk solution effectively decreases the exposed hydrophobic surface and this reduces the tendency to form polymolecular aggregates even though the monomer is calculated to be more hydrophobic through its HLB number. Another explanation of the trends may be that when the polyoxyethylene chains are short the molecules do not display sufficient amphipathy. Amphipathic properties increase with increase in the size of the hydrophile. Some evidence for this is that the addition of sodium chloride to a solution of poloxamer L64 causes a reduction in the measured mean radius of the aggregates in solution, suggesting that salting out of the hydrophile at both ends of the molecule converts it into a non-aggregating species, by making it more closely resemble a hydrocarbon chain [241].

Nuclear magnetic resonance has been used [248] to study the interaction of poloxamer F68 and phenol. Starting with low phenol concentrations, up to 2%, in a 10% aqueous poloxamer F68 solution, it was reported that the phenol was associated mainly with the polyoxypropylene chain. However, as the ratio of phenol to poloxamer increased, it appeared that the polyoxypropylene chain became saturated with phenol and relatively more phenol entered the polyoxyethylene chain.

A chlorhexidine gluconate–poloxamer 187 solution has been developed as an antiseptic skin cleansing formulation [249]. This contains 25% poloxamer 187, chosen to produce the greatest foaming capacity and also because the poloxamers as a class interfere with the activity of the chlorhexidine less than other non-

ionic surfactants tested. An alcohol-based mouthwash has also been described. Choice of poloxamer rested on lack of noxious taste (cf. some other non-ionics) and its ability to solubilize aromatic flavours [250].

Marked increases in the dissolution rate of digitoxin and digoxin has been achieved by dispersing the drugs in solid poloxamer 188 (Pluronic F68) as a carrier [251] (see Fig. 6.34). Poloxamer 188, in concentrations equivalent to that in the digoxin co-precipitates studied, increased the solubility of the digoxin as shown in Table 6.29 in which results are compared with the effects of deoxycholic

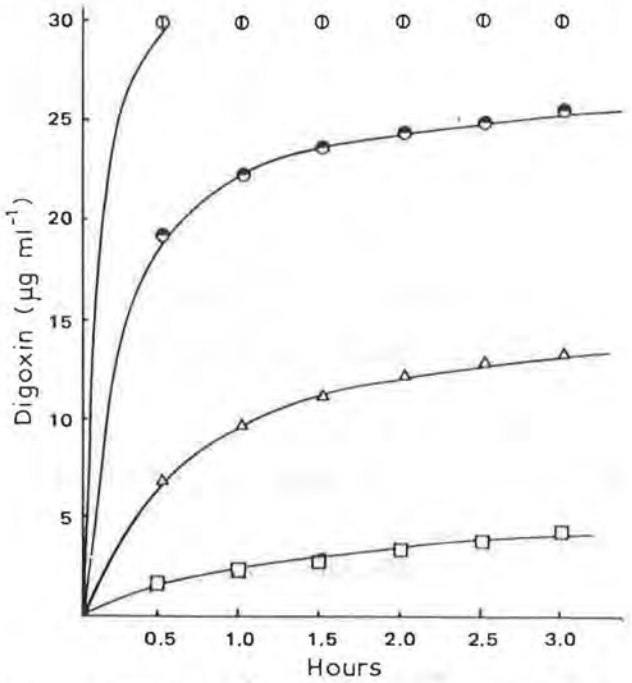


Figure 6.34 Dissolution of digoxin from poloxamer 188 test preparations. □, Untreated drug; △, 10 and 1 % physical mixtures; ◓, 10 % co-precipitate; and ⊕, 1 % co-precipitate. From Neddy *et al.* [251] with permission.

Table 6.29 Effect of poloxamer 188 and deoxycholic acid on the solubility of digoxin in water at 37° C

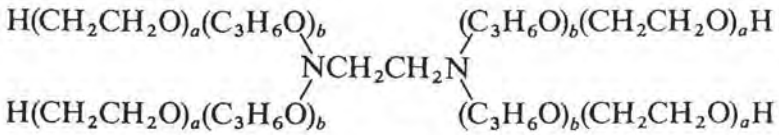
Test system	Solubility mg/100 ml
Water	3.47
Poloxamer 188 in concentration equivalent to 10 % co-precipitate	4.77
Poloxamer 188 in concentration equivalent to 1 % co-precipitate	5.38
Deoxycholic acid in concentration equivalent to 10 % co-precipitate	4.62
Deoxycholic acid in concentration equivalent to 1 % co-precipitate	4.25

From [251].

acid. Enhanced dissolution could be due to the presence of the drug in an amorphous state in the co-precipitate, to surface-tension lowering and to increase in the bulk solubility of the dry substance (see Chapter 7).

Poloxamers have also been incorporated into white petrolatum USP ointment bases in the presence of dimethylsulphoxide to modify the absorption of drugs presented in the base [252]. Percutaneous absorption of salicylic acid was increased significantly by poloxamers 231 and 182 and absorption of sodium salicylate by poloxamer 182.

Sheth and Parrott [244], in their study on the hydrolysis of esters, measured the solubility of benzocaine in a range of non-ionic surfactants including poloxamer 188. It was the least efficient, a Tetronic co-polymeric surfactant (Tetronic 908) having twice the solubilizing capacity. Tetronic is the proprietary name for the poloxamine series with the general structure,



(XXIV) Poloxamine (Tetronic) structure

Table 6.30 Nomenclature of the meroxapol and poloxamine block co-polymeric surfactants

Meroxapol series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
3100	31R1	31R2	—	31R4	—	—	—	—
2500	25R1	25R2	—	25R4	25R5	—	—	25R8
1700	17R1	17R2	—	17R4	—	—	—	17R8
1000	—	—	—	—	10R5	—	—	10R8

% Ethylene oxide

Poloxamine series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
6750	1501	1502	—	1504	—	—	—	1508
5750	1301	1302	—	1304	—	—	1307	—
4750	1101	1102	—	1104	—	—	1107	—
3750	901	—	—	904	—	—	—	908
2750	701	702	—	704	—	—	707	—
1750	—	—	—	504	—	—	—	—
750	—	—	—	304	—	—	—	—

% Ethylene oxide

From Schmolka [239].

The nomenclature of the poloxamers and the meroxapols (polyoxypropylene–polyoxyethylene–polyoxypropylene block co-polymers) 'reversed' poloxamers is explained in Table 6.30. Another class of block co-polymers which has no generic name has the name Pluradot (Wyandotte). These have three block co-polymer chains with the general formula,

$$R[O(C_3H_6O/CH_2CH_2O)_n-(CH_2CH_2O/C_3H_6O)_mH]_3$$

$$\left(\frac{C_3H_6O}{C_2H_4O}\right)>1 \qquad \left(\frac{C_2H_4O}{C_3H_6O}\right)>1$$

Pluradot structure
XXV

The solubilizing ability of these complex polymers has not been reported.

6.5 Polymer–surfactant interactions

Pharmaceutical formulations are rarely simple solutions. The increasing likelihood of the presence of polymers in formulations should alert us to the possibility of surfactant–polymer interactions which can influence the capacity of the surfactants to perform their function of increasing the solubility of drug substance. Polymer–surfactant interactions are of some interest in view of the use of polymers as viscosity modifiers and suspension stabilizers [253]. Interactions between surfactants and non-ionic polymers such as polyethylene oxides [254], polypropylene oxides [255], polyvinylpyrrolidone [256, 257] and polyvinylalcohol [260] have been studied [259]. An interesting property of some of these polymer–surfactant complexes, e.g. polyvinylpyrrolidone–NaLS, is the synergistic effect of the polymer on the capacity of the surfactant to solubilize oil-soluble dye [256, 257]. An instance of such synergism occurring in hydrocarbon media has also been reported [260]. Interactions between polymer and a given surfactant increase with the increasing hydrophobicity of the macromolecule; indeed it has proved possible to solubilize poorly soluble hydrophobic polymers by the addition of surfactant [261, 262]. Polyelectrolytes form precipitation complexes with oppositely charged surfactants which can in many cases be completely re-solubilized by the addition of excess surfactant [259]. Maximum precipitation has been found to occur when a single layer of adsorbed surfactant formed on the polymer chains; the resolubilized form appearing when a double layer of surfactant was achieved. Goddard and Hannan's detailed study [259] has revealed that optimal interactions between polymer and surfactant occurred when the surfactant had a long, straight hydrocarbon chain with the polar group terminal to the alkyl chain. Departure from this structural constraint reduces the extent of the interaction and also renders the resolubilization difficult, the latter being difficult to achieve if the charge density on the polymer is also high [259]. As might be expected, the complex formed between some surfactants and polymers has a solubilization capacity which is different from that of the surfactant alone. Fig. 6.35 shows the effect of PVP on the solubilization of Yellow

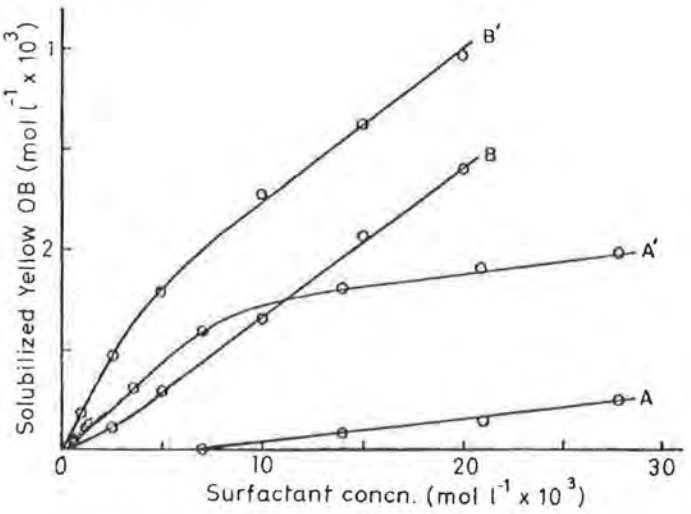


Figure 6.35 Effect of PVP addition on the solubilization of an oil-soluble dye, Yellow OB, in surfactant solutions at 30° C: A, NaDS; B, dodecyl-(oxyethylene)-ether. The primes refer to the addition of 0.1 % PVP to the corresponding surfactant solutions. From Saito [261].

OB in solutions of NaDS, a non-ionic detergent and sulphated non-ionics [263]. The latter seem to form complexes only when the number of oxyethylene groups is small; on the other hand, $C_{12}E_4$ with no sulphate groups shows no sign of complexation with PVP (Fig. 6.35 DD'). It is evident that the sulphate group contributes to the binding giving rise to enhanced solubilization. The mechanism of interaction of ionic surfactants and polyglycol ethers has been discussed by Schwuger [255]. In water only weak hydrophobic bonding between cationic surfactants and polyoxyethylene glycol ethers is evident. Complexing of anionic surfactants is very marked, the interactions being the result of both hydrophobic interactions and, more importantly, the lone pair on the ether oxygen confers a slight positive charge on the ether linkage which favours interaction with sulphate ions. With increasing pH the positive charge of the ether oxygens is reduced and the tendency to complex formation also is reduced.

Studies on the interaction between surfactants and styrene–ethylene oxide block co-polymers, however, indicate that the polymers exhibit, in the presence of surfactant, typical polyelectrolyte character. This, it has been suggested [264], is due to interaction repulsions between like charges of the NaDS ions adsorbed onto the polyoxyethylene blocks. Investigating the interaction of the same detergent with methylcellulose and poly(vinyl alcohol), Lewis and Robinson [265] also observed the polyelectrolyte character of the polymer–surfactant complexes. A complex between non-ionic surfactants and a polycarboxylic acid in water can solubilize oil-soluble dyes below the surfactant CMC [268]. The complex containing the solubilizate can be precipitated; the solubilizate remains in the precipitated complex and is leached out only slowly on placing the precipitate in fresh solvent. This has potential pharmaceutical implications. Halothane uptake by coacervate systems of gelatin–benzalkonium [269] has

been considered to indicate the formation of a highly structured phase with non-polar domains similar to surfactant micelles in a polar medium. Consideration of these complex surfactant systems is essential if progress is to be made in developing solubilizers for pharmaceutical use. Solubilizers are rarely if ever used alone in a formulation, and, as indicated above, the 'capacity' of simple micellar systems is only rarely sufficient for practical formulations except for a handful of drugs of high potency.

In most of the work on solubilization of drugs and other solutes by single surfactant species a linear relationship between solubility and surfactant concentration has been noted. Chlorhexidine uptake into non-ionic micelles was one example where the solubility plot deviated from linearity because of an assumed change in micellar structure (see p. 313). As ionic surfactant is added to a macromolecule the conformational change that will be observed will almost certainly lead to deviations from linearity. Fig. 6.36 shows one example [266]. Solubilization of Orange OT occurs below the CMC of NaDS in the presence of additive. Two transition points are seen, the transition which occurs at the highest NaDS concentration designated as the 'second transition', should correspond to the concentration at which all the adsorption sites along the polymer backbone become saturated with surfactant molecules, and it was shown that a reasonable estimate of the NaDS concentration at the second transition could be obtained from the contour length of the polymer if it was assumed that the DS^- ions were fully extended and bound linearly [266]. Interaction of NaDS with a cationic substituted polymer leads to maximum precipitation at ratios of polymer to surfactant at which the charge of the polymer is balanced by that of the surfactant. As the surfactant level is increased above this ratio the precipitated polymer is solubilized [267].

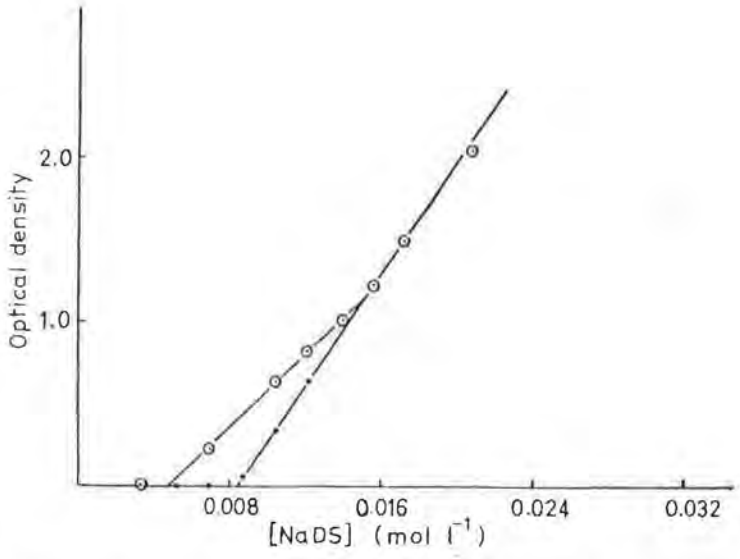


Figure 6.36 Optical density versus [NaDS] in the presence of Orange OT: ●, in the absence of polymer, ⊙, PEO concentration 0.071 %. From Jones, [266].

Significantly increased surface activity in some cationic polymer–anionic surfactant systems is observed in the low surfactant concentration range even when the added polymer is only weakly surfactive. It has been suggested [267] that this effect arises from the adsorption of surfactant or ions onto each cationic site rendering the polymer more surface active. Progressive addition of surfactant leads to further adsorption until the polymer now acts as an anionic polymer. The changes are represented diagrammatically in Fig. 6.37. A non-ionic surfactant (Tergitol 15–5.9) and a C_{14} betaine had no effect on the same cationic polymer.

Both ionic and non-ionic surfactants influence the rheological behaviour of gum arabic solutions [253]. Brij 96 increases the relative viscosity of gum arabic up to a 5% surfactant concentration at concentrations of gum up to 10%. NaLS also increases the viscosity of the gum but beyond 1% NaLS the viscosity is reduced (Fig. 6.38).

As we have seen the rheological properties of polymer–ionic surfactant systems suggest that the individual polymer chains adsorb a large number of the detergent anions so that they behave as polyanions with chains highly expanded because of the mutual electrostatic repulsion of the adsorbed species. Although the gum arabic molecules are polyanions, sodium lauryl sulphate may adsorb on the hydrophobic residues of the side chain and, in spite of the relatively high concentration of gegenions, the increased charge arising through adsorption would maintain a more expanded molecule than in the presence of an equivalent amount of NaCl. The effectiveness of the cetyltrimethylammonium bromide in reducing the intrinsic viscosity at low concentrations undoubtedly arises from the

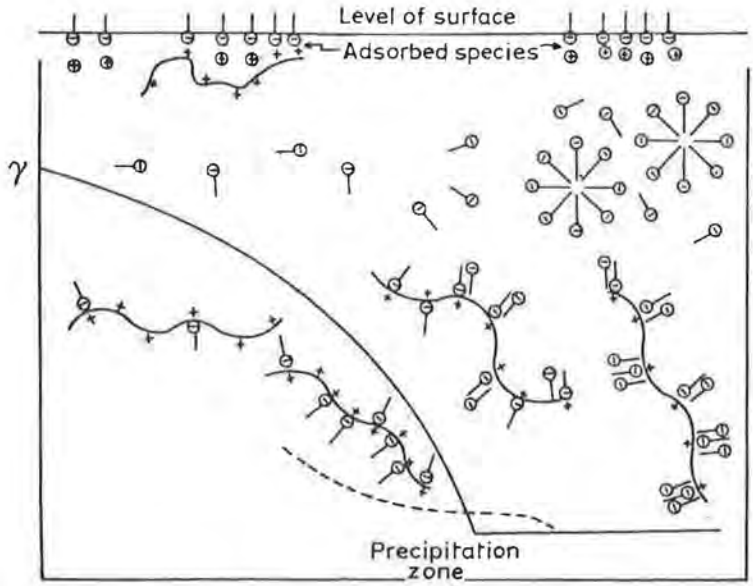


Figure 6.37 Conditions in bulk and surface of solution containing a polycationic electrolyte and anionic surfactant. The full line of curve is the hypothetical surface tension concentration plot of the surfactant alone; dashed line is that of mixture with polycation. Simple gegen-cations are depicted only in the surface zone. From Goddard *et al.* [267].

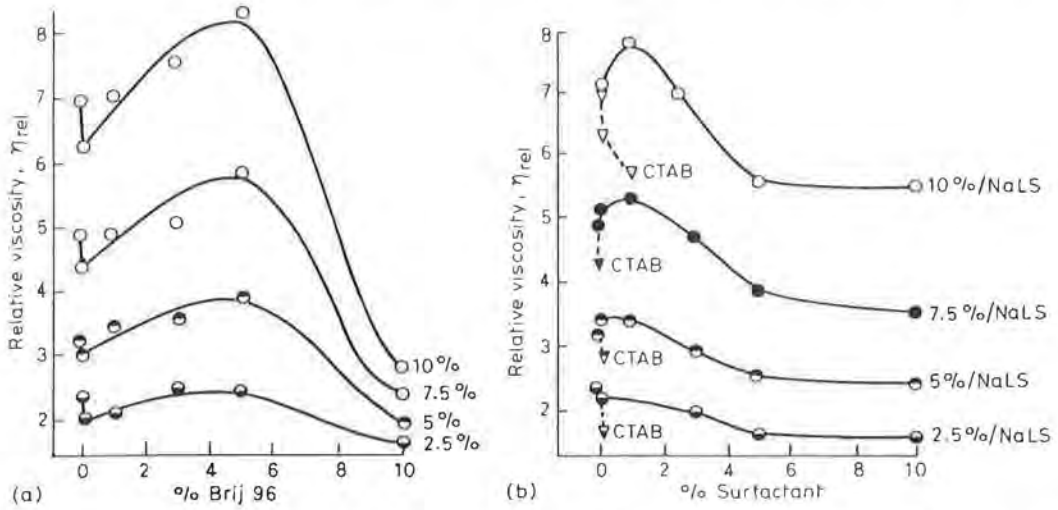


Figure 6.38 Relative viscosity of gum arabic solutions (a) in the presence of increasing concentrations of Brij 96, concentrations of gum arabic as shown on plots, and (b) in the presence of sodium lauryl sulphate (NaLS) and cetyltrimethylammonium bromide (CTAB) at the concentrations of gum shown, from 2.5% to 10%. From [253].

cumulative effect of the counterions and adsorption of the positive species, possibly directly with the anionic groups. At higher concentrations hydrophobic adsorption of further cetyltrimethylammonium bromide molecules could increase the positive charge on the macromolecule such that expansion occurs again. However, in this system, physical changes (e.g. coacervation) occur such that measurements cannot be made in the intermediate concentration range. If adsorption of NaLS occurs, undoubtedly the non-ionic polyoxyethylene-oleyl ether Brij 96 is also adsorbed. The increase it induces in the relative viscosity of the system may thus be due to the increased hydration of the surfactant–gum complex, water being trapped in the adsorbed polyoxyethylene layers.

6.6 Surfactant interactions with oppositely charged species

The possible interactions that may occur between a surfactant ion and an oppositely charged organic ion are outlined in Fig. 6.39.

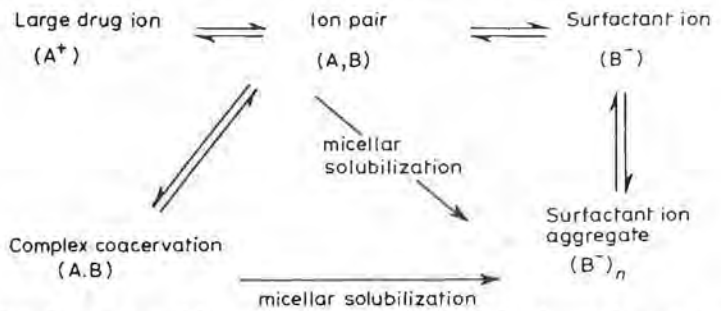


Figure 6.39 Equilibria possible in mixtures of oppositely charged organic ions when one is a surface-active agent (B^-) and the other a solute or drug molecule (A). From Tomlinson [270] with permission.

At low concentrations complexation occurs between the ions and usually turbidity occurs as a result, leading to phase separation of the so-called coacervate. On increasing the concentration of the surfactant ion above the CMC in the system, the coacervates may be solubilized resulting in a loss of turbidity. The interaction between the di-anionic drug disodium cromoglycate (cromolyn sodium) and cationic surfactants has been studied by Tomlinson *et al.* [271]; equilibrium between the ions can be represented quantitatively by the solubility product K_s and the ion-pair association constant K_{ip}. In aqueous solution, the value of K_{ip} increases with an increase in the carbon number of the ions forming the ion pair. A composite phase diagram showing the primary phase boundaries between sodium cromoglycate and a homologous series of alkylbenzyldimethylammonium chlorides is shown in Fig. 6.40. As is seen, an increase in alkyl chain length causes a shift in the phase boundaries to lower anion and cation concentrations, that is there is an increasing tendency for coacervation to occur. On the other hand, the CMC of the surfactant ion decreases with increasing alkyl

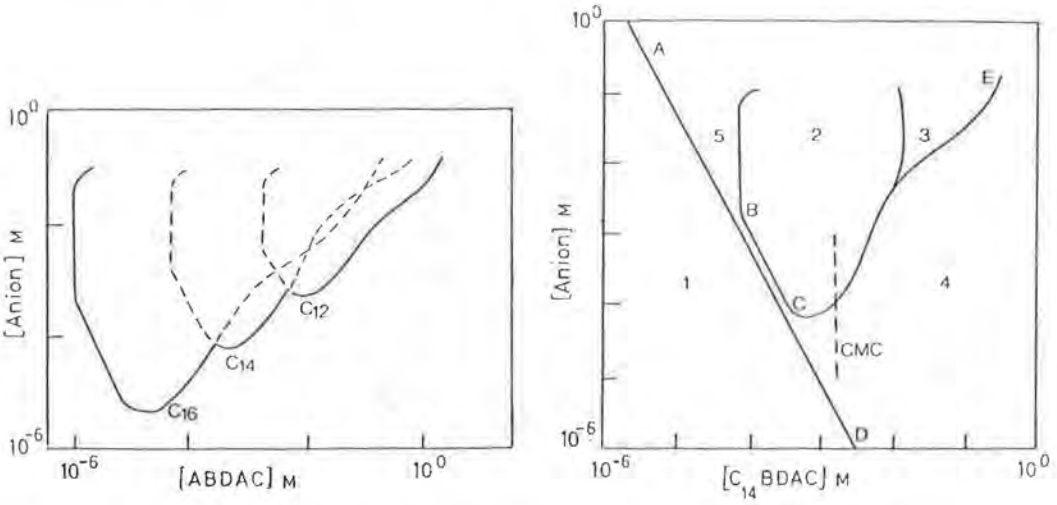


Figure 6.40 Composite diagram showing primary phase boundaries between sodium cromoglycate and an homologous series of alkylbenzyldimethylammonium chlorides at 25°C. The diagram for the C_{14} compound is shown with details of the phases observed.

Region 1 represents that area in which complexation does not occur, and has as its boundary the solubility product line A-D. In Regions 2 and 3 visual evidence of complexation is apparent. In Region 2 this is observed as a grey/white complex, somewhat milky in appearance, whereas in Region 3 a brown viscous oil is observed. Although Regions 4 and 5 are above the theoretical solubility product line, no evidence of turbidity can be seen. In area 4 the concentrations of surface-active agent used are above its measured critical micelle concentration, and it is apparent that up to a limiting amount, (represented by line C-E), formed complex is solubilized within the surfactant micelles and also that above the critical micelle region insufficient surfactant monomer is available to ensure complexation. It needs to be appreciated here that the presence of free cromoglycate ion will tend to depress the measured surfactant critical micelle concentration. At high sodium cromoglycate concentrations and low surfactant concentrations (Region 5), no turbidity can be observed. From Tomlinson *et al.* [271] with permission.

chain length and the point of solubilization thus is reduced. Solubilization of the coacervate is achieved as these are hydrophobic species and can partition to the micellar phase. The solubilization of dye–detergent salts in excess detergent was first observed by Mukerjee and Mysels [272]. There are thus regions where anion and cation form an isotropic solution in spite of being incompatible at lower concentrations.

6.6.1 Solubility product

Tomlinson *et al.* [271] gave the following derivation of K_s for an interaction between an anion A^{x-} and a cation B^{m+} thus

$$A^{x-} + B^{m+} = A_m B_x. \tag{6.23}$$

The equilibrium constant is given by

$$K = \frac{a^m[A^{x-}]a^x[B^{m+}]}{a[A_m B_x]} \tag{6.24}$$

where a terms are the activities. As the coacervates form a separate phase $a = 1$ so that the solubility product, K_s is given by

$$K_s = a^m[A^{x-}]\ a^x\ [B^{m+}]. \tag{6.25}$$

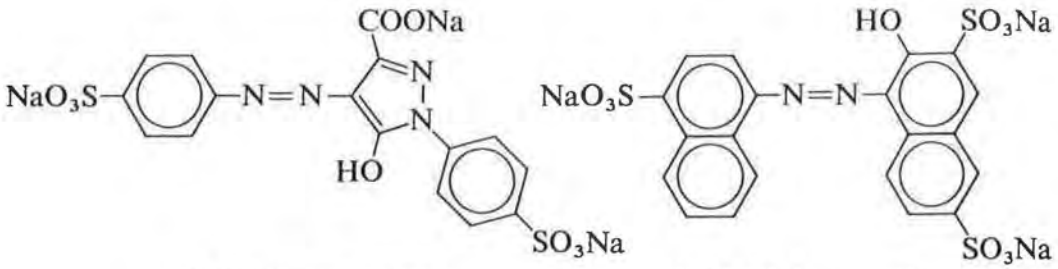
As $a = c\gamma$ we can write

$$K_s = [A^{x-}]^m[B^{m+}]^x(\gamma_{A^{x-}})^m(\gamma_{B^{m+}})^x. \tag{6.26}$$

At low concentrations $\gamma_i = 1$ so that

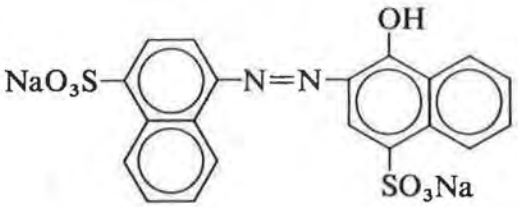
$$K_s = [A^{x-}]^m[B^{m+}]^x. \tag{6.27}$$

Complexation has frequently been correlated with the hydrophobic character of one (or both) of the interacting ions [273–279]. Details of the interaction between a series of dyes and alkyltrimethylammonium bromides have been published [277]. The structure of the dyes used, tartrazine (XXVI) amaranth (XXVII) carmoisine (XXVIII) and erythrosine (XXIX) are shown below. These are all important colours used in the food, drug and cosmetic industries. Phase separation diagrams were constructed to indicate the relationship between surfactant concentration and the anisotropic solution–coacervate boundary. Differences between the interactions of a hydrophilic dye, tartrazine and amaranth, carmoisine and erythrosine which have both hydrophobic and hydrophilic moieties were exhibited. Tartrazine appears to behave like a simple electrolyte interacting simply with the charged groups at the micellar surfaces while the other dyes complexed and were solubilized as a complex in addition to interacting with the micelle surface [277]. These dyes also induced the formation

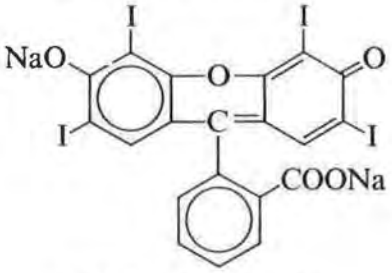


(XXVI) Tartrazine

(XXVII) Amaranth



(XXVIII) Carmoisine



(XXIX) Erythrosine

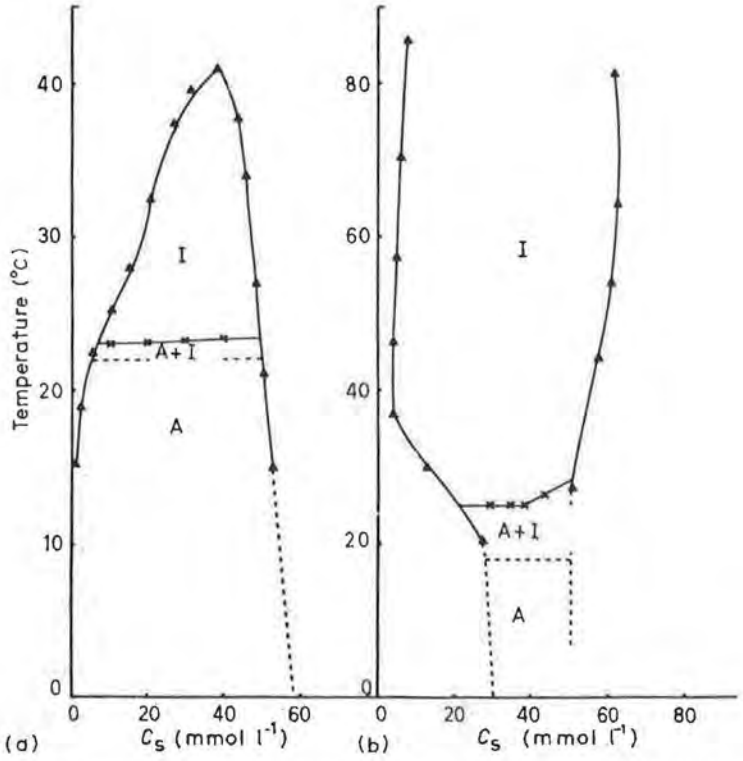


Figure 6.41 Diagrams showing temperatures at which dye–tetradecyltrimethylammonium bromide interaction products changed phase, as determined by microscopy: (a), 15 mmol l^{-1} tartrazine–tetradecyltrimethylammonium bromide; (b) 15 mmol l^{-1} amaranth–tetradecyltrimethylammonium bromide; in each case the surfactant concentration is C_s, mmol l^{-1}. I, separated phase is isotropic; A, separated phase is anisotropic; and A + I, separated phase is mixed anisotropic and isotropic. From Barry and Gray [277] with permission.

of surfactant micelles at concentrations well below the curve of the surfactants in water. The quite different phase diagrams for tartrazine–tetradecyltrimethylammonium bromide and amaranth–tetradecyltrimethylammonium bromide systems are shown in Fig. 6.41. Warming suppressed coacervation in the tartrazine–detergent system and a maximum temperature for coacervation occurred in each system while heating increased the area of coacervation in the other systems. Surfactant chain length effects are shown in Fig. 6.42.

The viscosity of these mixed systems can vary considerably due to the complex interactions and the formation of colloidal particles. The effect of surfactant concentration and alkyl chain length on the specific viscosity of amaranth solutions is illustrated in Fig. 6.43. Viscosity increases sharply as the ratio of dye to surfactant increases up to the point where the system coacervates. Ratios of surfactant to dye at the maximum agree with the ratios for compatability in these systems. Dye solutions which contain short-chain homologues have a smaller viscosity maximum than those which contain long-chain homologues.

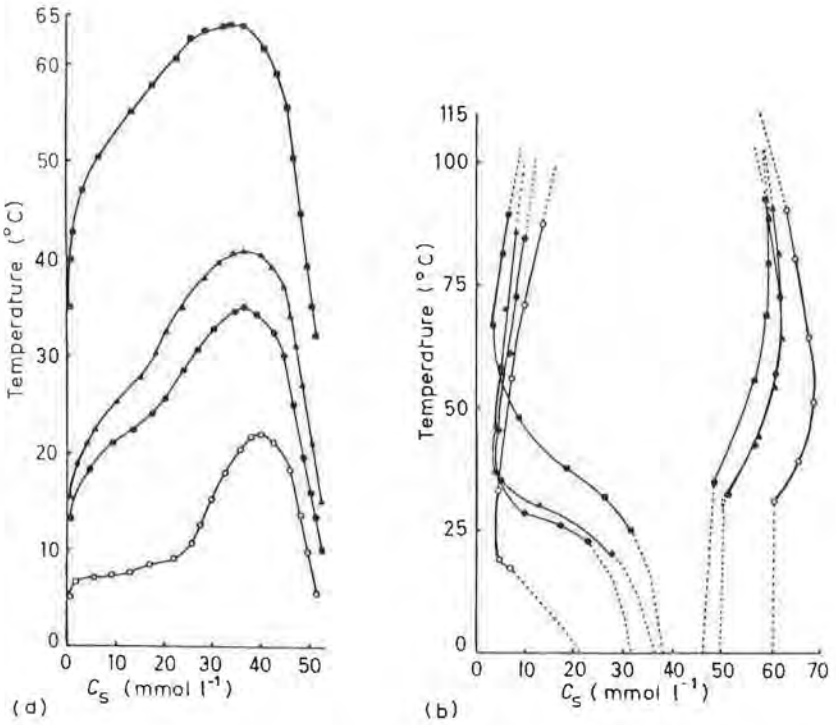


Figure 6.42 Diagrams showing temperatures and surfactant concentration (C_s) at which (a) tartrazine and (b) amaranth–alkyltrimethylammonium bromide solutions separate into two or more phases. Dye concentration 15 mmol l^{-1}. ■; hexadecyltrimethylammonium bromide system ▲ tetradecyltrimethylammonium bromide; ●: cetrimide; ○: dodecyltrimethylammonium bromide. From Barry and Gray [277] with permission.

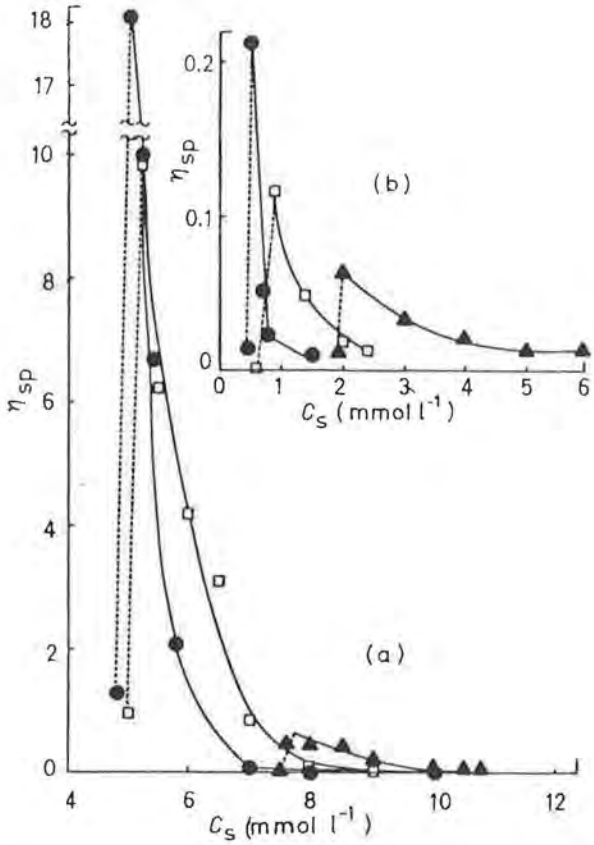


Figure 6.43 Effect of surfactant concentration (C_s, mmol l^{-1}) and alkyl chain length on the specific viscosity (η_{sp}) of aqueous amaranth solutions. (a) surfactant above and (b) surfactant below the CMC and 1.5 mmol/l dye, ▲ dodecyltrimethylammonium bromide; □, tetradecyltrimethylammonium bromide; and ●, hexadecyltrimethylammonium bromide. Dotted regions represent coacervated systems. From [266] with permission.

Barry and Russell explain 'At the viscosity maximum the concentration of surfactant required to reach reversal of charge point has just been exceeded and the excess surfactant acts as added salt and suppresses the coacervation by screening the charges on the reacting species. With further addition of surfactant, the ξ-potential progressively rises, colloidal particles repel each other and the solutions become more mobile. In the limit, the viscosities approach those of the dye-free surfactant solutions. Results above and below the CMC indicate that surfactant micelles are not necessary for interaction to occur between the dye and surfactant.'

6.7 Hydrotropy in pharmaceutical systems

Although much of this book is concerned with solubilization in micellar systems, there is a need to discuss the phenomenon of hydrotropy, as there is now a considerable body of literature on the pharmaceutical aspects of the subject. As has been discussed, hydrotropy is the term reserved for the action of increasing the solubility of a solute by a third substance which is not highly surface active – at least one which does not form micelles at low concentrations. The mechanism of

action of hydrotropes is varied, and we shall deal first with hydrotropes which exert their action through complexation. Caffeine is such a compound.

The presence of hydrotropes in drug formulations may be expected to influence the activity of the drug *in vivo*, although little work seems to have been done on this point. This may be a fruitful topic of research, as in these systems the lack of surface activity makes experimentation and interpretation of results less difficult. Higuchi and Drubulis [278] suggest that data on the complexing of drugs is important because the action of drugs is often the result of complex formation in an aqueous environment, and because the thermodynamic activities of the drugs in that environment may be modified by this phenomenon.

Because of the limited solubility of the xanthine derivatives in water, their solubilization by hydrotropes has been the subject of much interest. Such diverse compounds as piperazine [279], sodium salicylate [280], adenosine [281], and diethanolamine [282] have been used to solubilize theophylline. The action of each is presumably due to complex formation. Neish [283] found that caffeine, a xanthine derivative, increased the solubility of a number of aromatic amines, including sulphapyridine, sulphathiazole, and certain dyes.

It is perhaps relevant to note here that in clinical use sulphonamide mixtures are preferred to single drugs, to minimize the formation of crystal deposition in the kidney. The use of mixtures of related sulphonamides results in enhanced mutual solubility [284]. This is perhaps a case of hydrotropy. Lehr [285] has determined the solubility of a number of sulphonamide combinations, and Frisk *et al.* [286] have reported on the solubility of the combination sulphadiazine, sulphamerazine, and sulphathiazole. The influence of sulphanilamide on the solubility of sulphathiazole indicated that a 1 : 1 molecular complex was formed [287].

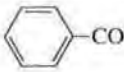
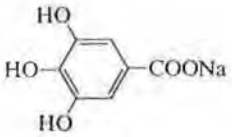
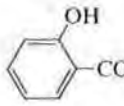
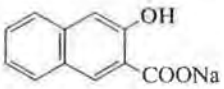
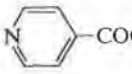
Apart from the possible prevention of unwanted physiological effects, hydrotropes can have a direct action on efficacy. Theobromine is soluble in water to the extent of 1 in 2000; an equimolar mixture with sodium acetate has a solubility of 1 in 1.5, and a mixture with sodium salicylate, 1 in 1. Clinical evaluation of various theophylline and theobromine preparations in the treatment of angina pectoris [288] showed a theobromine–sodium acetate mixture to be the most effective. Ergotamine levels have been shown to be enhanced when the drug is administered in combination with caffeine, which increases the solubility and rate of solution of the ergotamine [289].

Description of some of the hydrotropes used in the solubilization of riboflavin will illustrate the diversity of compounds employed. Nicotinamide increases the solubility of riboflavin in polar liquids [290], and it has been observed [291] that ascorbic acid also has a hydrotropic effect on riboflavin. A 20% aqueous ascorbic acid solution increases the aqueous solubility of riboflavin at room temperature by 4.5 times. This is important in the formulation of multi-vitamin preparations. Concentrated solutions of (−)−, or (+)− tryptophan dissolve riboflavin to the extent of 4 mg ml^{-1} at pH 6.8, and the addition of nicotinamide markedly increases the solubility, giving stable solutions, suitable for injection [292]. *N*-(2-hydroxyethyl) gentisamide may also be employed as solubilizer [293], as can

water-soluble salts of benzoic acid and its amino- or hydroxyl-substituted derivatives [294]. Riboflavin in concentrations of 1, 2, and 120 mg ml^{-1} requires 15, 25, and 625 mg, respectively, of sodium salicylate per ml to effect its solution.

A comprehensive study of the solubility of riboflavin in a range of hydrotropes [295] revealed some interesting differences due to structural changes in the hydrotrope (Table 6.31). The effect of a range of nicotinic acid and *iso*nicotinic acid derivatives was not affected by the structure of the side chain to any great extent, but alterations to the hydrophobic radical proved more startling: 3-hydroxy-2-naphthoic acid and its mono-ethanolamide has approximately ten times the effect of salicylic acid and its mono-ethanolamide.

Table 6.31 Solubility of riboflavin in solutions of hydrotropes (solubility in mg ml^{-1})

Hydrotropic compound	Conc. of hydrotrope (%)				
	1	2	3	5	10
	0.38	0.48	0.64	1.10	3.10
	0.67	0.92	1.46	2.85	7.34
	0.53	0.96	1.30	2.90	7.70
	5.60	12.50	19.60	34.30	97.80
	0.37	0.50	0.66	1.10	2.40

From [298].

In an investigation of the solubility of theophylline, hydrocortisone, prednisolone, and phenacetin in a range of hydroxybenzoic acids and their sodium salts and several hydroxynaphthoates, it was concluded [278] that the major factor in the interactions were the donor–acceptor interactions; hydrophobic bonding and hydrogen bonding were thought to play a less-important role. Table 6.32 presents some of these results; the figures represent first-order constants, i.e. apparent stability constants. Complex formation between riboflavin and caffeine has been demonstrated and the solubilizing properties of caffeine and theophylline and dimethyluracil have been studied [296]. The marked difference in the solubilizing powers of the caffeine and dimethyluracil

Table 6.32 Solubility of hydrocortisone, prednisolone, and phenacetin in solutions of naphthoates and hydroxy naphthoates: apparent stability constants K ($l\,mol^{-1}$)

	Hydrocortisone	Prednisolone	Phenacetin
1-Naphthoate	8.2	8.0	2.5
2-Naphthoate	19.0	20	5.8
2-Hydroxynaphthoate	21	23	6.6
1-Hydroxy-2-naphthoate	35	35	7.0
2-Hydroxy-2-naphthoate	32	39	6.3

$$\begin{array}{c} A + B \rightleftharpoons AB \\ \Updownarrow \\ [B]\ \text{solid} \end{array}$$

$$K = \frac{[AB]}{[A][B]}$$

The results are listed as first-order interaction constants, since the amount of solubilizate increased linearly with concentration of aromatic hydrotrope.
From [278].

suggests that the imidazole ring of the xanthine nucleus is involved in the interaction which, it is thought, leads to the formation of 1 : 1 complexes. The molecular interaction of caffeine with benzoic acid, methoxybenzoic acid, and nitrobenzoic acid [297] has been investigated in detail. Fig. 6.44 shows the typical picture with an initial increase in the solubility of the acid with increasing caffeine concentration followed by a plateau region which results because of the limited solubility of the caffeine. Similar behaviour is exhibited by theophylline–acetylsalicylic acid mixtures [298]. Of the three xanthines studied, caffeine has the greatest solubilizing power towards acetylsalicylic acid. While 1 : 1 complexes are formed between caffeine and sulphathiazole (1 % w/v caffeine increases the solubility of sulphathiazole by 50 %), sulphadiazine, benzocaine, and *p*-aminobenzoic acid, and the barbiturates are capable of forming 2 : 1 complexes [298].

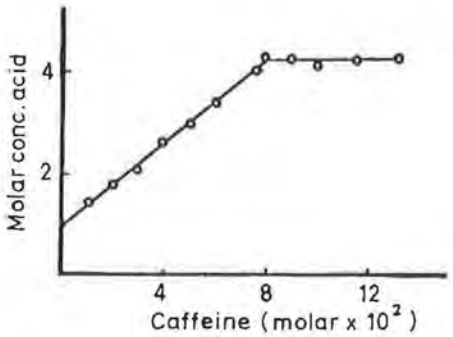


Figure 6.44 Solubility of *p*-methoxybenzoic acid in aqueous solutions of caffeine showing the plateau region caused by precipitation of the caffeine. From Donbrow and Jan, [297].

Some rationalization of drug complexation is possible by the use of Hückel frontier molecular orbitals [300]. These confirm π-donor-π-acceptor mechanisms for the interactions with niacinamide of the compounds shown below in aqueous solution. Phase-solubility diagrams all showed positive deviations from linearity, behaviour attributed to first- and second-order interactions between the solute (S) and the hydrotrope (H):

$$S + H \rightleftharpoons SH \qquad \text{(i)}$$

$$K_{1:1} = \frac{[SH]}{[S][H]}$$

$$SH + H \rightleftharpoons SH_2 \qquad \text{(ii)}$$

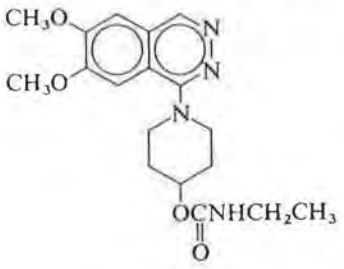
$$K_{1:2} = \frac{[SH_2]}{[SH][H]}.$$

Table 6.33 gives values for these two equilibrium constants [300].

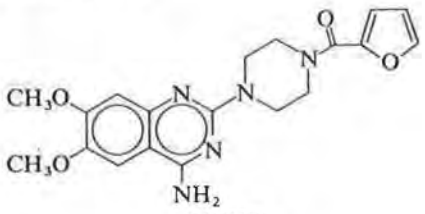
Table 6.33 Equilibrium constants and calculated stabilization energies for niacinamide* complexes

Compound	$K_{1:1}$	$K_{1:2}$	ΔE	$\log K_{1:1}$	Calculated $\log K_{1:1}$
XXX	12.31	14.76	0.598	1.090	1.022
XXXI	7.36	0.33	0.561	0.861	0.876
XXXII	18.45	0.51	0.660	1.266	1.267
XXXIII	9.88	2.26	0.607	0.995	1.058

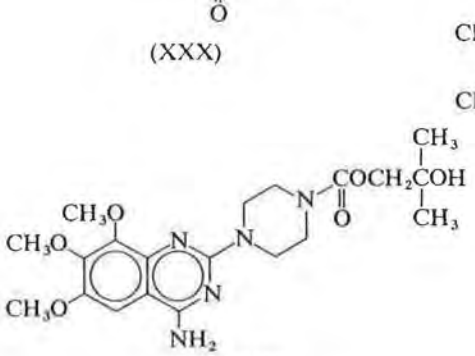
* Niacinamide concentration was 0.0–2.0 M for II and 0.0–0.2 M otherwise [300].
The ΔE value is a partial measure of stabilization.



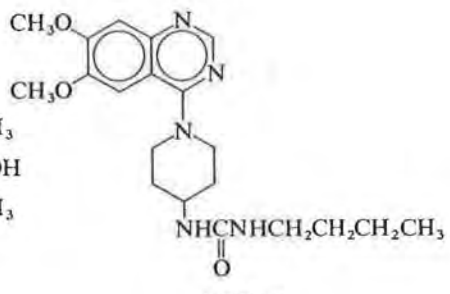
(XXX)



(XXXI)

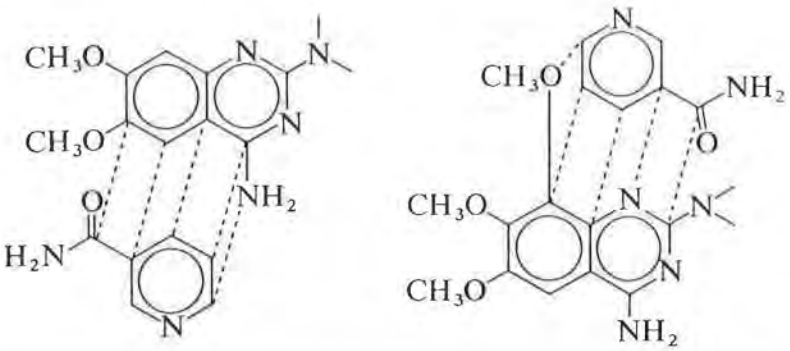


(XXXII)



(XXXIII)

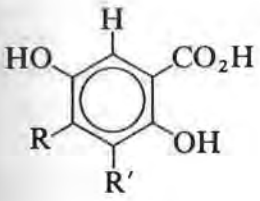
The complexation of (XXXI) is shown in the diagram below and may be compared with the complex formed by compound (XXXII). The small change in structure gives rise to a change in the topology of the complex to give maximum degree of interaction



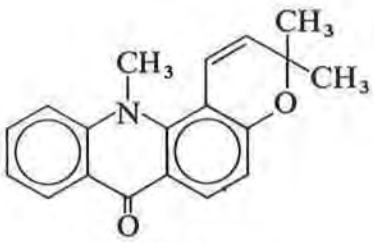
Schematic representation of interaction between niacinamide and (XXXI) and (XXXII) from Fawzi *et al.* [300] with permission.

The difficulty in using the xanthines in pharmacy is that they have a pharmacological action of their own and limited solubility. However, a number of medicaments contain hydrotropes for their therapeutic effect and not their solubilizing action, such as in aspirin, phenacetin, and caffeine mixtures; it is unlikely that the caffeine in this preparation is inactive.

Gentisic acid (XXXIV) and its alkyl derivatives have been reported to form complexes with several solutes including acronine (XXXV) [299].



(XXXIV) (a) R = R′ = H; gentisic acid
(b) R = H, R′ = CH_3; 3-methyl gentisic acid
(c) R = H, R′ = CH_2CH_3; 3-ethyl gentisic acid
(d) R = CH_3, R′ = H; 4-methyl gentisic acid
(e) R = CH_2CH_3, R′ = H; 4-ethyl gentisic acid



(XXXV) Acronine

The complexation of acronine with gentisate, and 3-methyl, 4-methyl, 3-ethyl, and 4-ethyl-substituted gentisates was studied by solubility techniques in aqueous solutions at 25° C. In all cases both 1 : 1 and 1 : 2 (acronine : gentisate) complexes were found and apparent increases in the solubility of acronine were

observed with 3-methyl gentisate bringing about the largest increase. Both the nature of the substituent and its position were important in the complexation and the effects appear to be due to opposing steric and hydrophobic contributions [299]. In none of the systems was there evidence of precipitate formation. While a methyl substituent at the 3 or 4 position increases the solubility, a further increase in the chain length of the substituent decreases the extent of complexation. (Fig. 6.45). The suitability of 3-methyl gentisate for intravenous use has not been reported, although aqueous gentisate solutions have been studied (Cradock, see [299]) and deemed to be suitable for parenteral use.

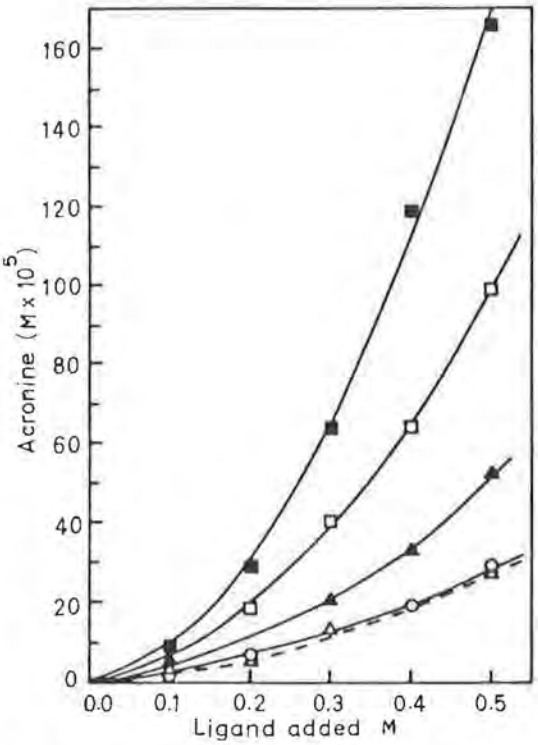


Figure 6.45 Plot of the apparent solubility of acronine at 25° C as a function of the concentration of various gentisic acid ligands in aqueous buffer (0.1 M succinate, pH 5.5, ionic strength ~ 0.6 M with sodium nitrate). The solubility of acronine in the absence of ligands is 8.5×10^{-6} M. Gentisic acid (○, ———); 3-ethyl gentisic acid (□, ———); 4-ethyl gentisic acid (△, – – –); 3-methyl gentisic acid (■, ———); 4-methyl gentisic acid (▲, ———). From Repta and Hincal [299].

6.7.1 Benzoates and salicylates as hydrotropes

Solutions of sodium *p*-toluene sulphonate enhance the solubility of phenolic compounds in general; however, of sodium benzoate, sodium *p*-toluene sulphonate, and sodium salicylate the last compound is the best hydrotrope [301]. Sodium benzoate is used to solubilize chlorocresol in solution of sodium benzoate and chlorocresol and to increase the solubility of the haemostatic

adrenochrome monosemicarbazide [302]. Injection of caffeine and sodium benzoate is the parenteral form in which caffeine is usually administered. A 25:1 salicylic acid–adrenochrome complex dissolves in water up to 25 mg mol^{-1} [303]. Iwao [304] found that a 25:1 mixture can be diluted with water to any degree without precipitation.

The solubility of the antitubercular drug, pyrazinamide, is directly proportional to the concentration of sodium *p*-aminosalicylate (sodium PAS) or sodium hydroxybenzoate in aqueous solution [305]. Thermal analysis has confirmed the complex formation between the drug and sodium PAS, but the authors [305] list the alternatives of complexation and normal increase in solubility in the presence of additive as the causes of solubilization. As the antituberculars are always used clinically in combination – sodium PAS is also an effective drug – this study may have some bearing on the efficacy of the combinations. It might be of interest for an investigation to be carried out on the solution properties of isoniazid, streptomycin, and sodium PAS mixtures, especially as streptomycin is thought to have some colloidal electrolyte properties of its own.

Saleh *et al.* [306] have studied the solubility of diazepam in sodium salicylate solution as a potential parenteral formulation. At present diazepam, which is practically insoluble in water, is formulated with propylene glycol as the main solvent component but undesirable clinical effects following intramuscular and intravenous injection have been attributed to the propylene glycol. The solubility of diazepam increases significantly at concentrations of salicylate greater than 15 to 20%. At 30%, the solubility has increased to over 16 mg ml^{-1} (Fig. 6.46). The

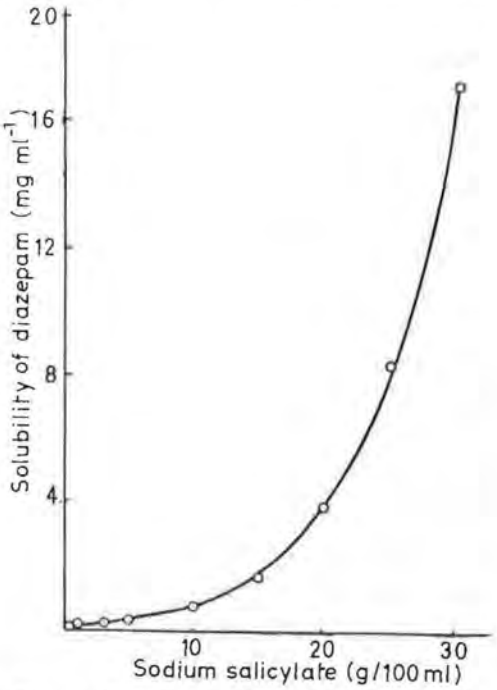


Figure 6.46 Effect of sodium salicylate on the solubility of diazepam in water at 37° C. From Saleh *et al.* [306].

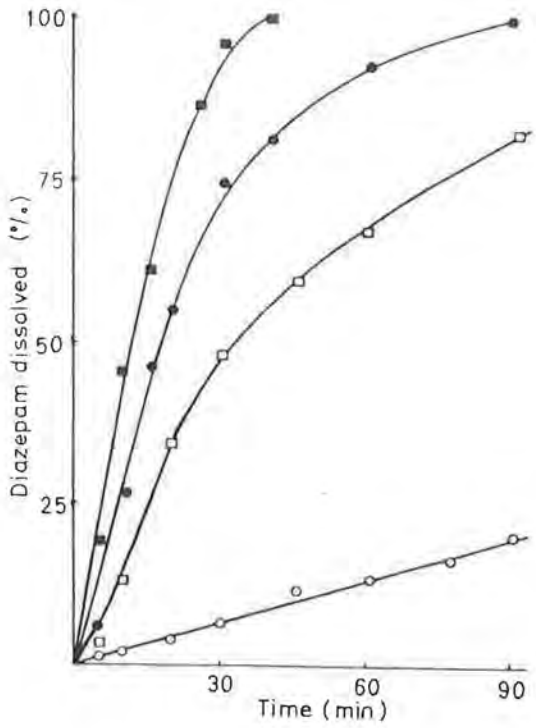


Figure 6.47 Effect of various concentrations of sodium salicylate on the dissolution rate of diazepam in water at 37° C. Water, ○; and 4 %, □, 8 %, ●; and 12 %, ■; sodium salicylate. From El-Khordagui *et al.* [307].

concomitant increase in rates of solution can be seen in Fig. 6.47. As sodium salicylate decreases the surface tension of water the effect on dissolution may be partly due to this. There is, however, some evidence that at concentrations greater than 20 % w/v, sodium salicylate associates in solution. The compatability and stability of diazepam in 30 % sodium salicylate solutions following dilution with 5 % dextrose and normal saline has been studied by El-Khordagui *et al.* [309] who found that 1 : 1 and 1 : 100 dilutions remained clear for up to 3 h, although microcrystal formation was noted at longer times. The diazepam–sodium salicylate combination also induced higher degrees of haemolysis *in vitro* than a commercial diazepam injection containing Cremophor EL. The interpretation of the haemolytic activity may be complicated by the fact that Cremophor EL has previously been implicated in the inhibition of haemolysis at concentrations of 0.8 to 4 mg ml^{-1} [308].

Sodium salicylate has been found to enhance rectal absorption of drugs [309] but contrary to the action of some surfactants the absorption promotion was not found to be the result of a permanent change in the rectal mucosa.

The effect of the caffeine–sodium salicylate molar ratio in the distribution of caffeine to chloroform from an aqueous phase has been studied by Blake and Harris [310] and is reproduced in Fig. 6.48. This effect might in itself cause a change in the physiological action of the caffeine. Sodium salicylate does not affect the biological availability of riboflavin in solutions containing 25 % sodium

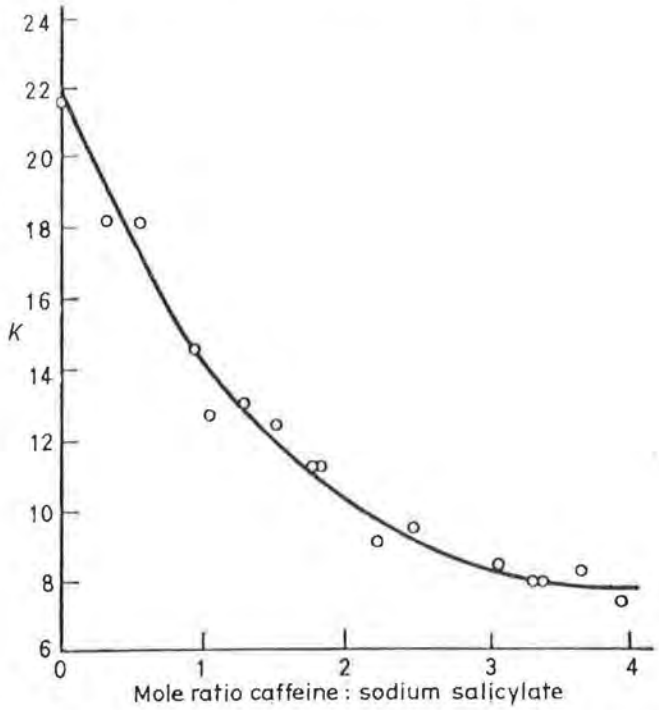
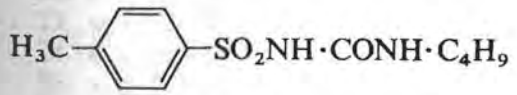


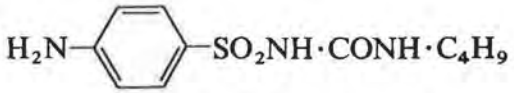
Figure 6.48 The effect of sodium salicylate on the distribution coefficient (K) of caffeine between chloroform and water. From Blake and Harris [310].

salicylate and 1.2% vitamin, the riboflavin activity being measured by two biological procedures. No difference was detected in response between riboflavin powder and solubilized preparations [311].

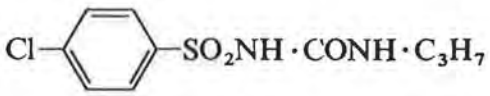
It is possible that the use of sodium salicylate in doses of 4 to 9 g daily in chronic gout and its ability to lower serum uric acid levels is due to a hydrotropic action on the acid, preventing its reabsorption by the kidney tubules. According to Lieber [312] the concept of hydrotropy allows some understanding of the etiology of metabolic diseases, such as atherosclerosis, diabetes, lithiasis, and gout. Lieber suggests that the efficacy of the oral hypoglycaemic agents used in the treatment of diabetes is due to their hydrotropic properties, by which they liberate insulin from its protein complex and thereby activate it. Tolbutamide is a derivative of *p*-toluene sulphonic acid (see below), and other agents used orally in diabetes are similar.



(XXXVI) Tolbutamide

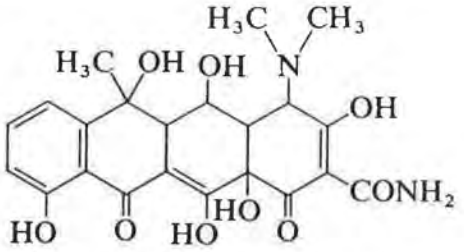


(XXXVII) Carbutamide



(XXXVIII) Chlorpropamide

The tetracyclines are a group of drugs which form soluble complexes with typical hydrotropes. Oxytetracycline dihydrate and tetracycline dihydrate complex with sodium salicylate, sodium saccharin, sodium *p*-aminobenzoate, and *N*-methylpyrrolidone [313] which is hardly surprising considering the polar, multifunctional character of the drugs:



(XXXIX) Oxytetracycline

Since many hydrotropic agents possess strong negative groups, it seemed logical to ascribe the solubilization to a displacement reaction whereby the acidic hydrogens of the solute co-ordinate with the negative centres of the additive, replacing water molecules. This interaction may be rendered more favourable by

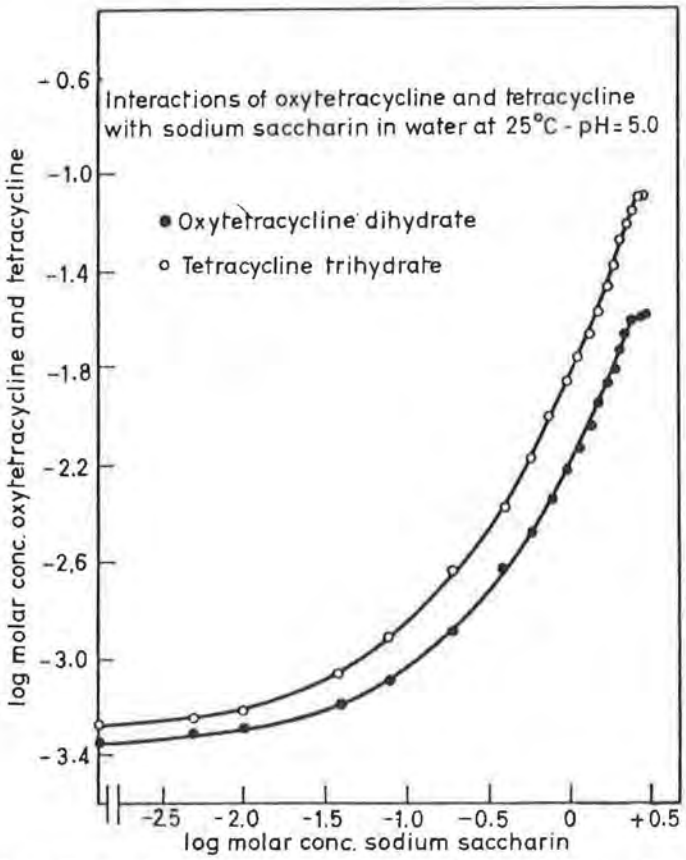


Figure 6.49 The effect of sodium saccharin on the solubility of tetracycline and oxytetracycline in water at 25°C. From Gans and Higuchi [313].

the formation of hydrophobic bonds between the hydrocarbon parts of the interacting molecules. The large aromatic nucleus of the tetracycline antibiotics makes this a possibility. Fig. 6.49 shows the effect of sodium saccharin on the solubility of the two tetracyclines. The typical hydrotropic solubility curve is not, apparently, a linear function of concentration of the hydrotrope, but shows considerable sigmoidal character [314]. Relatively weak complexing tendencies exist between saccharin and various substances in aqueous solution [315], a 1:1 complex being formed with theophylline but there being no interaction with *N*-methyl pyrrolidone or γ-butyrolactone.

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