# SURFACTANT SYSTEMS

*Their chemistry, pharmacy and biology*

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# 7 *Biological implications of surfactant presence in formulations*

## 7.1 Introduction

The use of surfactants as emulsifying agents, solubilizers, suspension stabilizers and as wetting agents in formulations intended for administration to human subjects or to animals can lead to significant changes in the biological activity of the active agent in the formulation. A drug is seldom administered as such but as a complex formulation. Surfactant molecules incorporated into the formulation can exert their multifarious effects in several ways, e.g. by influencing the deaggregation and dissolution of solid dose forms (Fig. 7.1), by controlling the rate of precipitation of drugs administered in solution form, by increasing membrane permeability and affecting membrane integrity. Complex interactions occur between surfactants and proteins and thus there is the possibility of a surfactant-induced alteration of drug metabolizing enzyme activity. There has also been the suggestion that surfactants may influence the binding of the drug to the receptor site. The determinants of the effectiveness of surfactants on drug absorption are several. Drugs in which dissolution and not membrane transport is the rate-limiting step in absorption and drugs in which the latter is the rate-determining step may be affected differently. Water-soluble drugs will not and water-insoluble drugs will interact with surfactant micelles thus high concentrations of surfactants are likely to affect lipophilic and hydrophobic drugs to differing degrees. Some surfactants have direct physiological activity of their own and in the intact animal can thus affect the physiological environment, e.g. by altering gastric residence time such that without physico-chemical intervention, a surfactant-effect will be seen. It is only possible to isolate some of these effects and to examine the effect of surfactants in each. Studies in whole animals have sometimes given what appear to be contradictory results.

Numerous studies on the influence of surfactants on drug absorption have shown them to be capable of increasing, decreasing, or exerting no effect on the transfer of drugs across biological membranes [1]. Perhaps the earliest report of the effect of soap on drug activity is that of Billard and Dieulafe [2], who noted that the toxic effect of curare injected intraperitoneally into guinea-pigs could be increased by the addition of low concentrations of soap and decreased by high concentrations. This biphasic action of surfactants has been noted several times

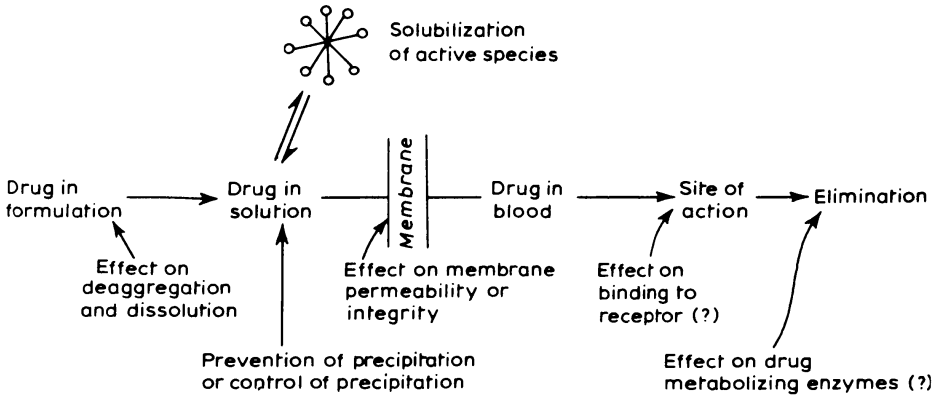



**Figure 7.1** Possible sites of surfactant influence on drug absorption and activity. Utilization of a drug involves its release from the formulation, its solution in the body fluids, and its passage through barrier membranes into the systemic blood stream before transport into tissues and eventual arrival at the target organ. Release of poorly soluble drugs from tablets and capsules for oral use may be increased by the presence of surfactants, which may decrease the aggregation of the drug particles and therefore increase the area of particle available for dissolution. The lowering of surface tension may also be a factor in aiding the penetration of water into the drug mass; this wetting effect is operative at low concentrations. Above the critical micelle concentration (CMC) the increase in the saturation solubility of the drug substance by solubilization in the surfactant micelles can result in more rapid rates of drug solution. Where dissolution is the rate-limiting step in the absorption process, as it is with many poorly soluble drugs, an increase in rate of solution will increase the rate of drug entry into the blood and may affect peak blood levels. Very high concentrations of surfactant can decrease drug absorption by decreasing the chemical potential of the drug. This results when surfactant is present in excess of that required to solubilize the drug.

since, but nonetheless the literature tends to be confused. The observed influences of surfactants depend on the concentration of the agent used (which is difficult to assess when the formulation has been administered to man or intact animal) and even in model systems this leads to complications in elucidating effects especially when the surface-active agent exerts several actions simultaneously. Much of the confusion in the literature on this subject arises from discussion of the influence of different concentrations of surfactant, and from attempts to generalize on the action of varied surfactants on many different types of biological membrane. As with the physical effects noted above, distinct changes in the activity of the surfactant can frequently be observed on increase of surfactant concentration. This can be demonstrated by experiments in model systems, for example, in goldfish immersed in solutions of drug and surfactant [3–5]. Low concentrations of polysorbate 80 increase the absorption of secobarbitone; concentrations above the CMC decrease absorption. Similarly, the influence of surfactant structure and properties on drug absorption can also be demonstrated with the goldfish; some of these experiments will be discussed later in this chapter.

## 7.2 Effect of surfactants on dissolution of drugs

It is readily apparent that the rate of solution of poorly soluble drugs can be increased by the presence of surfactants in the dissolution medium. Most experiments have been carried out *in vitro*; the effect *in vivo* is more complex with the concomitant dilution of the surfactant by a complex medium, the absorption of the surfactant itself and the adsorption of other substances onto the dissolving particles.

Surfactant adsorption on to hydrophobic drug particles below the critical micelle concentration can aid wetting of the particles and consequently increase the rate of solution of particulate agglomerates [6–10]. Surfactants may be incorporated into solid dosage forms [11] so that their solubilizing action comes into play as the disintegration process starts and water penetrates to form a concentrated surfactant through lowering of surface tension solution around the drug particles or granules. Both facilitation of wetting and solubility increase will aid dissolution of the drug. Finholt and Solvang's results [12] on the dissolution *in vitro* of phenacetin and phenobarbitone in the presence of polysorbate 80 show clearly the influence of surface tension (Fig. 7.2). The solubility of phenacetin is little affected by the concentrations of polysorbate 80 used and thus enhanced wetting is the primary cause of improved dissolution rates, a result in accord with the finding that sodium lauryl sulphate (NaLS) increased the rate of solution of salicylic acid from compressed tablets owing to better solvent penetration into the tablets and granules [13]. Finholt and Solvang [12] determined the pH and surface tension of gastric juice from 27 patients. Surface tension ranged between 35 and 50 mN $m^{-1}$ and pH between 1 and 7.5, and was independent of secretion rate. Such are the complications of the *in vivo* environment and the problems of determining the effect of synthetic surfactants on dissolution rates *in vivo*; the rate of solution of a drug such as phenobarbitone is significantly higher in diluted gastric juice than in 0.1N HCl because of the

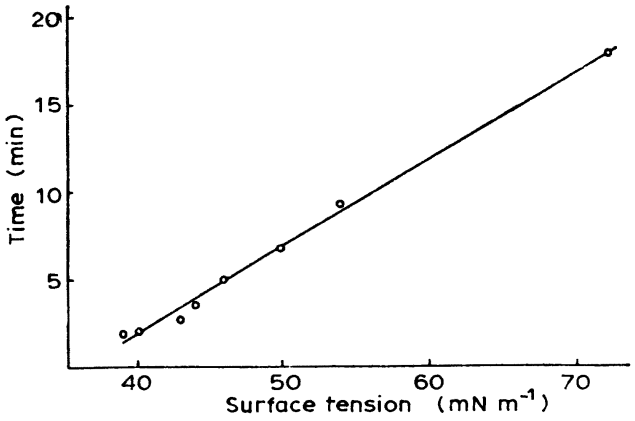



**Figure 7.2** Relationship between the surface tension of the dissolution medium and the time necessary for dissolution of 100 mg phenacetin. Dissolution media: 0.1 N HCl containing different amounts of polysorbate 80. From Finholt and Solvang [12] with permission.

difference in surface tension. In addition, the amount of a soluble salt such as phenobarbitone sodium dissolved in diluted gastric juice at 1 h has been shown to be considerably increased, presumably because the precipitation of the free acid is reduced by components in gastric fluid. Nevertheless increased absorption of paracetamol has been observed *in vivo* [14]. Enhanced absorption of digoxin and digitoxin [15] and sulphadiazine and sulphisoxazole [16] have been ascribed to increased dissolution rates of these drugs brought about by the incorporation of surfactants into the formulation. The effect of poloxamer 188 and dioctyl sulphosuccinate (DOSS) on absorption of sulphisoxazole from rat intestinal loops is shown in Table 7.1, and the influence of these surfactants on dissolution rate shown in Fig. 7.3. Poloxamer 188 and DOSS are both used below their critical micelle concentrations, at concentrations likely to be found *in vivo* where they are used as faecal softeners in laxative products. In some systems negligible effects are noted below the surfactant CMC. Such is the case with hydrocortisone [17]; neither polysorbate 80 nor two Solulan surfactants (Solulan 25 and 16, American Cholesterol Products Inc., USA) increased the dissolution rate of this steroid until their respective CMCs were exceeded. However, the solubility of hydrocortisone was increased much less than the increased solution rate would imply suggesting that the solubility increase was not of major importance in this case. Short *et al.* [8] have also considered the effect of surfactant on hydrocortisone dissolution. An increased dissolution rate constant below the CMC of polysorbate 80 is observed, this decreasing just above the CMC; Short *et al.* suggest that this might be related to a surface tension effect, the maximum in dissolution rate constant coinciding with the surface tension minimum of the polysorbate. A minimum surface tension around the CMC value implies the presence of surface-active impurities [18] which may adsorb preferentially on the drug particles decreasing dissolution rate.

Concentrations of polysorbate 20 well in excess of the CMC have been used by Collett and Rees in their studies on salicylic acid dissolution [10, 19]. Dissolution rates were measured over a pH range from 1.0 to 4.0; the dissolution rate increases very slowly above 12% surfactant (Fig. 7.4) but there was no evidence of a decreased dissolution rate such as found by Parrott and Sharma [20], e.g. above

**Table 7.1** Effect of poloxamer 188 and dioctyl sodium sulphosuccinate on the absorption of sulphisoxazole from rat intestinal loops*

| Surfactant | Concentration, % w/v | Dose absorbed, % ± S.D. |
|---|---|---|
| Control | — | 45.3 ± 6.5 |
| poloxamer 188 | 0.01 | 56.1 ± 3.9 |
| | 0.10 | 57.3 ± 10.1 |
| Dioctyl sodium sulphosuccinate | 0.01 | 53.9 ± 9.4 |
| | 0.10 | 55.0 ± 8.4 |

* Values represent mean of 6 animals.
From [16].

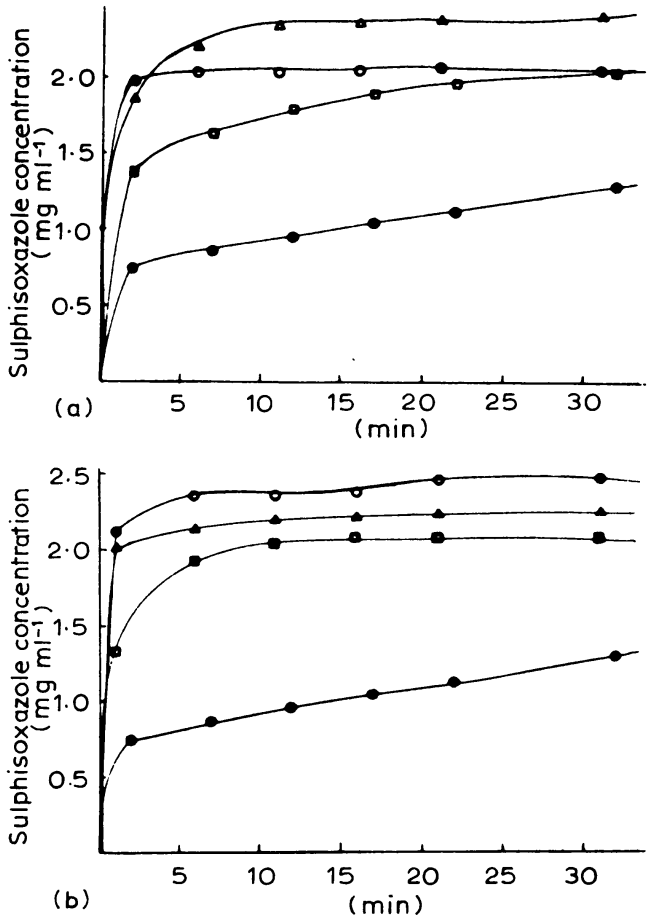



**Figure 7.3**(a) Effect of poloxamer 188 on sulphisoxazole dissolution ●, control; □, 0.001 %; △, 0.01 %; and ○, 0.1 %. (b) Effect of dioctyl sodium sulphosuccinate on sulphisoxazole dissolution. ●, control; □, 0.001 %; △, 0.01 %; and ○, 0.1 %. From Reddy *et al.* [16] with permission.

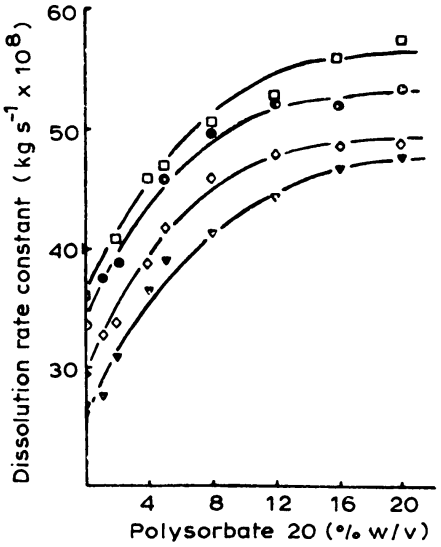



**Figure 7.4** Plot of dissolution rate constants ($kg\,s^{-1} \times 10^8$) of salicylic acid against concentration of polysorbate 20 at several pH values ▼pH 10, ◇pH 2.0,●pH 3.0, □pH 4.0. From Rees and Collett [10] with permission.

12% polysorbate 80 with benzoic acid. Collett and Rees [19] suggest that the decreased dissolution rates are not a function of the viscosity of the dissolution medium but rather an artefact due to lack of pH control in the system, the decreased pH resulting from the dissolution of benzoic acid leading to decreased solubility and thus solution rate. However, such an explanation cannot be put forward to discuss the decreased rate of solution of griseofulvin [21] at high concentrations of non-ionic surfactant.

### 7.2.1 Theoretical approaches to dissolution rates in high concentrations of surfactant

Higuchi [22] has analysed the dissolution process in the presence of micellar solutions. His equations predict that the effect of surfactant on dissolution rate will be less than predicted by the Noyes–Whitney equation on the assumption of increased bulk solubility. The Noyes–Whitney relation in the form

$$\frac{dc}{dt} = kA(c_s - c) \tag{7.1}$$

shows the rate of change of concentration of solute, $c$, related to its surface area, $A$, and its saturation solubility, $c_s$. When $c_s \gg c$ there is a direct proportionality between the rate of solution, $dc/dt$ and $c_s$. The studies discussed above have shown that this is frequently not observed, as clearly demonstrated in Fig. 7.5.

Higuchi [24] assumes that an equilibrium exists between the solute and the solution at the solid–liquid interface and that the rate of movement of solute into the bulk is governed by the diffusion of the free and solubilized solute across a stagnant diffusion layer. Drugs solubilized in micelles will have a lower diffusion coefficient than free drug so that the effect of additive on dissolution rate will be related to the dependence of dissolution rate on the diffusion coefficients of the diffusing species, and not to their solubilities, as suggested by simple interpretation of Equation 7.1. The effective diffusion coefficient ($D_{eff}$) is given by [24]:

$$D_{eff} = \frac{D_f c_f + D_m c_m}{c_s + c_m}, \tag{7.2}$$

subscripts f and m referring, respectively, to the free and micellar drug; $c_m$ is thus the *increase* in solubility due to the micellar phase. This leads to the following equation for dissolution of a solid at constant area $A$ and under sink conditions, i.e. $c_s \gg c$,

$$\frac{dc}{dt} = \left[\frac{D_f c_f}{h} + \frac{D_m c_m}{h}\right] \tag{7.3}$$

where $h$ is the diffusion layer thickness. Substituting Equation 7.2 into Equation 7.3 gave, where $c_t$ is the total solute concentration,

$$\frac{dc}{dt} = D_{eff} c_t / h. \tag{7.4}$$

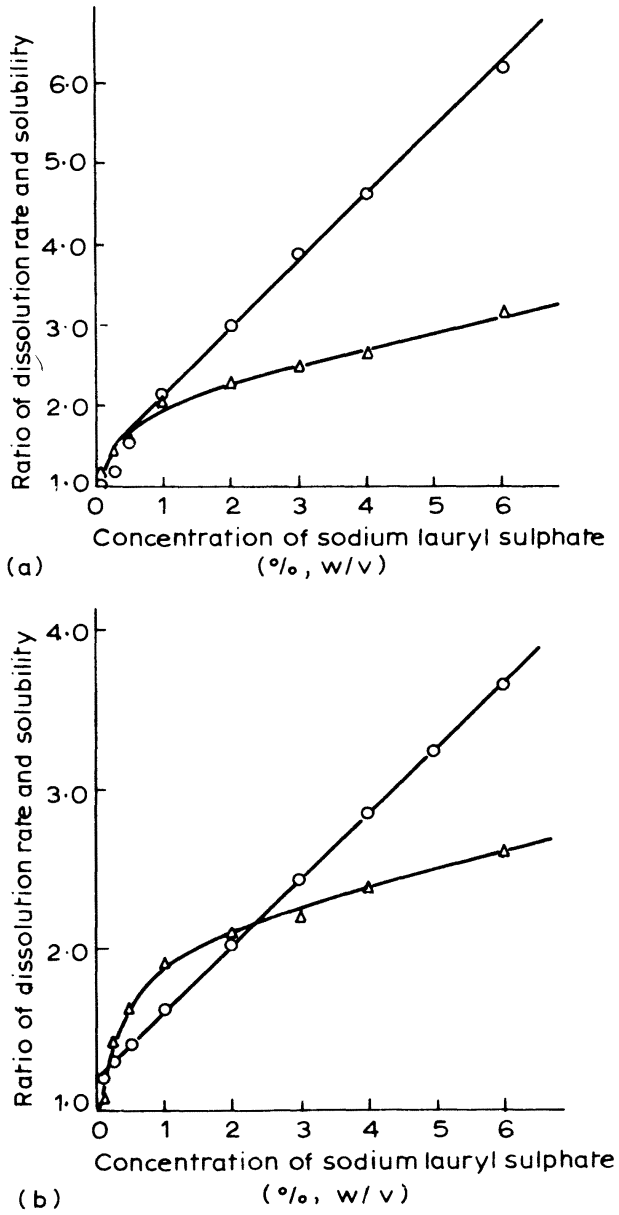



**Figure 7.5**(a) Ratio of dissolution rates and solubilities of sulphamethizole in surfactant solution to those in distilled water. (b) Ratio of dissolution rates and solubilities of sulphadiazine in surfactant solution to those in distilled water.
△: ratio of dissolution rate constant.
○: ratio of solubility.
From Watari and Kaneniwa [23] with permission.

However, both Collett and Rees [19] and Gibaldi *et al.* [25] find that dissolution rate is proportional to the effective diffusion coefficient raised to the power 0.5 to 1.0, thus placing in some doubt the diffusion coefficients of salicylic acid calculated assuming Equation 7.4 to hold [20]. The lack of agreement between the dissolution data and the predictions of Equation

7.4 leads to the conclusion that alternative models are required. A 'film-penetration' model incorporating the surface renewal concepts of Danckwerts [26] has been proposed [27]. In this, mass transfer from the surface is believed to occur by two simultaneous processes – one involving a stagnant film in which steady state molecular transfer occurs, and the other encompassing non-steady state mass transfer by eddy formation in the surface layer. The film-penetration model predicts a dependence of dissolution rate on diffusion coefficient with an exponent between 0.5 and 1.0 [25, 27].

Predictions of dissolution rate may be made using diffusion coefficients of the solutes in their solubilized state by applying the Stokes–Einstein equation.

$$D = \frac{RT}{6\pi\eta N_A} \sqrt[3]{\left(\frac{4\pi N_A}{3M\bar{v}}\right)}, \tag{7.5}$$

where $D$ is diffusion coefficient, $R$ is the molar gas constant, $T$ is the absolute temperature, $\eta$ is the viscosity of the solvent in poise, $\bar{v}$ is the partial specific volume of the micelles, $M$ is the micellar molecular weight, and $N$ is Avogadro's number. More direct measurements of $D_m$ are now possible by photon correlation spectroscopy and this should lead to a better analysis of dissolution models for solubilizing systems.

Elworthy and Lipscomb [28] considered dissolution to consist of two processes occurring simultaneously:

(1) a zero order reaction for the transfer of griseofulvin molecules from the solid surface into the solution, with rate constant $k_1$;
(2) a first order reaction for the deposition of solute from solution to solid surface, with rate constant $k_2$.

The rate of increase of concentration in solution:

$$\frac{dc}{dt} = k_1 - k_2 c. \tag{7.6}$$

The solution to this equation with the condition that at $t = 0$, $c = 0$ is

$$c = \frac{k_1}{k_2}(1 - e^{-k_2 t}). \tag{7.7}$$

Expanding the exponential term and rearranging gives

$$\frac{c}{t} = k_1 - \frac{k_1 k_2 t}{2} + \frac{k_1 k_2^2 t^2}{6} - \frac{k_1 k_2^3 t^3}{24} + \ldots.$$

At fairly early times in the dissolution process, terms in $t^2$ and $t^3$ etc. can be neglected giving:

$$\frac{c}{t} = k_1 - \frac{k_1 k_2 t}{2}. \tag{7.8}$$

A plot of $c/t$ versus $t$ will have an intercept $k_1$, and a slope $k_1 k_2/2$, enabling both constants to be evaluated. Trial calculations show that Equation 7.8 gives 1 %

error in $c$ compared to the exact Equation 7.7 provided that the $k_2t$ term does not exceed 0.25.

Equation 7.8 reduces to the Noyes–Whitney equation. When equilibrium is reached, i.e. a steady state between dissolution and redeposition,

$$\frac{dc}{dt} = 0 = k_1 - k_2 c_s,$$

where $c_s$ is the saturation solubility,

$$c_s = k_1/k_2, \tag{7.9}$$

and from Equation 7.7

$$c = c_s(1 - e^{-k_2 t})$$

or,

$$k_2 = \frac{1}{t} \ln\left(\frac{c_s}{c_s - c}\right), \tag{7.10}$$

which is the more usual form of the Noyes–Whitney equation. The rate constant of Equation 7.6 thus appears to be the first order constant arising in the consideration of the dissolution–redeposition process. Equation 7.8 is useful if the saturation solubility is not known; when it is, Equation 7.9 can be used to evaluate one constant when the other has been determined from Equation 7.8 or 7.10.

A result of this analysis is shown in Fig. 7.6 for the cetomacrogol–griseofulvin system [29]. The considerable effect of stirring rate on the dissolution rate of the powdered drug is seen, leading to the conclusion that it is necessary to choose

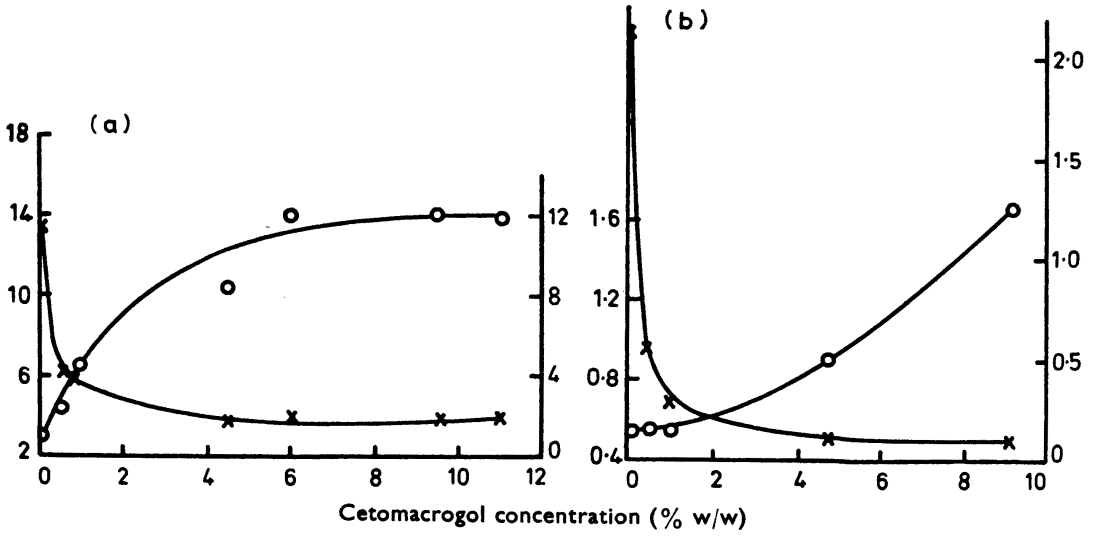



**Figure 7.6** Effect of cetomacrogol concentration on $k_1$ (○) and $k_2$ (×) at a stirring rate of (a) 200 rev min$^{-1}$ (b) 60 rev min$^{-1}$. Left hand ordinates $10^7 k_1$. Right hand ordinates $10^3 k_2$. The solute griseofulvin, is in powdered form. From Elworthy and Lipscomb [29] with permission.

carefully the rate of stirring in attempts to obtain *in vitro–in vivo* correlations. It has been found [30] that *in vitro* rates of methyl prednisolone, for example, correlated with *in vivo* absorption rates only when the rate of stirring employed in the dissolution test was low.

It seems likely [28] that the presence of surfactants facilitates the transfer of drug molecules from the crystal surface into solution as the activation energy for this process was found to be lower in surfactant than in water. In the case of $k_2$, the activation energy increases in the surfactant solution which probably reflects the viscosity increase and also the possibility that a layer of adsorbed surfactant molecules interferes with the redeposition process.

Chan *et al.* [31] have presented a theory of solubilization kinetics and its relation to the flow of dissolution medium, based on an analysis of five steps depicted in Fig. 7.7. Surfactant molecules diffuse to the surface as micellar species (step 1). These molecules are adsorbed on the surface of the solid (step 2) and on the surface the surfactant and solubilizate form a mixed micelle (step 3). In step 4 the mixed micelle is dissolved and it diffuses away into the bulk solution in the last step (step 5). The solubilization rate is assumed to be controlled by steps 4 and 5 in Fig. 7.7. If these steps are rate controlling

$$\frac{d[M]}{dt} = k_i A[M_i] \tag{7.11}$$

where $[M]$ is the concentration of mixed micelles in the bulk solution, and $[M_i]$ is the concentration of micelles at the interface. $A$ is the surface area per volume, $k_i$ is the forward reaction rate constant for step $i$.

$$\frac{d[M_i]}{dt} = k_4[M_s] - k_{-4}[M_i][S] - k_5 A[M_i] = 0 \tag{7.12}$$

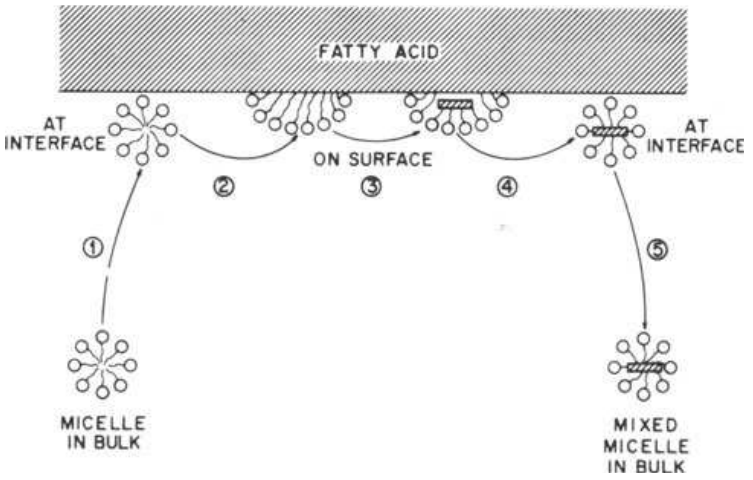



**Figure 7.7** Schematic mechanism for initial solubilization. Mixed micelle desorption and diffusion (steps 4 to 5) are assumed to control stearic acid solubilization. From Chan *et al.* [31].

where $[M_s]$ is the concentration of mixed micelle on the surface and $[S]$ is the number of free sites for micelle adsorption

$$[M_s] = K_3[B_s] \tag{7.13}$$

$$[B_s] = K_2[B][S] \tag{7.14}$$

$$[S_o] = [S] + [B_s] + [M_s]. \tag{7.15}$$

$[B]$ is the concentration of surfactant micelles in bulk, $[B_s]$ at the surface and $[B_i]$ in the interface. $[S_o]$ are the total number of sites in the surfaces. $K_i$ is the equilibrium rate constant for step $i$.

Combining Equations 7.11 to 7.15 we obtain

$$\frac{d[M]}{dt} = \frac{\{k_4K_3[S_o]/(1+K_3)\}[B]}{\{k_{-4}[S_o] + k_5A/k_5AK_2(1+K_3)\} + [B]}. \tag{7.16}$$

$d[M]/dt$ is difficult to measure. It is assumed that the solubilizate concentration $[F]$ is proportional to $[M]$ and that $d[F]/dt \propto d[M]/dt$.

Obtaining $[F_{sat}]$ and $[B]$ by experiment, Equation 7.16 can be rewritten in the form,

$$\left(\frac{d[F]}{dt}\right)^{-1} = \left\{\frac{1+K_3}{nk_4K_3[S_o]}\right\} + \left\{\left(\frac{[F_{sat}]}{nK_2K_3[B]}\right)\left[\frac{1}{k_4[S_o]} + \frac{1}{k_5AK_4}\right]\right\}\frac{1}{[F_{sat}]}. \tag{7.17}$$

This equation predicts that, providing steps 4 and 5 are rate controlling, a plot of $(d[F]/dt)^{-1}$ versus $[F_{sat}]^{-1}$ will be linear; the intercept of the plot is independent of $k_5$ and hence independent of flow; the slope of the plot is flow dependent, being dependent on $k_s$. In experimental studies of fatty acid dissolution into NaLS solutions the validity of the first two predictions was established (see Fig. 7.8).

The model on which the above derivations are based is by no means unequivocal. There is no proof that micelles diffuse to the surface and adsorb, or, indeed, that hemi-micelles as depicted in Fig. 7.7 form, although Somasundaran *et al.* [32] have previously postulated their existence. The transfer of solute molecules to the micelle at the surface probably involves complex interactions between surfactant, fatty acid and water perhaps with liquid crystal formation as an intermediate stage following penetration of surfactant molecules. As the earlier steps in the process are not rate limiting their formulation is perhaps less important. Diffusion of the solubilizate-laden micelle is a process which must occur.

Higuchi's analysis [24] predicts that substantial effects on dissolution rate will only be evident when the drug concentration in solution approaches or exceeds saturation solubility. The dissolution model used by Higuchi assumes that an equilibrium exists between the solid and the solution at the interface and that the rate is controlled by the diffusion of free and solubilized solute across the diffusion layer which has a thickness $\delta$.

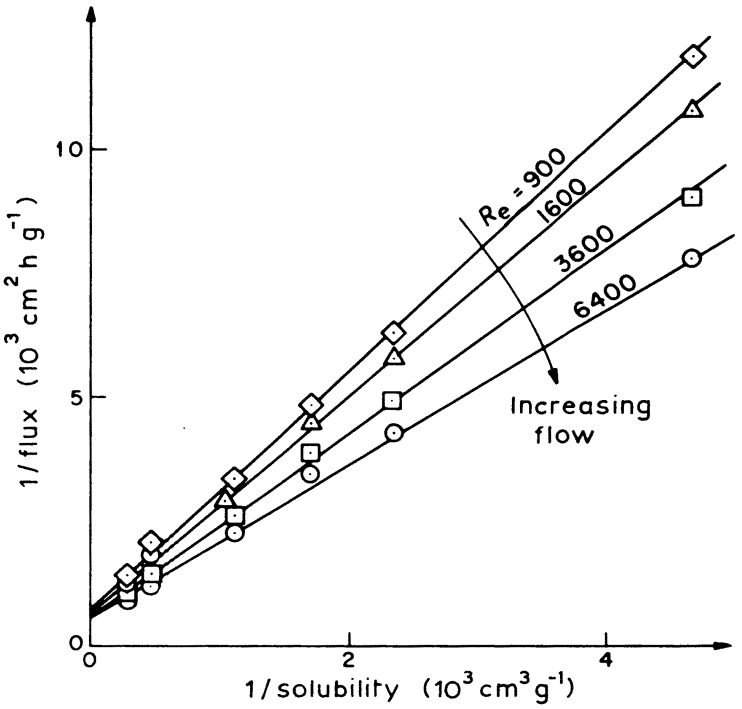



**Figure 7.8** Solubilization kinetics of stearic acid. These data support the hypothesis that mixed micelle desorption and diffusion are rate controlling. From Chan *et al.* [31] with permission. $R_e$ is the Reynolds number.

Provided sink conditions obtain (i.e. $c < 0.1\,c_s$);

$$dc/dt = A[(Dc_s/\delta) + (D_m c_m/\delta)] \tag{7.18}$$

where $c_m$ is the increase in solubility due to the surfactant and $D_m$ is the diffusion coefficient of the drug in the micelle, it being assumed that $\delta$ is the same for both.

## 7.2.2 Dissolution from drug–surfactant mixtures

The work on dissolution rate, rather than solubility, tends to be of rather academic interest as a drug is rarely to be found dissolving into concentrated surfactant solutions. It is of more practical interest to consider dissolution from intimate mixtures of drugs and surfactants into water [34]. Application of the technique of formation of solid dispersions by fusing poorly soluble drugs with water-soluble carrier has been shown to increase the solution rate of drugs; carriers used include polyoxyethylene glycol, polyvinylpyrrolidone [34] but also surfactants [33, 35] in their solid or waxy state. The enhanced rate of dissolution of testosterone [35] from Myrj 51 (but also from polyoxyethylene glycol 1000 and PVP 11500 dispersions) was attributed to the small particle size of the drug in the solidified melt and to a lesser degree to the increased solubility in the carrier solution which formed. Ford and Rubinstein [33] made a more detailed study of a glutethimide–non-ionic surfactant system using Renex 650, a nonylphenyl-

polyoxyethylene condensate. Phase diagrams showed the presence of a eutectic at 21% of the drug, 79% surfactant with a eutectic temperature of 35° C. Solid solutions of the drug in the surfactant and of Renex in the drug also existed. When placed in water, drug and carrier do not dissolve at rates directly proportional to their concentration in the dispersion and the dissolution rate of the drug is maximal when the drug concentration reaches about 25% in the disc (Fig. 7.9). Dissolution of digitoxin from co-precipitates of the drug with poloxamer 188 or deoxycholic acid has been shown to be enhanced over dissolution from physical mixtures and administration of the co-precipitates to mice significantly increased the oral toxicity [15] (Table 7.2).

Other techniques involving attempts to utilize the properties of surfactants have included crystallization of poorly soluble drugs such as sulphathiazole, prednisone and chloramphenicol in the presence of small amounts of surfactants [36]. Increases in the rate of solution were observed in each case when polysorbate was used as a 2.5% solution as the crystallization medium. While the result might be partly ascribed to adsorption of surfactant molecules on to the hydrophobic crystal surface, differential thermal analysis also suggests that some surfactant is incorporated into the crystal structure. Interference of a surfactant in the crystallization process could lead to defect formation. Model studies with

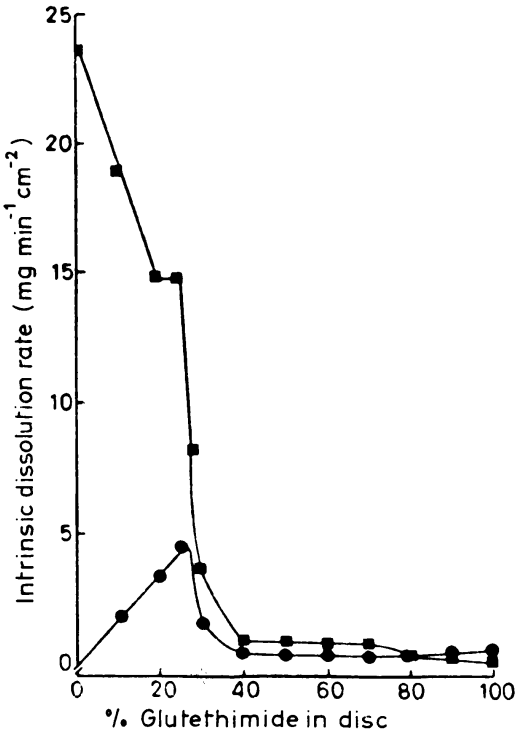



**Figure 7.9** Dissolution rate–composition profile. Effect of glutethimide-Renex composition on the intrinsic dissolution rates of 1 h old resolidified melts into distilled water at 30°C. ■ Renex 650. ● Glutethimide. From Ford and Rubinstein [33].

**Table 7.2** Oral toxicity of various digitoxin preparations in mice*

| Test system | Number of animals dead† | Mortality (%) |
|---|---|---|
| Digitoxin | 6 | 20 |
| Digitoxin–poloxamer 188‡ co-precipitate | 29 | 97 |
| Digitoxin–deoxycholic acid‡ co-precipitate | 30 | 100 |
| Digitoxin–poloxamer 188‡ physical mixture | 11 | 37 |
| Digitoxin–deoxycholic acid‡ physical mixture | 9 | 30 |
| Poloxamer 188§ | 0 | 0 |
| Deoxycholic acid¶ | 0 | 0 |

* A dose of 70 mg of digitoxin/kg was administered as a suspension in 0.5% methylcellulose. Thirty animals were used for each test system. † Animals were observed for 7 days post-administration. ‡ A 700 mg/kg dose was administered containing 10% (w/w) digitoxin. § A 2.7 g/kg dose was used. ¶ A 630 mg/kg dose was used.
From [15].

adipic acid have shown that surfactant adsorption on to growing crystal faces can change crystal habit [37, 38] (see Chapter 9).

## 7.3 Effect of surfactants on membrane permeability

Before we discuss some of the work which has been carried out on surfactant effects on drug absorption in whole animals, we review in this section some of the work which has been done using model systems. Foremost amongst these has been the goldfish *Carassius auratus*. In choosing this system Levy *et al.* [39] explain: 'Most of the studies of surfactant effects on drug absorption have been carried out on microbial systems. The results thus obtained may have limited applicability to multicellular organisms, since the latter are able to maintain homeostasis much more effectively. Moreover, the presence of enzymes and other vital cell constituents in the cell membrane makes unicellular organisms particularly sensitive to direct effects of surfactants.'

Use of small animals or humans presents great difficulties, not the least being the difficulty of maintaining a constant, known concentration of surface-active agent and drug. The major advantage of the fish system is that large quantities of test solution can be used, permitting the maintenance of constant concentration gradients across the membranes, which behave, as far as passive diffusion characteristics are concerned, in a similar way to human membranes. Fig. 7.10 shows the effect of polysorbate 80 on the time of death of goldfish immersed in sodium secobarbitone solution. The results show an enhancement of activity of the barbiturate at low concentrations and a decrease at higher concentrations, in common with other studies using alternative systems.

The end point in the experiment is the turnover time or death time of the fish.

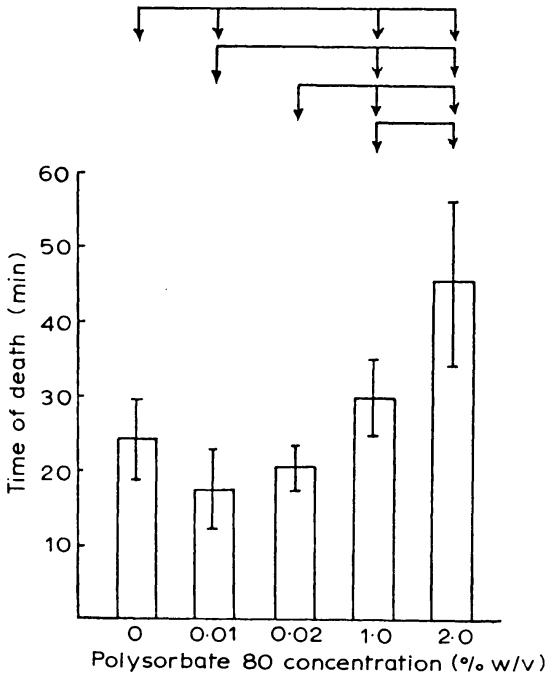



**Figure 7.10** The effect of polysorbate 80(I) on the time of death of goldfish immersed in 0.02% sodium secobarbitone solution at pH 5.9 and 20° C. Mean values of 10 fish are shown. Vertical bars indicate ± 1 standard deviation. Arrows connect values which differ significantly ($p < 0.05$) from one another. From Levy *et al.* [39].

The reciprocal death time ($T^{-1}$) is proportional to the rate of absorption of the drug, $k_1$

$$\frac{1}{T} = k_1 c_B / c_F - k_2/2, \tag{7.19}$$

where $c_B$ and $c_F$ are the concentrations in the bathing solution and the threshold concentration in the fish, respectively, and $k_2$ is the rate of elimination of the drug.

A range of non-ionic surfactants has been studied for their effect on absorption of drugs in goldfish. Not all surfactants do increase absorption [40–42] some exhibiting only an inhibiting effect as seen in Fig. 7.11. Three main types of activity have been noted [43] when surfactant concentration is increased (Fig. 7.12), namely (a) the increase and decrease depicted in Fig. 7.12 when a drug is solubilized in the surfactant micelles (e.g. thioridazine–Renex 650 mixtures); (b) an overall decrease in activity when solubilization occurs, the surfactant having no influence on membrane permeability (e.g. thioridazine–Cremophor EL 120 (Fig. 7.12b), and (c) (Fig. 7.12c) an overall increase in activity when the surfactant increases the flux through the membrane and the drug is not associated with the micelles (e.g. paraquat–non-ionic surfactant systems) [44].

In some systems where the drug concerned interacts to a small degree with a surfactant which has a significant effect on permeability, only the increase in absorption is detectable. This is the case with thiopentone and a series of non-

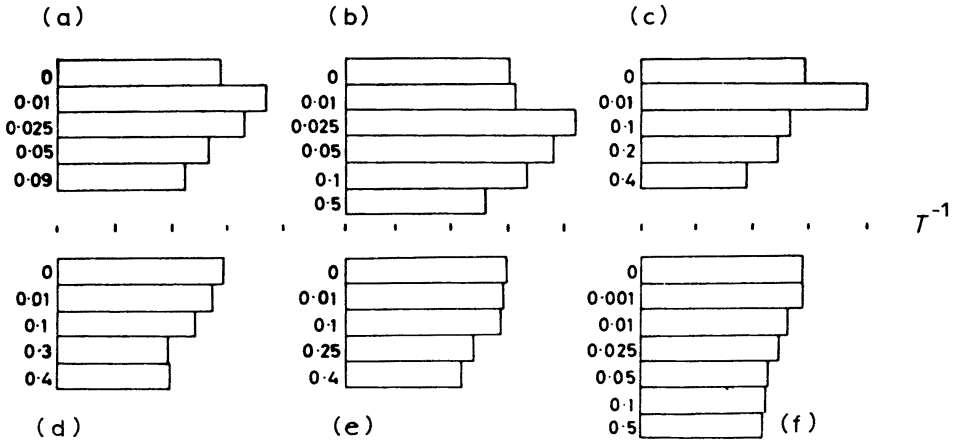
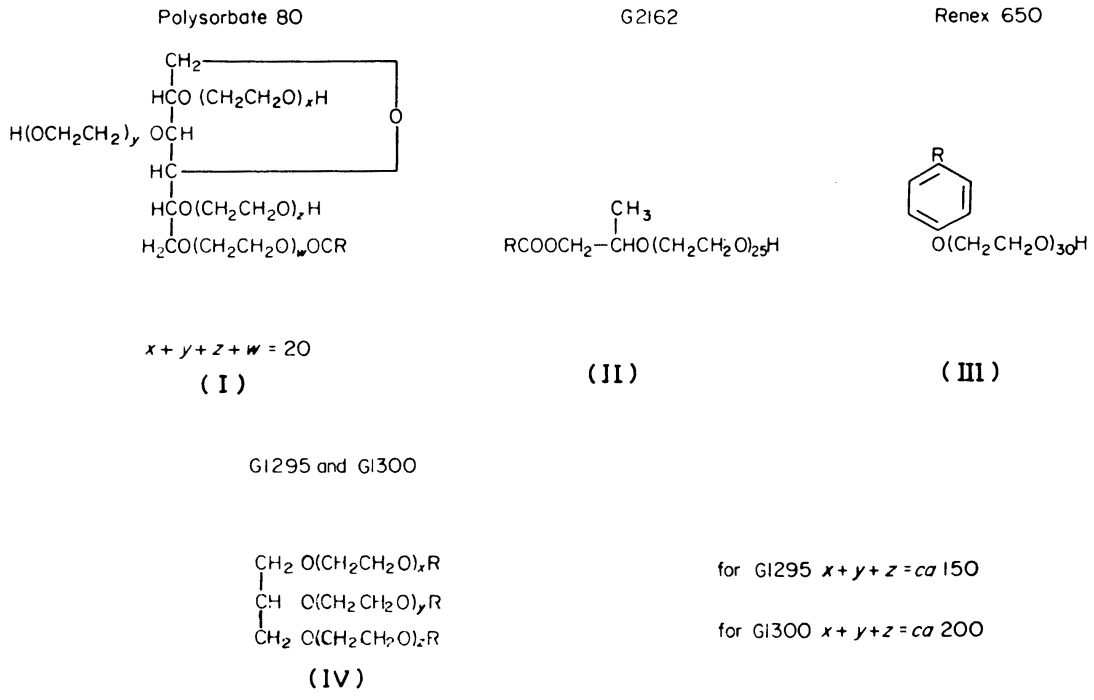



**Figure 7.11** Absorption of thioridazine in goldfish in the presence of increasing concentrations of various non-ionic detergents, the rate of absorption being proportional to the reciprocal of the death time of the fish, reciprocal death time is plotted on the ordinate concentrations of surfactants (% w/v) are marked. Lack of enhancement of absorption by some surfactants is probably due to poor ability to penetrate lipid membranes because of shape factors. Decrease in absorption is due to non-ionic micelle formation. From Florence and Gillan [41] with permission. The surfactants are all Atlas products (Honeywill-Atlas, UK).
(a) Atlas G2162 (II); (b) Renex 650 (III); (c) Atlas G1790; (d) G1295 (IV); (e) G1300 (IV); (f) Cremophor EL.




ionic surfactants studied in goldfish [45] using mean reciprocal overturn time as an index of the rate of absorption. Some results are shown in Table 7.3.

There are several competing mechanisms for surfactant-induced effects when solid oral dosage forms are administered. When solutions are administered,

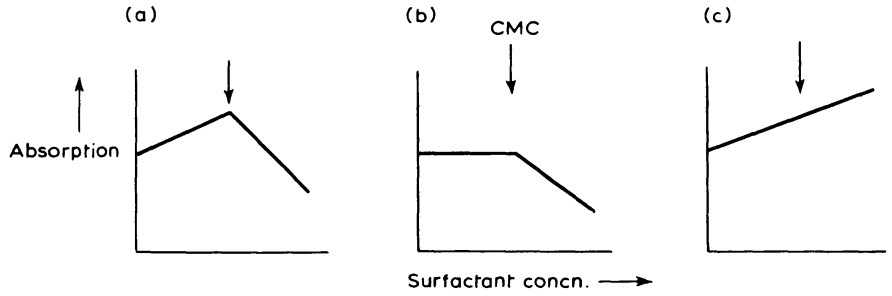



**Figure 7.12** Representation of three forms of absorption–surfactant concentration profile (see text for discussion).

**Table 7.3** Reciprocal turnover times ($min^{-1}$) ($\pm$ S.D.) of thiopentone in presence of surfactants

| Surfactant | HLB | 0.0005% | 0.1% |
|---|---|---|---|
| None | — | 0.09 ± 0.03 | |
| POE (4) lauryl ether | 9.7 | 0.11 ± 0.02 | —* |
| POE (10) lauryl ether | 12.0 | 0.54 ± 0.02 | —* |
| POE (23) lauryl ether | 16.9 | 0.25 ± 0.09 | 0.18 ± 0.02 |
| POE (2) stearyl ether | 4.9 | 0.07 ± 0.01 | (0.07 ± 0.03)† |
| POE (10) stearyl ether | 12.4 | 0.15 ± 0.02 | 0.41 ± 0.07 |
| POE (20) stearyl ether | 15.3 | 0.21 ± 0.01 | 0.31 ± 0.02 |
| POE (2) oleyl ether | 4.9 | 0.11 ± 0.02 | (0.11 ± 0.01)† |
| POE (10) oleyl ether | 12.4 | 0.17 ± 0.03 | 0.34 ± 0.14 |
| POE (20) oleyl ether | 15.3 | 0.19 ± 0.04 | 0.29 ± 0.04 |

* At this concentration these surfactants were toxic. † Cloudy dispersion.
From [45].

provided the drug is maintained in solution in the gut and is not solubilized in the surfactant micelles, the only effect will be that of the surfactant on membrane permeability, if the surfactant does not itself alter the physiological status of the GI tract. When a drug is partly in solution, as in a suspension, the results are perhaps perplexing.

Fig. 7.13 illustrates the complexity of surfactant effects. It shows the influence of increasing surfactant concentration on drug absorption at several pH values. At pH 7.4 (where all the drug is in solution) increasing the concentration of polysorbate 80 from 0.01 to 0.1% decreases the absorption, as the saturation of the system is reduced by incorporation of free drug in the micellar reservoirs. On increase of pH to 8.6 and 9.0 there is a decrease in absorption of drug as some of the drug is now in its insoluble form and has precipitated from solution. However, at these pH values increasing the surfactant concentration increases the rate of absorption, as solubilization increases the solubility of the drug and thereby increases its concentration gradient across the membrane [41].

There is no simple explanation of the absorption-promoting effect of the surfactant. Penetration of the surfactant into the liquid membrane seems to be

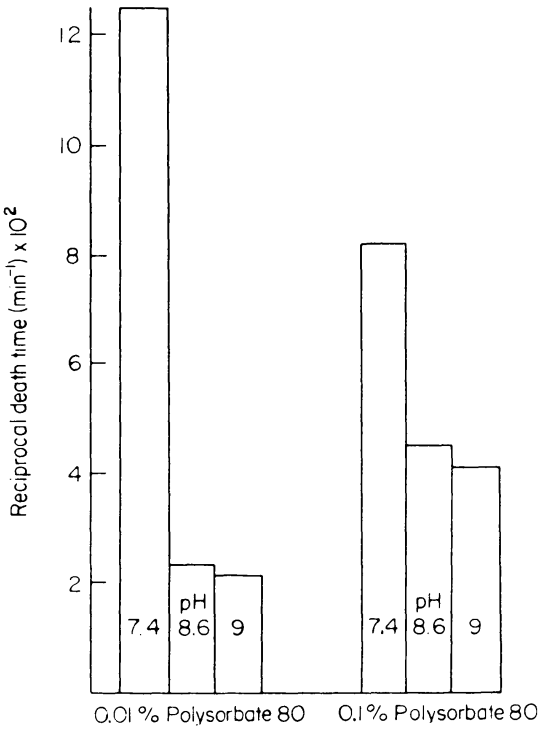



**Figure 7.13** The influence of pH and polysorbate 80 concentrations on the absorption of solutions or suspensions containing 0.08% thioridazine as shown by reciprocal death times of goldfish. From Florence and Gillan [41] with permission.

one step in the action as the interpolation of a foreign hydrocarbon chain certainly would result in an increase in the fluidity of the hydrocarbon interior of the membrane. This should lead to decreased resistance to passage of solutes through the membrane. In some experiments it appears that there is a decrease in permeability at higher surfactant concentrations which is not fully explained by the interaction of the permeant with the surfactant micelles. This suggests that a physical blocking mechanism is operating, perhaps in the manner suggested by Smith *et al.* [46] to explain the decreased penetration of pesticides into plants. Kameda *et al.* [47] have also noted inhibition of the absorption of species which did not interact with the micellar phase of polysorbate 80.

### 7.3.1 Influence of surfactant structure on membrane permeability

Until more is known of the molecular interactions of surfactants with membrane components and the factors controlling such interactions it will remain virtually impossible to predict which surfactants will be capable of enhancing permeability of membranes without causing damage. Careful choice of solubilizer both of appropriate structure and optimum concentration is obviously paramount. In experiments on goldfish the effects of polyoxyethylene non-ionic surfactants on the absorption of various barbiturates is dependent on the surfactant hydrophobic and hydrophilic chain lengths and possibly also on the size of the

surfactant molecule. The range of molecular areas obtained from surface-tension measurements was not large enough for a categorical statement on the importance of surfactant dimension. However, it appears that surfactants having $C_{12}$–$C_{16}$ hydrocarbon chains, polyoxyethylene chain lengths between 10 and 20, and molecular areas of between 1.00 and 1.60 $nm^2$ induce the greatest increase in absorption. Fig. 7.14 reveals that the effectiveness of a surfactant depends also on the solute, as the results with thiopentone, secobarbitone and phenobarbitone show a different order of effect. If membrane disruption occurs as well as increased fluidity these results are difficult to interpret.

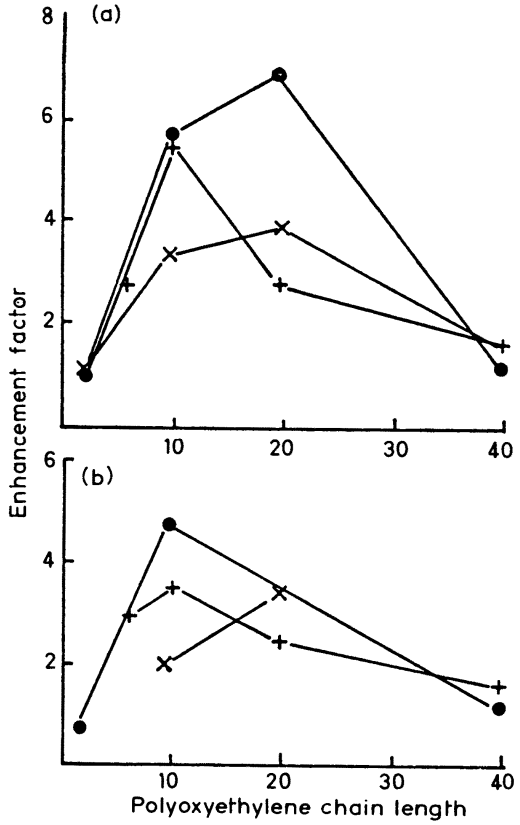



**Figure 7.14** The mean effect of two groups of nonionic surfactants: (a) of the Brij 50 series and (b) of the Brij 70 series compared in goldfish ($n$ = 6) on the absorption of • thiopental, + secobarbital, and × phenobarbital. All surfactants at 0.1 % level, from [53].

Experiments in whole animals are even more difficult to decipher. The relative effects of different surfactants on intestinal absorption have been studied recently by Whitmore *et al.* [48] using the everted sac preparation from rat small intestine. A range of anionic, cationic and non-ionic surfactants were used and a relationship was found between the absorption of salicylates and L-valine and the release of protein and phospholipid from the preparation as a result of membrane disruption. Sodium lauryl sulphate increased the rates of uptake of salicylate and L-valine but cetyltrimethylammonium bromide had no effect on L-valine absorption and in fact decreased salicylate absorption. The non-ionic surfactant on the other hand, increased valine absorption but had no effect on salicylate

transfer. CTAB has been shown before to decrease absorption of glucose, methionine and acetylsalicylic acid [49, 50]. Whitmore's data showed that CTAB appeared to prevent the loss of a protein of molecular weight of about 39 000 which is perhaps crucial in determining permeability. But it is almost impossible to obtain a consistent picture of action from different publications; one reason is that concentrations of surfactants studied are so different and the complications of surfactant interactions with drugs and with tissue components can obscure mechanisms of action. This is especially true when intact animals are used, although these are the most crucial test of solubilizer effects in relation to clinical bioavailability and to the use of solubilizers in pharmaceutical systems. One type of surfactant effect on drug absorption that can occur which would only be detected *in vivo* is the indirect effect such as that reported recently [51]. An increase in the absorption of tripalmitate by a detergent was attributed to the increase in gastro-intestinal motility induced by the surfactant.

Isolated tissue work should not suffer from such complications. In measuring the effect of a range of alkyl polyoxyethylene ethers on paraquat transfer across rat stomach epithelium, Walters *et al.* have found [44] no simple correlation between surfactant structure and transport. However, with a group of surfactants such as these with a given polyoxyethylene chain length a certain dependency on alkyl chain length can be seen (Fig. 7.15).

Permeability changes have been observed in reconstituted cell 'membranes' following treatment with surface-active agents [52] producing a selective permeability for cations. Addition of surfactant lowered the initially high resistance by several decades.

Investigation of the interaction of polyoxyethylene alkyl ethers with cholesterol monolayers [53] interestingly reveals a biphasic effect when surface pressure

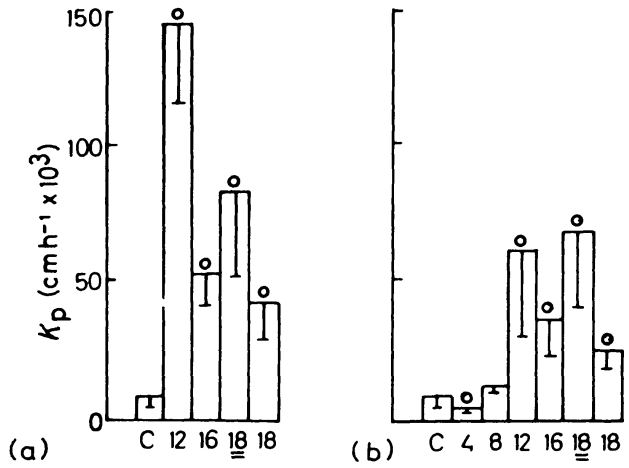



**Figure 7.15** Values of $K_p$ for paraquat obtained at 1.0% surfactant levels with isolated rabbit gastric mucosa as a function of alkyl chain: $C_{12}$, $C_{16}$, $C_{18}$ and oleyl, marked 18 on the abscissa. (a) compounds with 10 ethylene oxide units and (b) compounds with 20 ethylene oxide units. Results which are statistically significantly different ($P < 0.05$) from the control values without surfactant are marked (○). From [44] with permission.

is measured as a function of surfactant concentration (Fig. 7.16). Increasing penetration of the surfactant into the cholesterol monolayer causes increased surface pressure; at higher concentrations solubilization of the cholesterol molecules results in a decrease in surface pressure. Seeman [54, 55] has clearly demonstrated – with surface-active drug molecules – stabilization of erythrocyte membranes at low drug concentrations and labilization of the membrane at higher concentrations. We did not find [53] that decreased surface pressures of cholesterol monolayers coincided with the surfactant CMC, suggesting perhaps that micelle formation was occurring in the interfacial region and solubilization taking place in the concentrated interfacial surfactant layer (Fig. 7.16). While penetration and labilization of the membrane are undoubtedly factors in enhanced permeability, some workers have implicated solubilization of membrane components [48]. The release of protein and phospholipid from rat jejunal tissue has been related to the absorption of salicylate and L-valine (Figs 10.5(a) and (b)). Fig. 7.17 shows the extent of membrane protein extraction from rat gastric mucosa incubated with three surfactants. Of these, only Brij 76 and 78 had any significant effect on permeability. It is perhaps relevant here to discuss work which was carried out in a biochemical context aimed at selective solubilization of membrane components for further study. Since, as we have just discussed, simple penetration is unlikely to be involved in permeability enhancement, these results may illuminate the problem.

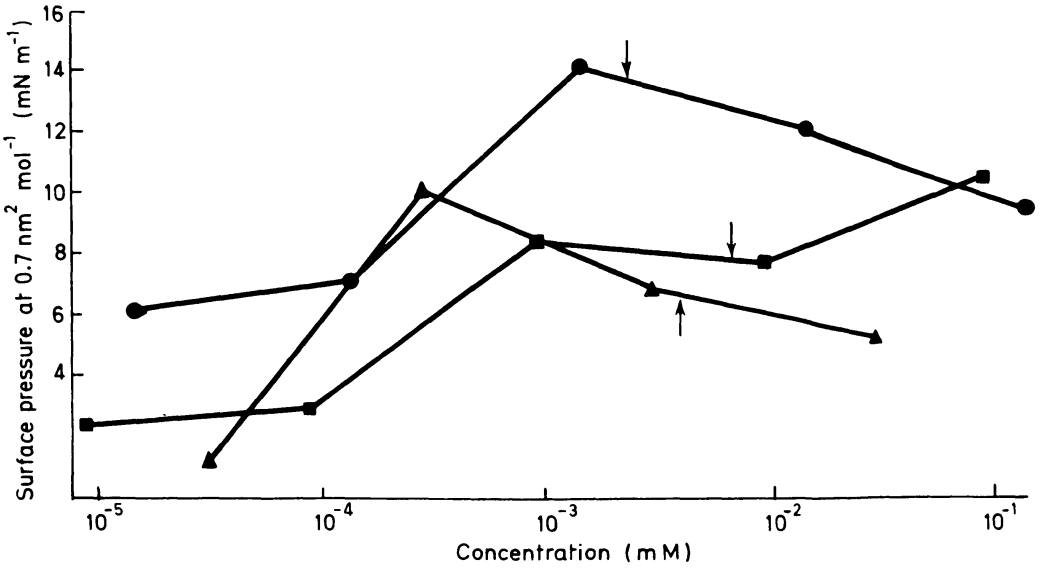



**Figure 7.16** Plot of surface pressure of cholesterol monolayers at constant molecular area against surfactant concentration. ▲ Brij 72; ● Brij 76; ■ Brij 78. Arrows denote the CMC for each surfactant. From K. A. Walters *et al.* [53].

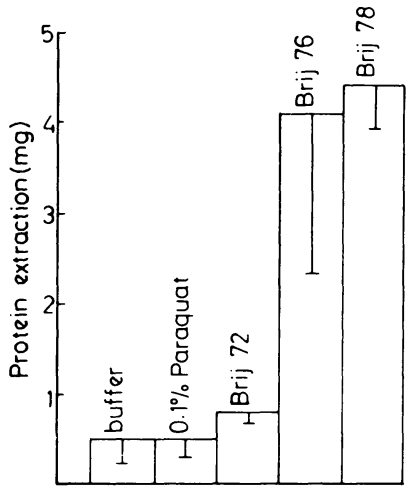



**Figure 7.17** Protein extraction (mg) in bovine serum albumin equivalents occurring in 3 h following incubation in the medium as marked. Surfactant concentration 0·1 %.

The solubilization of mitochondrial components by non-ionic Tritons was found to depend on the ethylene oxide chain length; longer-chain detergents are less effective on a molar basis and volume basis in their clearing action on mitochondrial suspensions. Swanson *et al.* [56] have made a detailed study of the use of solubilizers in the extraction of the constituents of cerebral microsomes. The effect of polyoxyethylene chain length is shown in Fig. 7.18.

Certain features of the solubilization of microsomes by detergents suggest that the mechanism involved may be similar to that postulated as occurring in the lysis of erythrocytes by detergents. In this mechanism haemolysis was pictured as resulting from breakdown of a lipoprotein–detergent complex formed by penetration of the detergent into the erythrocyte membrane. Analogous penetration of microsomal membranes by detergents is suggested by the marked effects on the activity of the $Na^+$ ion-stimulated adenosine triphosphatase even at concentrations of these agents too low to bring about solubilization [57]. For maximal removal of protein, cholesterol and phospholipid, an ethylene oxide chain length of 10 to 13 units is required when the alkyl chain is a $C_{16}$ hydrocarbon. These results should be compared with those in Fig. 7.17 above.

Some non-ionic surfactants have been found [58] to inhibit transmucosal absorption of water from the gut containing hypotonic solutions. As water flow affects drug movement, this is an additional factor, as yet not widely studied, which might have a bearing on the interpretation of surfactant effects on absorption.

Further aspects of surfactant and membrane interactions will be discussed in Chapter 10.

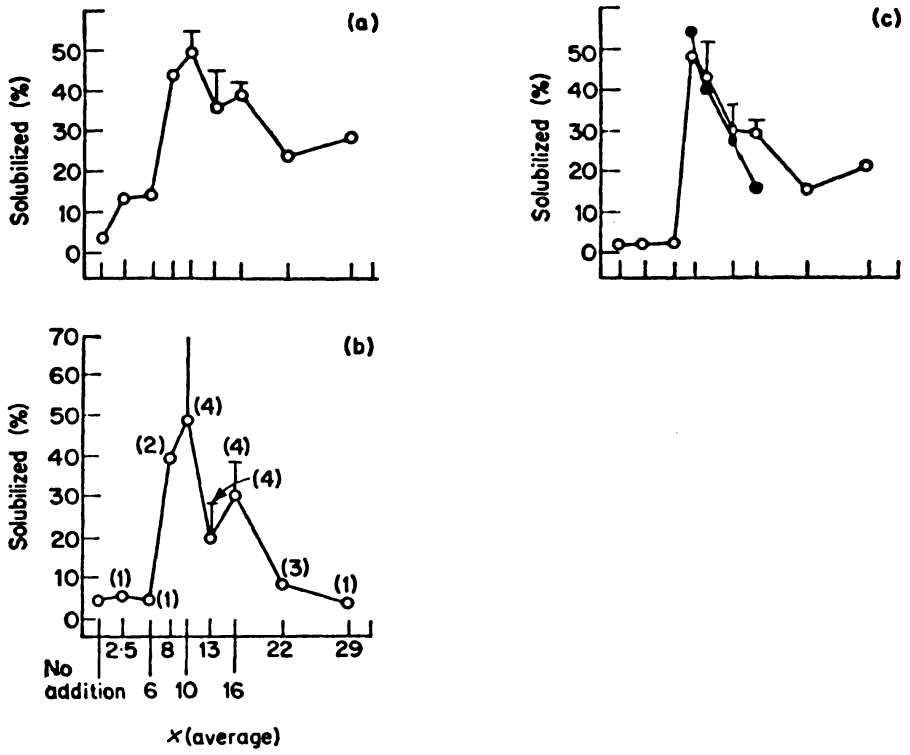



**Figure 7.18** Extraction of microsomes with non-ionics of general formula $R(OCH_2CH_2)_xOH$ where R = cetyl for $x$ = 16 to 29 and a mixture of oleyl and cetyl for $x$ average 2.5 to 13. The detergent concentration was 1.3 mM in each case. (*a*) Percentage solubilization of protein; (*b*) protein solubilization in presence of 100 mM NaCl; (*c*) percentage solubilization of cholesterol (●) and phospholipid (○). From Swanson *et al.* [56].

## 7.3.2 Effect of surfactants on transfer of solutes across membranes and interfaces *in vitro*

It is pertinent to discuss the effect that surfactants have on permeation of solutes across artificial membranes as the solute–micelle interaction which is reflected in reduced transport rates, will be obtained generally without the complication of alteration to the permeability of the membrane.

The presence of polysorbates 20 and 80 decreases the transfer rate constant of salicylic acid across cellophane membranes at low pH [59]. Ionized salicylic acid does not partition into the micelles and thus at pH values above 5 polysorbate has little effect on permeation as cellophane membranes with small pore size are regarded to be impermeable to surfactant micelles [60]. The effect of solubilization is to reduce the concentration gradient of the solute across the membrane. Taking into account distribution of drug between the aqueous and micellar phases, Juni *et al.* [61] have derived an equation to describe the permeation profiles of drugs from systems containing micelles. A simplified model is shown in Fig. 7.19.

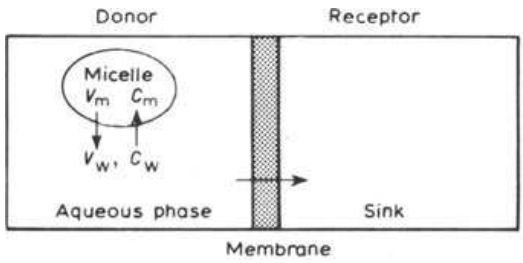



**Figure 7.19** Schematic representation of sustained release of drug through membrane from a system containing micelle. From Juni *et al.* [61].

The distribution coefficient, $P_m$, of the drug between these two phases is given by

$$P_m = \frac{C_m}{C_w} = \frac{M_m/V_m}{M_w/V_w}, \tag{7.20}$$

where $C$, $M$, and $V$ denote the concentration and the amount of the drug in each phase, and the volume of each phase, respectively, and the subscripts m and w indicate a micellar phase and an aqueous phase, respectively. Under these conditions, if sink conditions are maintained in the receptor side, the permeation rate of drug is given by Fick's law:

$$\frac{dM_r}{dt} = \frac{APC_w}{l}, \tag{7.21}$$

where $M_r$ is the amount of drug in the receptor solution at time $t$, $A$, the area of the membrane available for permeation, $l$, the membrane thickness, and $P$, the permeability. The total amount of drug in the donor solution, $M_t$ is given by:

$$M_t = M_m + M_w = M_t^\circ - M_r, \tag{7.22}$$

where $M_t^\circ$ is the total amount of drug initially introduced into the system. Rearrangement of Equations 7.20 to 7.22 leads to:

$$M_r = M_t^\circ\left[1 - \exp\left\{-\frac{APt}{l(K_pV_m + V_w)}\right\}\right]. \tag{7.23}$$

By definition:

$$M_t^\circ = V_mC_m^\circ + V_wC_w^\circ \tag{7.24}$$

$$C_m^\circ = P_mC_w^\circ, \tag{7.25}$$

where $C_m^\circ$ and $C_w^\circ$ are the initial concentrations of drug in the micellar phase and in the aqueous phase, respectively. When the volumes of the donor and receptor compartments are equal and represented by $V$, rearrangement of Equations 7.23 to 7.25 leads to Equation 7.26

$$-\ln\left(1 - \frac{C_r}{C_t^\circ}\right) = \frac{APC_w^\circ}{lVC_t^\circ}t \tag{7.26}$$

where $C_t^\circ$ denotes the total initial concentration of drug in the donor solution. The ratio $C_w^\circ/C_t^\circ$ is equal to $C_s^\circ/C_s$ at equilibrium, where $C_s^\circ$ and $C_s$ are the solubility of drug in water and that in a surfactant solution, respectively. Then Equation 7.26 becomes:

$$-\ln\left(1-\frac{C_r}{C_t^\circ}\right)=\frac{APC_s^\circ}{lVC_s}t. \tag{7.27}$$

Release profiles of the drug butamben (*n*-butyl *p*-amino benzoate) shows how release can be controlled by the presence of surfactant (Fig. 7.20). Slight increases in permeation of this solute from suspensions were caused by 0.5 NaLS and 0.5% dodecyltrimethylammonium chloride because of melting effects and promotion of dissolution; such effects require the solutions to be saturated.

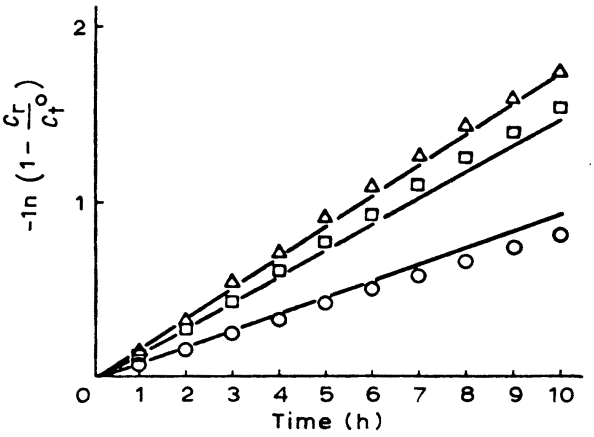



**Figure 7.20** Release profiles of butamben through the silicone membrane from its initially saturated solutions in ○, 0.5% sodium lauryl sulphate; □, 0.5% polysorbate 80 and △, 0.4% dodecyltrimethylammonium chloride solution at 30° C.
—, theoretical profile.
From Juni *et al.* [61] with permission.

The approach described above simplifies the *in vitro* situation and it has been found that the assumption of drug absorption from the aqueous phase only, underestimates the extent of absorption occurring *in vivo* [62] presumably because the enhanced membrane permeability is only detected in biological membranes.

The concentration of salicylic acid in the aqueous phase of a 1.0% w/v polysorbate 20 solution at pH 1.0 can be calculated if the total salicylic acid concentration is known [62] using the equation,

$$C_a = C_t\left[\frac{V_t}{(P^\circ V_m/V_a)+P^- V_m/[(1/f_i)-1]V_a+1+1/[(1/f_i)-1]V_a}\right]\times \left[1+\frac{1}{(1/f_i)-1}\right] \tag{7.28}$$

where $C$ represents concentration, $V$ volume and $P$ partition coefficient; subscripts a, m denote aqueous and micellar phases and $t$ is the sum of aqueous and micellar phases. Superscripts $^{\circ}$ and $^{-}$ denote unionized and ionized salicylic acid, respectively. $f_i$ is the fraction of salicylic acid ionized at any pH. If only aqueous salicylic acid was available for absorption and provided that the surfactant did not influence absorption by mechanisms other than solubilization, an average of 18.4% and 26.6% of a 0.011 mg ml$^{-1}$ salicylic acid solution should be absorbed from polysorbate 20 solutions after 15 and 30 min, respectively. These figures are equivalent to 10.1% and 14.6% of the total salicylic acid concentration and are lower than the corresponding experimentally determined values (*in vivo*) of 14.6% and 19.1%, respectively [63].

Salicylic acid–polysorbate 80 mixtures have been used in several other investigations including that of Hikal *et al.* [64]. In this work the apparent partition coefficient of the salicylic acid between chloroform and phosphate buffer (pH 6.5) was measured with polysorbate 80 in the aqueous phase at and above its CMC. Their results show that the surfactant increased the partitioning of the drug into the non-aqueous phase, perhaps indicating inverse micelle formation in the chloroform layer or, as the authors suggest 'complexation' between surfactant and salicylate forming a more lipid soluble species. At pH 6.5 little salicylate would be present in the micellar phase; these data require further investigation. More extensive investigations of mass transfer between aqueous and non-aqueous phase in the presence of surfactants have been carried out by Brodin [65]. Most workers have shown that surfactants reduce the rate of mass transfer either through their influence in reducing the circulation of bulk phases (especially in small droplets) or by the barrier of surfactant molecules aligned at the interface. Very low concentrations of surfactant inhibit circulation by the formation of a monolayer at the droplet–water interface. Thus Garner and Hale have observed [66] the rate of extraction of diethylamine from toluene droplets by water was reduced to 45% of its normal value by the addition of 150 ppm of Teepol. Kitler and Lamy [67], however, have reported that lecithin can increase the transport of some phenothiazine into cyclohexane. Lecithin forms micelles in organic solvents [68, 69] an event which may explain these results. Brodin found that cetyltrimethyl ammonium bromide, sodium lauryl sulphate and the non-ionic Pluronic F68 caused decreases in the rate constants for transfer of a range of drugs, the maximum decrease in the pH-dependent values being about 10 fold. In this work, the partition coefficients of the solutes were not affected by the low concentrations of surfactants used; Brodin concludes that the decreases are the result of changes in the effective area available for transport when the surfactant molecules block the interface. Owing to the special nature of the biological membrane–water interface it is unlikely that this effect is in operation *in vivo*; at the higher concentrations used pharmaceutically the effect on partition coefficient is much more likely to be paramount. Brodin demonstrated the effect of concentration of CTAB on the partitioning of phenylbutazone between cyclohexane and water (Fig. 7.21). The rate of transfer ($dm/dt$) of a solute across a

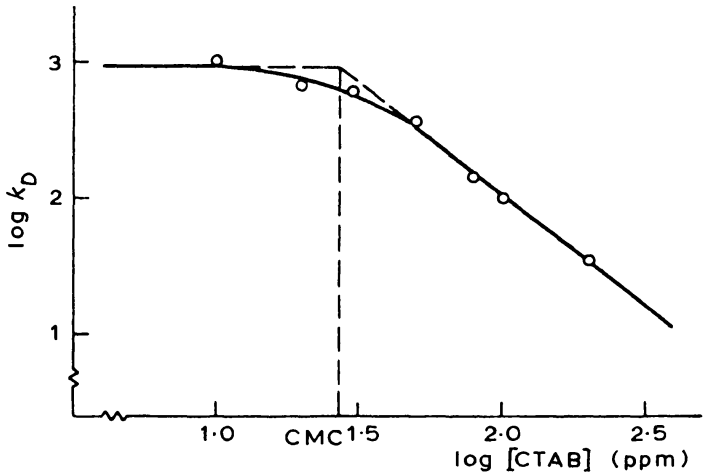



**Figure 7.21** The effect of cetyltrimethylammonium bromide on the partitioning of phenylbutazone between cyclohexane and water, plotted as the logarithm of $K_d$ the partition coefficient of the uncharged solute species. From Brodin [65].

membrane can be estimated from

$$\frac{dm}{dt} = K(\Delta c), \tag{7.29}$$

where $\Delta c$ is the difference in concentration across the membrane and $K$ is the dialysis rate constant. The integrated form of this equation is

$$\log(\Delta c) = -Kt + \text{constant}. \tag{7.30}$$

Experimental rate constants $K_{app}$ can be obtained from plots of log ($\Delta c$) versus time. From Equations 7.30 and 7.28, Collett and Koo [70] obtained Equation 7.31 to calculate the theoretical dialysis rate constant from information on $K°$ and $P°$ the dialysis rate constant and micellar partition coefficient of unionized solute molecules, respectively.

$$K_s = [K°(1-f_i)]\left[\frac{V_t}{[(P° V_m/V_a)+1+((1/f_i)-1)^{-1}]V_a}\right]\left[1+\frac{1}{(1/f_i)-1}\right]. \tag{7.31}$$

According to Equation 7.31 the dialysis rate constant should increase with decreasing $P°$. As log $P°$ is linearly dependent on $\pi$, the hydrophilic–lipophilic constant of the corresponding substituent in a homologous series, this equation allows one to predict the dialysis rate constants of a series of compounds. The equation should also predict the effect of surfactant concentration through its effect on $P°$. The values of $K_{app}$ and $K_s$ for a series of para-substituted benzoic acids in 1% polysorbate 20 at pH 1 are shown in Fig. 7.22 as a function of $\pi$.

The effect of surfactants on diffusion of substances through gels has biopharmaceutical overtones; one paper [71] has suggested that at or about the surfactant CMC the diffusion of malachite green through gelatin gels is increased.

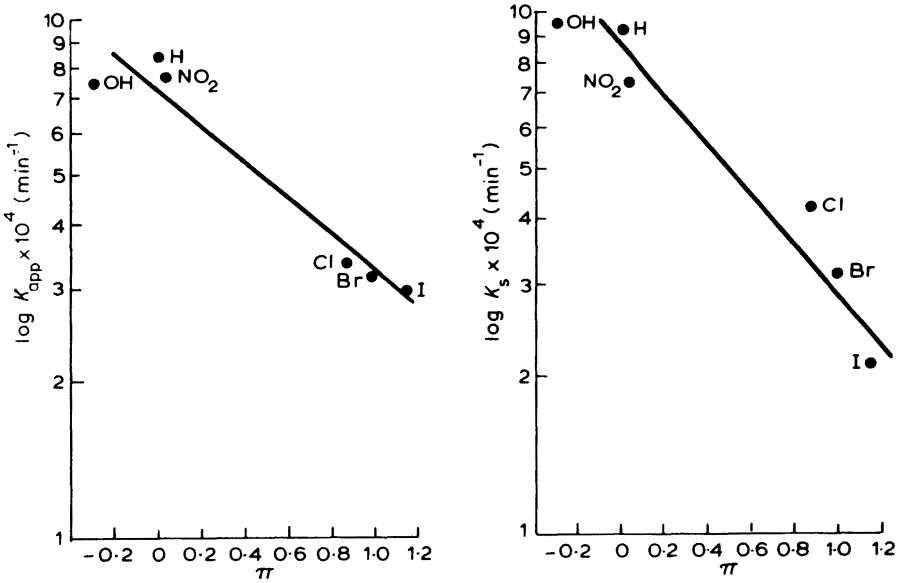
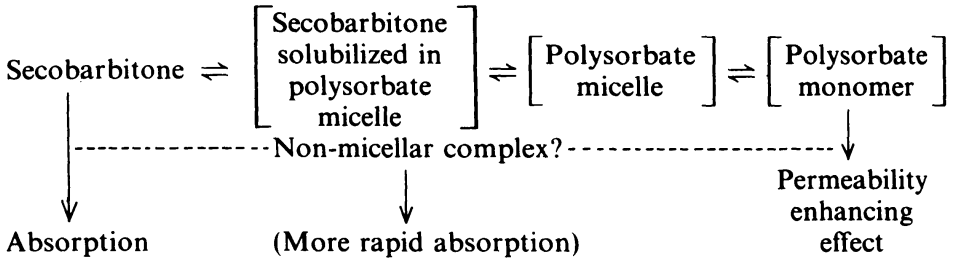



**Figure 7.22** Relationships between $\pi$ and experimental (left hand diagram) and theoretical (right hand diagram) dialysis rate constants, $K_{app}$ and $K_s$ respectively of para-substituted benzoic acids from 1 % polysorbate 20 solutions at pH 1.2. From Collett and Koo [70].

Post-CMC, the diffusion coefficients fall, as anticipated, although the maximum in diffusion coefficient does not coincide with known values of CMC. It might be that some ionic interactions either between dye and surfactant or surfactant and gel are complicating the interpretation. *In vitro* experiments using artificial membranes can define the physicochemical interactions between drug and micelle. So far we have seen the effects of the nature of the solute exerted through $P_m$, the pH of the solution and the capacity of the micelle for the drug, and their influence on dialysis rate. The reduction in free drug and the consequent reduction in transport rate can be quantified; it is not possible to quantify the increase in permeability caused by the surfactant monomers at low concentrations, or the increased permeability which can arise through solubilization of membrane components. It is unlikely that the membrane–surfactant–water interface bears much relationship to an oil–water interface and one can anticipate that we have much to learn about the nature of the interactions that occur.

It has been shown [72] that some biological membranes have a dissociating effect on certain types of complexes. Since the absorption-retarding effect of polysorbates 80 on secobarbitone was evident during rapid stirring of the solution and in the quiescent state, Levy *et al.* [73] concluded that the fish membrane does not have a dissociating effect on secobarbitone–non-ionic micelle complexes. 1 : 1 complexes formed between drugs and hydrotropes are probably broken because of the greater contact between drug and membrane. The following scheme was put forward by these workers to describe the effect of non-ionics on secobarbitone absorption:




Polysorbate 80 in concentrations of 0.01 % has no significant effect on the absorption of ethanol or other low-molecular-weight alcohols, but it increases significantly the absorption of another barbiturate, pentobarbitone. Ethanol can diffuse through pores, while the barbiturate must diffuse across the lipoidal barrier; the non-ionic might have a specific effect on the lipid content of the cell

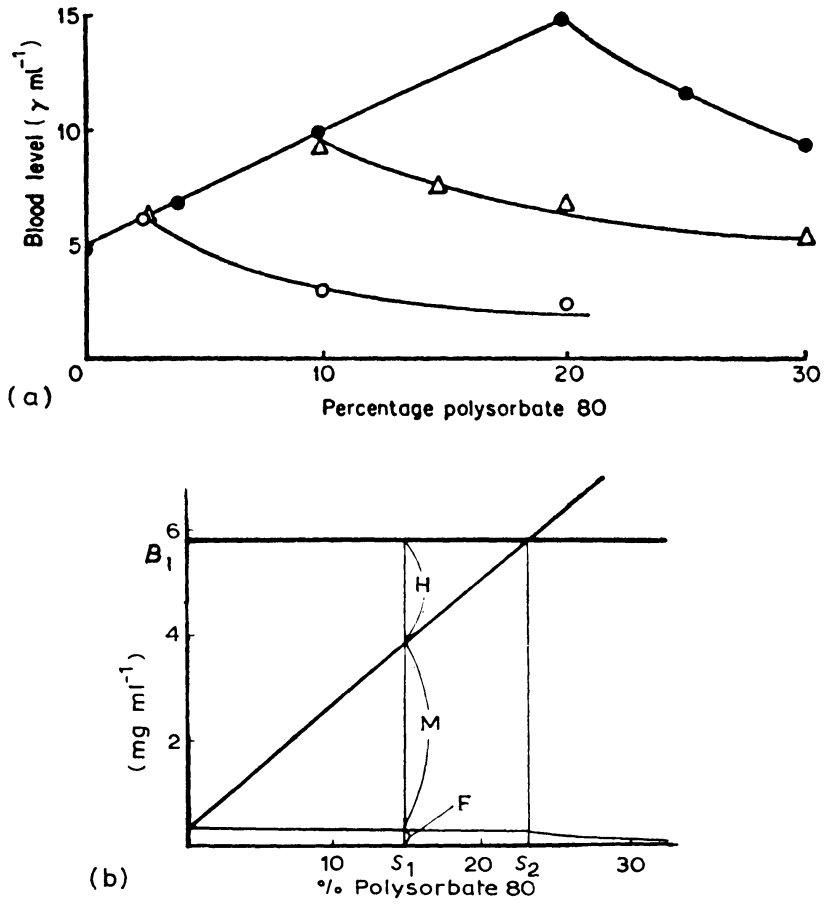



**Figure 7.23** (a) The effect of polysorbate 80 on blood levels of sulphisoxazole. Concentration of sulphonamide solutions and suspensions administered: ●—● 5 mg ml$^{-1}$; △ —△ 2.5 mg ml$^{-1}$; –○—○–: 1 mg ml$^{-1}$. Redrawn from Kakemi *et al.* [75].
(b) Diagram representing sulphisoxazole in solution of polysorbate 80
H : solid sulphisoxazole
M : sulphisoxazole in micelles
F : free sulphisoxazole in solution.

membrane, Kay [74] having found evidence for this in studies on the effects of polysorbate 80 on the *in vitro* metabolism of the Ehrlich–Lettre Ascites carcinoma.

The effect of solubilization on absorption, so far evidenced to reduce absorption of the drug, can be beneficial if the system is saturated. Solubilization, while reducing the amount of drug absorbed when it is present in solution, allows larger concentrations of drug to be administered. When suspensions consisting of free sulphisoxazole, solubilized sulphisoxazole, and solid drug were placed in the rectal sac it was found that the blood levels of the sulphonamide increased with increasing surfactant concentration as shown in Fig. 7.23. Fig. 7.24 which shows the effect on blood levels of increasing the drug concentration in the administered solution, should also be consulted. In Fig. 7.23 it is evident that when 2.5 mg drug is presented per ml solution its activity increases with increasing concentration of polysorbate 80 until at 10% polysorbate the blood level falls. At 10% polysorbate 80 the drug is completely dissolved and the normal reduction in activity due to solubilization takes place.

An equation relating the total absorption rate ($A_T$) to the observed absorption rate of free drug ($A_f$), in which $S$ is the concentration of surfactant (g/100 ml), $A_m$ the absorption rate of micellar drug, and $P_m$ the distribution constant, was

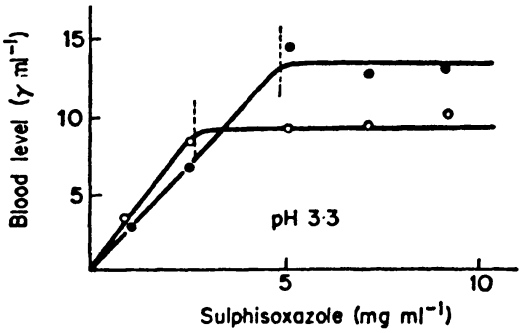



**Figure 7.24** The effect of the amount of sulphisoxazole administered at two different polysorbate 80 levels (○—○ 10% polysorbate 80; ●—● 20% polysorbate 80) on blood levels achieved. From Kakemi *et al.* [75].

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According to Kakemi *et al.* [75] the sulphisoxazole–polysorbate system can be explained by Fig. 7.23(b). $B_1$ is a concentration of sulphisoxazole, just solubilized in water at the concentration $S_2$ of polysorbate 80. When the surface-active agent is incorporated at the concentration $S_1$, a suspension is considered as the three-phase system consisting of the free sulphisoxazole in the solution (F), the drug entrapped in micelles (M), and the solid form of the drug dispersed in the solution (H). M increases with increasing polysorbate 80 up to $S_2$, and F is constant. Above $S_2$, the drug is completely solubilized and therefore M/F increases with increasing polysorbate 80; the free drug concentration decreases. Among three components, the free sulphisoxazole is readily absorbed, and the solid form of sulphisoxazole is not absorbed. If the drug in micelles is absorbed a little, it would be expected that the absorption rate increases as the concentration of surface-active agent below $S_2$, and decreases above $S_2$. This is demonstrated in Fig. 7.23a.

derived by Kakemi and co-workers and described their experimental results closely:

$$A_T = \frac{A_f}{1 + P_m S} + \frac{A_m P_m S}{1 + P_m S}. \tag{7.32}$$

This equation has a term for the absorption of the drug enclosed within micelles. It is unlikely that this is significant, a standpoint suggested by the experimental work of Kakemi *et al.* [75] and recently supported by Mysels' analysis [76] of the mechanism of transport of Orange OT through a membrane in the presence of sodium dodecyl sulphate. The rate of dialysis of solubilized dye was estimated at $3.6 \times 10^{-5}$ h$^{-1}$, which is negligible compared to the 1.0 h$^{-1}$ of the free drug. This is probably the general case, although electron micrographs of the intestinal microvilli seem to suggest that micellar particles can penetrate far into this specialized membrane during fat absorption.

## 7.4 Effect of surfactants on drug absorption

### 7.4.1 Effect of surfactants on intestinal absorption

In this section is reviewed a selection of the available evidence on this topic. Typical of the confusion that still exists is the conclusion arrived at in one paper [77] in which tetracycline, sulphanilamide, isoniazid and salicylic acid were used as test drugs and sodium lauryl sulphate, benzethonium chloride, polysorbate 80 and sucrose mono- and di-stearates as the surfactants. A perfusion technique involving the rat small intestine was employed. It was found that: (i) the ionic nature of the surfactants substantially influenced the absorption; (ii) the rate of absorption of tetracycline was accelerated by the presence of sodium lauryl sulphate, benzethonium chloride or sucrose esters; (iii) polysorbate 80 caused a marked reduction in the absorption of salicylic acid and tetracycline; (iv) benzethonium chloride reduced the absorption of salicylic acid; and (v) sucrose esters within the concentrations tested did not decrease the absorption of all the drugs tested [77]. Following oral administration of some of the solutions to adult human subjects the urinary excretion results supported the view that sucrose esters greatly enhanced, while polysorbate 80 markedly reduced the absorption of tetracycline and that the absorption of sulphanilamide was not affected significantly by the presence of sucrose esters. Here polysorbate 80 is having a negligible or detrimental effect on absorption. Similarly no significant change in the absorption of salicylic acid from the *in situ* rat intestine has been effected by polysorbate 80 at concentrations of 0.001%, 0.01% and 2% [64]. When polysorbate 80 is used as the vehicle for dicoumarol, griseofulvin and sulphisoxazole acetyl, there are significant increases in absorption in the rat [77]. It is important that formulation approaches, other than addition of surfactants, are considered in contemplation of the viability and wisdom of a surfactant-containing formulation. The results shown in Fig. 7.25 are of some significance in this regard. In these experiments the drugs in polysorbate are in solution form;

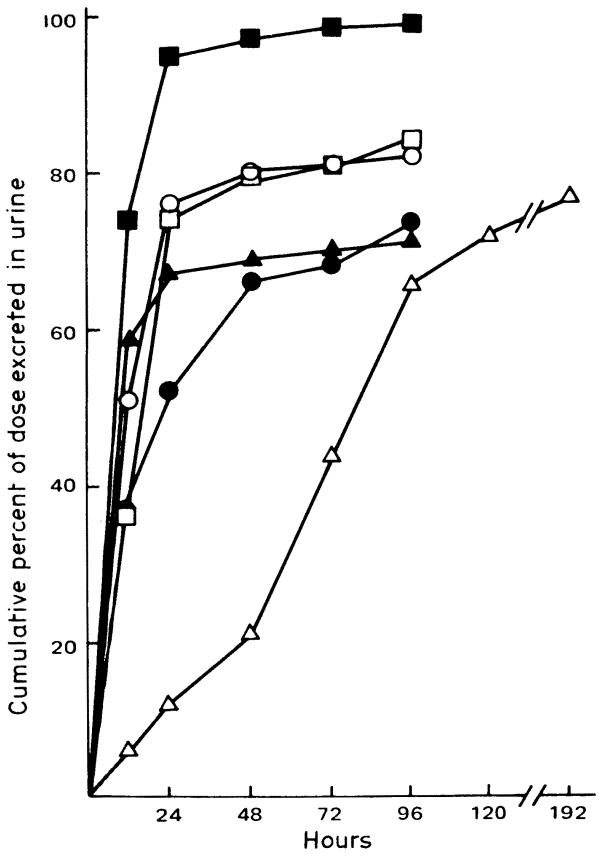



**Figure 7.25** Cumulative urinary excretion of free sulphisoxazole (expressed as a percent of the administered dose on a molar basis) following oral administration of a 100-mg/kg dose sulphisoxazole acetyl in lipid vehicles and water. Each point represents the average of six animals. ●, hexadecane; △, oleyl alcohol; ■, polysorbate 80 (solution); □, trioctanoin; ○, triolein; and ▲, water (with 0.5% methylcellulose). From Bloedow and Hayton [78].

Percent drug dissolved in the suspension dosage forms

| Vehicle | % dissolved* | | |
|---|---|---|---|
| | Sulphisoxazole acetyl | Dicoumarol | Griseofulvin |
| Hexadecane | <0.01 | 1.4 | <0.01 |
| Oleyl alcohol | 1.7 | 12 | 3.6 |
| Polysorbate 80 | 100† | 100† | 94 |
| Trioctanoin | 6.8 | 19 | 13 |
| Triolein | 3.1 | 13 | 3.4 |

* Calculated from solubilities. † Solutions.

the others in suspension in varying degrees (see legend of Fig. 7.25). Although polysorbate 80 increases the bioavailability of dicoumarol when in solution and in suspension, Bloedow and Hayton's results on griseofulvin suspensions indicate that the release rate of drug from suspension is the primary factor in enhancing absorption (Fig. 7.26).

In warfarin-pretreated Wistar rats the biological effect of phytomenadione is greatly increased when presented orally as a solubilized aqueous solution compared to an oily solution (Miglyol 812) [80]. When phytomenadione (30 mg $kg^{-1}$) dissolved in oil, was administered orally to the rats, the effect of the drug on prothrombin time was insignificant. The same dose of phytomenadione solubilized with polyoxyethylene(20)glyceryloleate, however, completely abolished the effect of warfarin in the pretreated animals: 3 hours after administration of the solubilized vitamin, prothrombin time was in the normal range. The effect of the surfactants is not on the clotting process according to other experiments carried out but due to the increased absorption of the phytomenadione. It is unlikely that the surfactant used would be absorbed significantly to exert its effect on other body systems, as after oral administration the ester bond is cleaved [81]; absorption is also poor because of their high molecular weight. Following hydrolysis of polysorbate 80 in the gut the oleic acid moiety is absorbed and the polyoxyethylene sorbiton moiety is eliminated in the faeces [82]. Thus the model experiments *in vitro* can only impinge slightly on the complex influence of surfactant behaviour *in vivo*. Apart from the largely unknown behaviour of the surfactant species, its location, absorption* and degradation and thus its ability to retain an effectiveness over a given period of

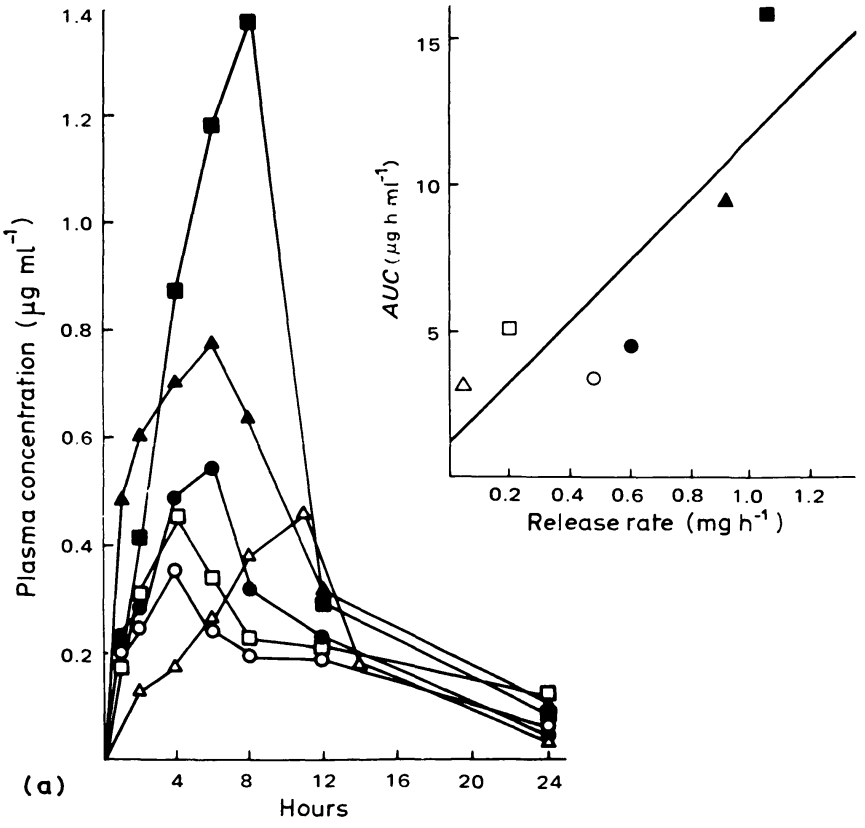



**Figure 7.26**(a)

* Recently the absorption of iodine-labelled polysorbate 80 from the rat gut has been studied [82a].

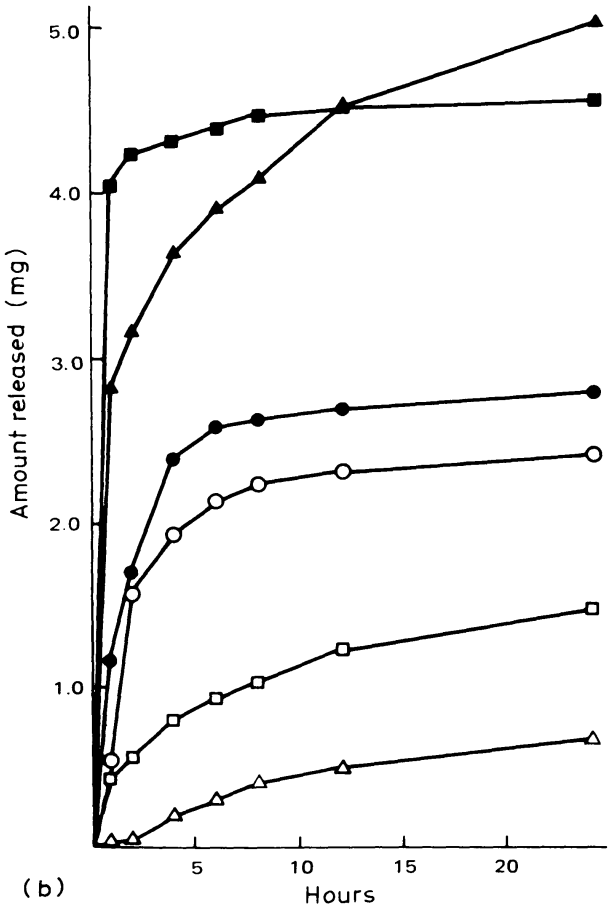



**Figure 7.26**(a) Representative plasma concentrations of griseofulvin following oral administration of 50 mg/kg of griseofulvin suspended in lipid vehicles and water. Each curve, representing data from one animal, has a peak plasma concentration and $t_{max}$ closest to the mean values for each group. For key, see Fig. 7.25. Inset: correlation of the area under the plasma concentration–time curve (AUC) with the average 0 to 4 h rate of release of griseofulvin *in vitro*. (b) Release of griseofulvin into water from suspensions containing 5 mg drug in lipid and water. Each point represents the mean of three experiments. Key as above. From Bloedow and Hayton [79] with permission.

time, there are the normal problems of defining the bioavailability of a drug and the influence of formulation. Reddy *et al.* [15] show that poloxamer 188 and sodium sulphosuccinate increase the absorption of sulphadiazine from rat intestinal loops, there is no significant effect on bioavailability when the drug is administered with these surfactants to rats, if the total urinary excretion of the sulphonamide is measured over 24 h. Absorption rate might well have been affected but 24 h bioavailability was not.

Absorption of normally non-absorbed or poorly absorbed water soluble drugs from a Thomas gastric fundic pouch of the dog is greatly increased by certain surfactants [83]. Vitamin B12 absorption from both stomach and intact gastro-intestinal tract of the rat is similarly enhanced [84]. As might be anticipated, while blood levels of cephaloridine are elevated several fold when surfactant is added to the ligated stomach, their influence in the intact GI tract is diminished and

confined to the first 30 min, after which approximately normal levels of drug are observed [85]. Kreutler and Davis commenting on their results conclude that the absorption promoters exert their rapid and transient effect in the duodenum–small intestine and exert little effect in the stomach: 'This may be due to rapid emptying of the stomach followed by dilution of the dose in the duodenum, or to the subsequent rapid passage of a liquid dose out of the more absorptive upper part of the small intestine. The comparatively poor results in the intact animals also raise the interesting question of possible specific incompatibilities of polyoxyethylene-20-oleyl ether with intestinal secretions in the intact GI tract' [85]. Results are shown in Table 7.4.

From previous results, for example those of griseofulvin and dicoumarol suspensions, one might have predicted that addition of polysorbate 80 to a suspension of a poorly soluble anticonvulsant, a piperazine derivative with a solubility less than 0.1 mg $ml^{-1}$, would have increased its bioavailability. But, responses in terms of the animal's protection from convulsant challenges was decreased by 0.8% polysorbate 80 (Fig. 7.27).

Recently, insulin absorption via the jejunum has been effected by administration of insulin–cetomacrogol solutions to diabetic rats [87]. Results presented in Table 7.5 are most likely to be due to a membrane effect rather than a surfactant-protecting effect on insulin degradation, as insulin administered $\frac{1}{2}$ h after cetomacrogol elicited a hypoglycaemic effect (see Section 7.4.2 below on rectal absorption). Sodium lauryl sulphate (0.75%) and sodium taurocholate (3.2%) have been reported to cause an increase in the percentage of insulin absorbed from the ligated rat jejunal loop from 0.4% to 3.2% and 3.4%,

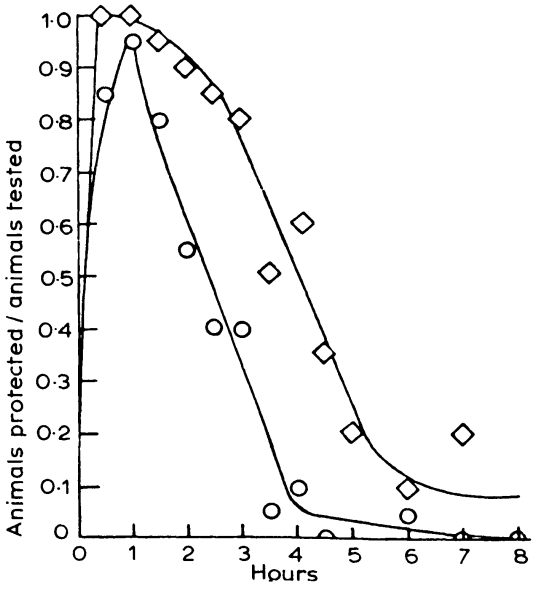



**Figure 7.27** Time course of pharmacological activity of 1-diphenyl-4-[6-methyl-2-pyridyl methyleneamino] piperazine [I] after oral administration of a suspension of I without (◇) and with (○) 0.8% polysorbate 80 solution in saline. From Sanvordeker and Bloss [86].

**Table 7.4** Normal and promoted absorption from doubly ligated duodenum–small intestine

| Drug combination | Number of animals | Minimum detectable levels ($\mu g\,ml^{-1}$) | Whole blood levels ($\mu g\,ml^{-1}$) and standard errors (time post-dosing, min) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 20 | 40 | 60 | 80 | 120 | 180 |
| Cephaloridine only | 5 | 0.25 | 0.41 ±0.13 | 0.95 ±0.19 | 1.90 ±0.35 | 2.03 ±0.37 | 1.66 ±0.46 | 1.54 ±0.38 |
| Cephaloridine with polyoxyethylene-20-oleyl ether | 5 | 0.25 | 3.44 ±0.72 | 9.36 ±1.14 | 10.52 ±0.62 | 8.36 ±1.71 | 3.58 ±0.64 | 0.95 ±0.18 |
| Cephalothin only | 4 | 0.10 | 0.17 ±0.11 | 0.34 ±0.04 | 0.40 ±0.05 | 0.35 ±0.04 | 0.18 ±0.01 | — |
| Cephalothin with polyoxyethylene-20-oleyl ether | 5 | 0.10 | 1.39 ±0.10 | 5.90 ±0.69 | 5.96 ±0.97 | 2.25 ±0.37 | 0.76 ±0.20 | — |

Normal and promoted absorption from intact rat gastro-intestinal tract

| Drug combination | Number of animals | Minimum detectable levels ($\mu g\ ml^{-1}$) | Whole blood levels ($\mu g\,ml^{-1}$) and standard errors (time post-dosing, min) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 20 | 40 | 60 | 80 | 120 | 180 |
| Cephaloridine only | 15 | 0.25 | 0.33 ±0.09 | 0.82 ±0.23 | 1.12 ±0.28 | 1.35 ±0.30 | 0.79 ±0.17 | 0.45 ±0.12 |
| Cephaloridine with polyoxyethylene-20-oleyl ether | 11 | 0.25 | 1.16 ±0.37 | 1.10 ±0.28 | 1.04 ±0.21 | 0.93 ±0.13 | 0.79 ±0.17 | 0.57 ±0.12 |
| Cephalothin only | 4 | 0.10 | 0.21 ±0.02 | 0.33 ±0.06 | 0.33 ±0.05 | 0.34 ±0.10 | — | — |
| Cephalothin with polyoxyethylene-20-oleyl ether | 5 | 0.10 | 0.50 ±0.06 | 0.30 ±0.04 | 0.25 ±0.06 | 0.17 ±0.05 | — | — |

From [85].

**Table 7.5** Effect of cetomacrogol on intrajejunal absorption of insulin in diabetic rats.

| Sample administered* | Initial blood glucose conc. mg % (mean ± S.E.M.) | Blood glucose at times after insulin administration† (% of initial content) (mean ± S.E.M.) 1 h | 2 h | 4 h |
|---|---|---|---|---|
| Saline ($n = 4$) | 326 ± 17.0 | 97 ± 2.9 | 96 ± 5.0 | 90 ± 4.3 |
| Insulin ($n = 5$) | 296 ± 18.8 | 104 ± 3.0 $P$‡ < 0.2 | 100 ± 3.5 $P$‡ < 0.6 | 95 ± 2.0 $P$‡ < 0.4 |
| Insulin-cetomacrogol ($n = 9$) | 309 ± 14.3 | 56.5 ± 2.8 $P$§ < 0.001 | 21.0 ± 2.0 $P$§ < 0.001 | 37.7 ± 4.1 $P$§ < 0.001 |

* Each run was carried out on a different animal; $n$ = no. of rats. For sample composition see text.
† Blood glucose content (% of initial) after interperitoneal injection of 4 i.u. of insulin was 36.1 ± 2.2, 28.7 ± 1.0, 39.4 ± 3.6 at 1, 2 and 4 h respectively (4 rats). Initial blood glucose concentration in mg %: 315 ± 32 (mean ± S.E.M.).
‡ Insulin versus saline.
§ Insulin-surfactant versus saline or insulin (same $P$ values).
From [87].

respectively, while a W/O/W emulsion system increased absorption to 30.6% [88].

Polysorbate 20 has been found to enhance the gastro-intestinal absorption of iron-59, but the mode of action was not clear [89]. The absorption of barium chloride ingested by cats was promoted by both polysorbate 20 and sodium lauryl sulphate at low concentrations and inhibited at high concentrations [90]. Non-toxic doses of sodium lauryl sulphate greatly increased the rate of glucose absorption in rabbits [91]. It has been claimed that sodium lauryl sulphate inhibits gastric motility in certain doses and Nissim concludes that large doses of ionic surfactants lead to structural damage, while small doses reduce the functional efficiency of mucosal cells [92]. Both sodium lauryl sulphate and dioctyl sodium sulphosuccinate, but not pluronic F68, increase the absorption of phenol red from the colon [93], as shown in Table 7.6. This table also shows the effect of administered drugs on the absorption of the dye. The fact that pharmacologically active agents can markedly affect the absorption rate suggests that the effect of the detergent may not be wholly physical. No data were quoted for the effect which the two drugs, atropine and chlorisondamine, had on absorption in the absence of surfactant. These results are of importance in pharmacy, as it is evident that drugs taken concomitantly with the solubilized preparation can seriously affect the theoretical performance of the formulation.

Preliminary data obtained by Lish and Weikel [93] indicate that dioctyl sodium sulphosuccinate increases the absorption of sulphathalidine. None of the surfactants studied influenced the absorption of the cationic dye, methyl violet; presumably there was interaction with the ionic detergents. The fact that the non-ionic surfactant has no effect with either phenol red or methyl violet may be the

**Table 7.6** Effect of drugs on the enhancement of absorption of phenol red by surfactants (1 % in normal saline)

| Solvent | Drug treatment | % Dye absorbed |
|---|---|---|
| Normal saline | — | 6 |
| Dioctylsulphosuccinate | — | 58 |
| | Chlorisondamine* (0.8 mg $kg^{-1}$) | 13 |
| | Atropine sulphate (2.0 mg $kg^{-1}$) | 36 |
| Sodium lauryl sulphate | — | 77 |
| | Chlorisondamine | 45 |
| | Atropine sulphate | 65 |
| Pluronic F68 | — | 1 |
| | Chlorisondamine | 5 |

* Ethylene-1-(4,5,6,7-tetrachloro-2-methyl*iso*indolinium)-2-trimethylammonium dichloride, a ganglion blocking agent used in severe hypertension. From [93].

result of mixed micelle formation. Mixed micelle formation and the phenomenon of therapeutic interference [94] will be discussed later.

(A) EFFECT OF BILE SALT

The bile salts have been studied for their effect on drug absorption. They are obvious objects of interest in view of their presence in the intestine and their involvement in fat absorption.

The bile salt concentration is 100 to 300 mM in human bile, and about one-tenth of this in human intestinal content and as the CMCs are in the region of 2 to 3 mM both bile and intestinal fluids contain bile salt micelles [95]. The ability of bile salt solutions to solubilize insoluble drugs such as griseofulvin and hexoestrol [96] suggests that the bile salts may be involved in the solubilization of drugs prior to absorption. Bates *et al.* [97] have found that physiological concentrations (0.04M) of sodium cholate and sodium deoxycholate enhance the rate of solution of hexoestrol and griseofulvin over their rate of solution in water, as shown in Table 7.7. This effect strengthens the view of their supposed action. It is interesting to note that the oxidized bile salt dehydrocholate does not micellize and does not enhance fat absorption [95].

**Table 7.7** Relative dissolution rates for griseofulvin and hexoestrol at 37° C [97] in sodium deoxycholate and sodium cholate solutions

| | Griseofulvin time (min) | | | Hexoestrol time (min) | | |
|---|---|---|---|---|---|---|
| Dissolution medium | 2 | 5 | 10 | 2 | 5 | 10 |
| Water | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Sodium deoxycholate | 7.5 | 6.6 | 6.0 | 14.6 | 18.6 | 24.0 |
| Sodium cholate | 7.2 | 6.1 | 5.5 | 20.3 | 30.4 | 36.0 |

The enhanced absorption of medicinals on administration with deoxycholic acid may be due to reduction in interfacial tension or micelle formation. The inefficient absorption of reserpine promoted an investigation into its absorption in combination with deoxycholic acid [98]. Deoxycholic acid was found to increase the rapidity of absorption of reserpine and to increase its potency. The solubility of reserpine is increased in hydro-alcoholic deoxycholic acid solutions [99], it being suggested that both micellar solubilization and inclusion formation is responsible. A combination of these effects may facilitate the absorption of the reserpine.

The administration of quinine and other Cinchona alkaloids in combination with bile acids has been claimed to enhance their parasiticidal action [100, 101]. Quinine, taken orally, is considered to be absorbed mainly from the intestine. A considerable quantity of bile salts is required to maintain a colloidal solution of quinine; one might argue that an efficient supply of bile salts was therefore a prerequisite of quinine absorption [102]. It is interesting to note in this context that recurrent attacks of malaria are sometimes found to be accompanied by hepatic disturbances which may prejudice the normal flow of bile [103].

A mechanism has been suggested to explain the enhancement of drug absorption following a meal of high fat content. Triglycerols and similar materials increase the flow of bile into the small intestine, which results in the increased solubility of any drugs present. The effect of lipid additives on the solubilization of glutethimide, hexoestrol, and griseofulvin in a simulated bile salt mixture is small; the lipids would simply increase the concentration of bile, and although they themselves will be solubilized, would not preclude the solubilization of other drugs [104].

A comparative study of the effect of sodium cholate, sodium deoxycholate, sodium chenodeoxycholate and taurodeoxycholate on the absorption of quinalbarbitone sodium by goldfish [105] has shown no correlation between their effectiveness as absorption promoters and their relative hydrophobicity or ability to lower interfacial tension. In general terms their ability to increase absorption is predictable because of their surface activity and their ability to abstract lipid from erythrocyte ghosts indicating their freedom to interact with biological membranes [106, 107].

20 mM sodium taurocholate increases the absorption of procaineamide from rat small intestine [108]; an effect abolished by the addition of 18mM oleic acid. Feldman and Gibaldi [109] reported that the addition of lecithin and fat digestion products to solutions containing sodium taurodeoxycholate produced a pronounced decrease in the permeability of the everted rat intestine to salicylate. The oleic acid perhaps decreases the ability of the bile salt to solubilize membrane components; more likely the oleic acid forms mixed micelles with the bile salt and thus solubilizes more procaineamide. Sodium taurocholate has no effect on the absorption of 2-allyloxy-4 chloro-*N*-(2-diethyl aminoethyl) benzamide (ACDB). Mixtures of this bile salt with lauric acid, palmitic acid or oleic acid reduced the intestinal absorption of ACDB [108].

In contrast to the findings on procaineamide absorption in the presence of

mixed micelles, the absorption of amino glycosides has been found to be little affected by bile salt alone yet significantly increased in the presence of monoolein-*N* oleic acid–bile salt mixed micelles [110]. Pretreatment of the gut with mixed micellar solution, 1 h prior to administration of the drug has no effect on absorption; there was no evidence of membrane damage. The mixture was much more effective in the large intestine rather than in the small intestine. To obtain an effect, concentrations of 40 mM of the mixed micelle are required hence as dilution rapidly occurs following oral administration in the intact animal, unspectacular results may be obtained. For this reason rectal absorption of the aminoglycoside–mixed micellar system was suggested [110] and shown to improve the absorption of both gentamicin and streptomycin.

Bile salts have achieved improved absorption of urogastrone, a glycoprotein with gastric antisecretory activity. Urogastrone alone or bile salts alone failed to inhibit $H^+$ secretion when administered intrajejunally in the rat, but presented together, a strong inhibitory response of gastric acid secretion was observed [111]. Sodium taurocholate was the least effective of the three bile salts studied and urogastrone administered in 0.2% polysorbate 80 was ineffective. Since EDTA facilitates intestinal absorption of heparin, presumably by chelation of membrane calcium and magnesium, and as bile salts possess an EDTA-like effect on the intestinal membrane [112, 113], it was suggested that they increase permeability to urogastrone by increasing the permeability of the absorptive membrane.

The importance of bile salt concentration on transport rates is clearly shown in Fig. 7.28 from the work of Feldman and Gibaldi [114] which suggests that two mechanisms are operating, one below and one above the CMC, leading to the

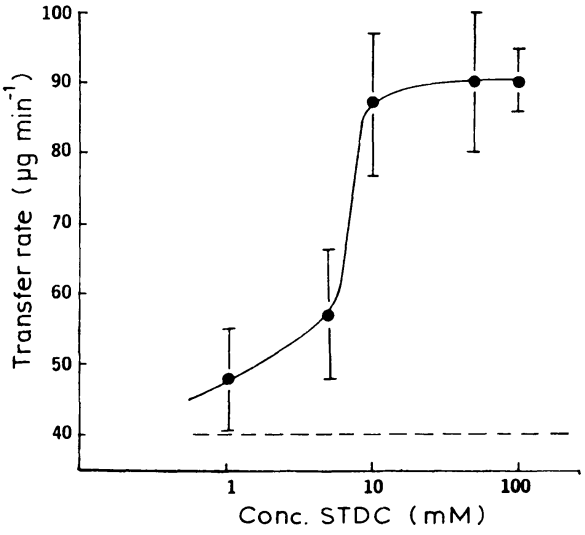



**Figure 7.28** Effect of mucosal concentrations of sodium taurodeoxycholate STDC (log scale) on mean steady-state transfer rates of salicylate across the everted intestine of the rat. Bars denote ± 1 S.D. Dashed line indicates mean control value. From Feldman and Gibaldi [114] with permission.

question as to whether monomeric and micellar bile salt species are absorbed in a different manner. Absorption of the bile salts has been studied [115] and it appears from this work that micellar taurocholate moves across intestinal membranes twice as fast as monomeric bile salt. This does not necessarily mean that micelles are involved in the transport process but as Feldman and Gibaldi rightly observe, it is likely that the higher concentrations of bile salt alteration of membrane permeability will enhance the possibility of transport of the bile salt across the membrane. Some researchers have found that the effect of bile salts on the permeability of the intestinal barrier is not readily reversible [116]. Direct comparison of sodium taurocholate, polysorbate 80 and an alkyl ether non-ionic surfactant [117] indicated that the presence of 10 mM oleic acid in 0.2% surfactant solution was essential for significant absorption of heparin (see Fig. 7.29). Thus it appears that the bile salts are not unique in their action. The role of the oleic acid or mono-oleic in these mixed micellar systems has yet to be elucidated.

A logical extension of this type of study, because of the natural presence of bile salts in the intestine and the presence of synthetic surfactants in formulations, is the consideration of bile salt–surfactant mixtures. One such study [118] has considered the effect of sodium glycocholate and its mixtures with NaLS and polysorbate 80 on the absorption and metabolism of a thiamine disulphide derivative, in rats (see Scheme 7.1). It had previously been shown that surfactants altered the reaction rates of the thiol-disulphide exchange reaction that these compounds undergo [119] and that *o*-benzoyl thiamine disulphide interacts with the lauryl sulphate anion to form a 1:2 complex; this complex is broken up by sodium glycocholate to form new mixed micelles of thiamine derivatives and the surfactants. NaLS decreases $k_A$ and $k_D$ promoting the conversion of V to VII. The reduction in absorption and the decreased enzymatic deacylation are both explained by complex formation, although inactivation of intestinal esterase by

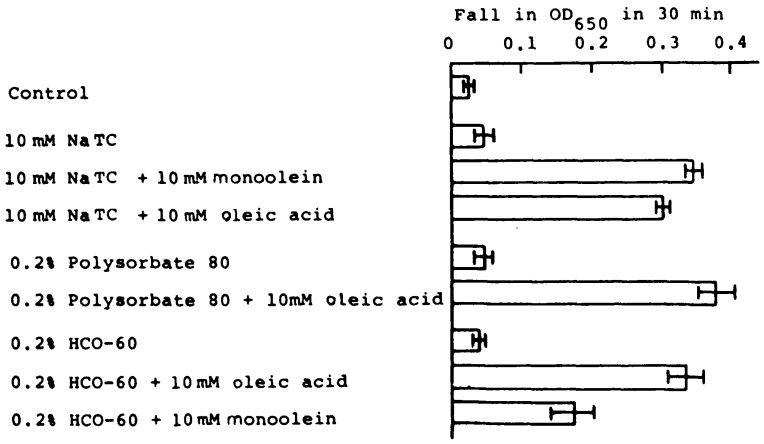
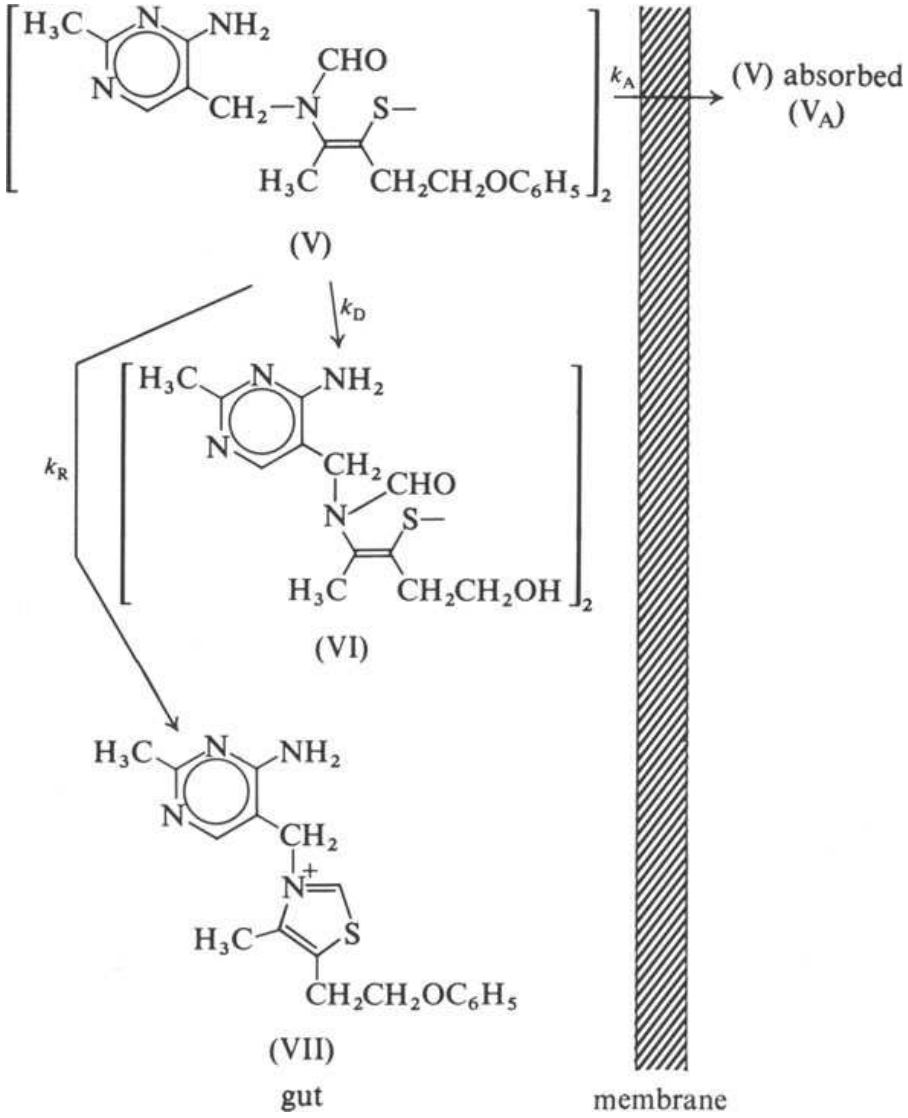



**Figure 7.29** Plasma clearing factor activity after the administration into the large intestine. Several types of mixed micelles containing oleic acid were tested. Each value is the mean ± SEM of 4 to 5 animals. NaTC = sodium taurocholate; HCO-60 = hydrogenated castor oil based non-ionic surfactant with 60 ethylene oxide units. From Taniguchi *et al.* [117] with permission.




Scheme 7.1

(V) *o*-benzoyl thiamine disulphide
(VI) thiamine disulphide
(VII) *o*-benzoyl thiamine

**Kinetic model for absorption and metabolism.** In the intestinal tract, (V) is absorbed in an intact form but is partially metabolized by two processes (Scheme 7.1). One process is a reduction, being considered nonenzymatic, to form *o*-benzoylthiamine (VII), the other is an enzymatic hydrolysis of ester linkage (deacylation) to form the less absorbable (VI). From [118].

the surfactant is possible. The increase in $k_R$ has also been observed *in vitro*. Sodium glycocholate at concentrations above 0.1 % increased $k_A$ and at 0.015 % and above decreased $k_D$. Polysorbate 80 (0.5 %) reduced absorption, the enzymatic deacylation and the reduction. The effect of concentration of sodium glycocholate on $k_A$ and $k_R$ in the presence of 0.1 % sodium lauryl sulphate is shown in Table 7.8. The bile salt is seen to cancel out the effect of the anionic

**Table 7.8** Effect of concentration of sodium glycocholate on the absorption of *o*-benzoylthiamine disulphide from mixtures of sodium lauryl sulphate and sodium glycocholate*

| System | Number of rats | Rate constants ($h^{-1}$) | |
|---|---|---|---|
| | | $k_A$ | $k_R$ |
| Control† | 3 | 0.40 ± 0.03 | 0.37 ± 0.05 |
| 0.1 % sodium lauryl sulphate | 3 | 0.18 ± 0.03 | 0.76 ± 0.14 |
| 0.1 % sodium lauryl sulphate–0.1 % sodium glycocholate | 3 | 0.22 ± 0.03 | 0.50 ± 0.07 |
| 0.1 % sodium lauryl sulphate–0.17 % sodium glycocholate | 3 | 0.23 ± 0.01 | 0.39 ± 0.03 |
| 0.1 % sodium lauryl sulphate–0.25 % sodium glycocholate | 3 | 0.37 ± 0.05 | 0.36 ± 0.06 |
| 0.1 % sodium lauryl sulphate–0.34 % sodium glycocholate | 3 | 0.43 ± 0.07 | 0.39 ± 0.03 |
| 0.1 % sodium lauryl sulphate–0.5 % sodium glycocholate | 3 | 0.38 ± 0.07 | 0.38 ± 0.07 |

* V in perfusate: 10 μg $ml^{-1}$, pH 6.4, 37° C. † Without surfactant.
From [118].

surfactant (which is to reduce absorption of V). *o*-Benzoylthiamine disulphide administered in surfactant solutions to intact animals is absorbed most efficiently from 0.1 % NaLS, least effectively from 0.5 % polysorbate 80 (Table 7.9), pointing to the complexity of the effects *in vivo*; endogenous surfactant interactions sometimes of an unpredictable nature will occur. The effect of endogenous bile on the intestinal absorption of indomethacin and phenylbutazone has been studied using normal and bile fistulated rats [120]. Lower plasma levels of both drugs were achieved in the latter and it was surmised that both bile salts and phospholipids influenced absorption via enhanced dissolution rates of drugs administered in suspension.

**Table 7.9** Urinary excretion of thiamine after administration of *o*-benzoylthiamine disulphide micellar solutions*

| Micellar solution | Urinary excretion of thiamine (%) |
|---|---|
| Control† | 18.1 ± 1.8 |
| 0.1 % sodium lauryl sulphate | 30.4 ± 7.7 |
| 0.5 % polysorbate 80 | 14.4 ± 3.5 |
| 0.5 % sodium glycocholate | 24.7 ± 4.2 |

* Dose: 200 μg/2 ml (pH 6.4). † Without surfactant.
From [118].

## 7.4.2 Surfactants and rectal absorption

The rectal route offers an alternative to the oral route of administration and offers some advantages in experimental work. Drug absorption from the rectum (of the

rat) has been said to be more consistent with the pH-partition hypothesis than is absorption from the small intestine [121]. Results shown in Fig. 7.23 earlier in this chapter were obtained by administration of solutions and suspensions of sulphisoxazole into the sac of the rectum of rats. This is probably one of the most significant experiments on surfactant effects, possibly because of the relatively stable conditions in the rectum compared with the rest of the gastro-intestinal tract. Polysorbate 80 produced no histological damage to the rectal mucosa [75].

Bioavailability of gentamicin after rectal administration of the drug as a 20 mM mixed bile salt–mono-oleic micellar solution is approximately 45% whereas without surfactant absorption it is negligible [110]; bioavailability is further improved by installation of a freeze-dried gentamicin–mixed surfactant powder presumably because of the high concentration of surfactant that is achieved (see Table 7.10). The effect of surfactant in the rectum can be compared with that in the duodenum. The influence of a surfactant ion on absorption may not be directly related to surface activity or solubilization but, when solute ions of opposite charge are involved, to lipophilic ion pair formation. Such is the conclusion [122] drawn from observations of the effect of sodium lauryl sulphate on the rectal absorption of a variety of amines (Table 7.11), although as the anion is not transported in equal amounts this cannot be the whole explanation of increased absorption. It has thus been postulated that the binding of the species to the mucosal tissue perhaps offers a better explanation.

Saccharin sodium produces qualitatively similar results yet is not known to be a surfactant ion [123]. At pH 7.4 NaLS has been found to increase the binding of ephedrine and quinine to rectal mucosal preparations by an unknown mechanism. It is presumed that Kakemi *et al.* [122] propose that the evidence of increased affinity for mucosal tissue signifies an increased concentration gradient of the drug at the interface but this is a concept that requires much more data and experimental evidence before being acceptable. The increased surface activities of the ion-pair may be a factor in increasing the interfacial concentration of the drug

**Table 7.10** Bioavailability of gentamicin in various preparations and routes of administration

| Preparation | Bioavailability (% ± S.E.M.) from AUC |
|---|---|
| Intravenous injection | 100 |
| Duodenal instillation | |
| None | 4.1 ± 1.6 |
| 40 mM mixed micellar solution | 6.8 ± 0.5 |
| Rectal instillation | |
| None | 0.1 ± 0.1 |
| 10mM mixed micellar solution | 18.4 ± 3.4 |
| 20 mM mixed micellar solution | 44.6 ± 4.9 |
| Rectal insertion | |
| Powdered mixed micelles | 58.1 ± 8.2 |

From [110].

**Table 7.11** Effect of NaLS on the rectal absorption of various amines at pH 7.4

| Drug | $pK_a$ | % absorbed in 1 h | | Apparent partition coefficient | | | |
|---|---|---|---|---|---|---|---|
| | | | | Chloroform | | Benzene | |
| | | Alone | With NaLS | Alone | With NaLS (0.4 mM) | Alone | With NaLS (0.4 mM) |
| Aminopyrine | 5.0 | 21.2 (2) | 26.5 (2) | — | — | 6.77 | 7.00 |
| ACDB* | 7.9 | 22.8 (2) | 27.8 (2) | ∞ | ∞ | 37.10 | 102.18 |
| Quinine | 8.4 | 14.9 (3) | 30.7 (3) | ∞ | ∞ | 1.45 | 12.60 |
| Procaine | 9.0 | 0.8 (3) | 8.9 (3) | 11.17 | 44.64 | — | — |
| Ephedrine | 9.6 | 2.9 (5) | 7.1 (5) | 0.07 | 0.22 | — | — |
| Fuchsin 'Basic' | — | 7.0 (4) | 13.4 (4) | 0.77 | 31.49 | — | — |
| Homatropine | 10.4 | 7.2 (4) | 24.5 (4) | 0.72 | 3.50 | 0.01 | 0.11 |

Numbers in parentheses represent number of experiments.
* 2-Allyloxy-4-chloro-*N*-(2-diethylaminoethyl)benzamide hydrochloride
Apparent partition coefficient is given by the following equation.

$$\text{apparent partition coefficient} = \frac{\left(\begin{matrix}\text{drug concentration in water phase}\\ \text{before the distribution is carried out}\end{matrix}\right) - \left(\begin{matrix}\text{equilibrium concentration}\\ \text{in water phase}\end{matrix}\right)}{(\text{equilibrium concentration in water phase})}.$$

Adapted from [122].

species in the interfacial region as suggested by Fiese and Perrin [124] and Patel and Zografi [125].

Compartmental kinetic analyses by the method of Doluisio *et al.* [126] of data for the *in situ* rectal absorption of quinine revealed that the rate constant of absorption from the gut lumen to the absorptive membrane was increased by four- to five-fold in the presence of the anions investigated. 'This phenomenon', state Suzuki *et al.* [123], 'can be interpreted as an increase of the binding tendency of the drug to the absorptive membrane. Binding or 'accessibility' seems to be favoured by the ion-pair formation'. They continue, 'This view was further substantiated by the results of the experiments in which the amount of intravenously administered drug being taken up by perfusion of the gut was measured. The apparent rate that the drug entered into the intestinal lumen was hardly affected by the intestinal perfusion of NaLS solution, thus ruling out the possibility of a general increase in permeability caused by NaLS, an anionic component of the ion-pair'.

These explanations are difficult to reconcile with the known effects of NaLS on membrane permeability.

Following on reports (referred to above) of macromolecule absorption facilitated by surfactants, there have been successful attempts to achieve insulin absorption *per rectum* [127–129, 126]. Non-ionic ethers, anionic, cationic and amphoteric surfactants, as well as bile acids, increased absorption. The optimal effect has been obtained with 1% polyoxyethylene (9) lauryl ether [128], the effect of both polyoxyethylene chain length and alkyl chain having been

**Table 7.12** Effects of polyoxyethylene (POE)(*n*) fatty alcohol ethers in insulin suppositories on blood glucose level in rabbits. Insulin suppositories contained 0.5% polyoxyethylene (*n*) fatty alcohol ethers and 1 U $kg^{-1}$ insulin in corn oil. The initial blood glucose concentration was 118.3 ± 6.2 mg/100 ml. Each value represents the blood glucose concentration at 30, 60, 90 and 120 min after rectal administration of insulin suppositories and mean of three rabbits ± S.E.M.

| Surfactants POE (*n*)—alcohol ethers | Decrease in blood glucose % | | | |
|---|---|---|---|---|
| | 30 (min) | 60 (min) | 90 (min) | 120 (min) |
| (3) lauryl | −8.8±7.7 | −3.0±3.5 | −11.2±2.3 | −9.8± 4.6 |
| (6) lauryl | −12.3±0.6 | −23.8±6.9 | −20.6±6.5 | −11.2± 6.1 |
| (9) lauryl | −12.7±8.5 | −47.9±5.6 | −47.1±7.4 | −32.6±11.2 |
| (25) lauryl | +0.6±1.2 | −4.2±2.6 | −4.0±2.8 | −0.9± 1.0 |
| (40) lauryl | +17.3±2.9 | +18.5±2.5 | +14.9±3.1 | +13.5± 8.2 |
| (9) octyl | +3.9±5.5 | +12.8±8.0 | +13.6±9.2 | +13.0± 6.2 |
| (9) decyl | −21.6±4.8 | −36.2±3.7 | −16.2±5.1 | −12.6± 6.8 |
| (9) cetyl | −28.4±3.6 | −43.1±2.6 | −35.9±5.7 | −16.8± 5.4 |
| (9) stearyl | −22.0±6.2 | −22.2±3.2 | −19.8±4.8 | −26.2± 7.9 |

From [128].

determined (Table 7.12). The dose of insulin in suppositories requires to be two to three times the intravenous dose to produce the same order of hypoglycaemia.

### 7.4.3 Surfactants and intramuscular injections

Drugs administered intramuscularly are absorbed after diffusion of the soluble molecular species across capillary walls. Molecular size and charge and protein binding of the drug are influences, and as diffusion of a soluble species is involved, as well as membrane transport, it is not surprising that surfactants can affect absorption of drugs from muscle. Both promotion and reduction in absorption have been detected.

The basic polypeptide antibiotic, enduracidin, isolated from *Steptomyces fungicidus* has a molecular weight of about 2500 and is poorly absorbed following i.m. administration [130]. Non-ionic surfactants promote absorption; polysorbate 80 and a series of surfactants based on hydrogenated castor oil (HCO) with $n$ = 30, 50, and 120 used at 5% levels enhanced absorption, an optimal effect being obtained with the surfactant HCO-50 (HLB = 13.4). The surfactant might both increase capillary permeability to the drug or prevent precipitation of the antibiotic in the tissues (it precipitates on the addition of sodium chloride in the absence of surfactant). Some results are shown in Fig. 7.30. An opposite effect on the absorption of some water-soluble drugs has been observed [131, 132].

Low concentrations of the polysorbate surfactant series reduced absorption of isonicotinamide, insulin, procaineamide and sulphanilamide [131]. Several mechanisms for the reduction in absorption and plasma levels of these drugs were considered. Micellar interaction was ruled out as a negligible effect in these

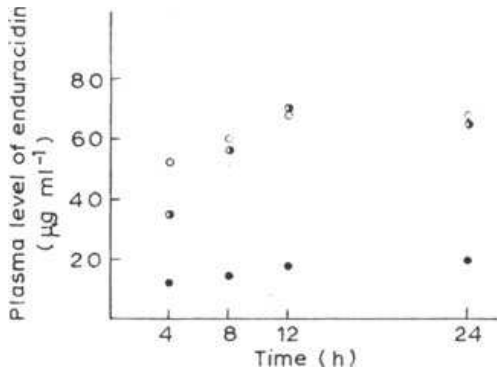



**Figure 7.30** Effect of HCO-50 on blood levels of enduracidin following intramuscular injections to rats. Concentration of Enduracidin; 2.5 % dose; 6.25 mg/rat (0.25 ml injected)
●: without HCO-50
○: with 2.5 % HCO-50
◑: with 5 % HCO-50
Each value is an average of four rats. From Matsuzawa *et al.* [130] with permission.

systems. Histological investigation showed no relationship between the inhibition of absorption and the inflammation caused by polysorbate 80 at the site of injection [132]. Neither was the effect of the surfactant exerted on the capillary walls. In the process of studying this problem the disappearance of polysorbate 80 from rat thigh muscle was measured (Fig. 7.31). Obviously for the surfactant to exert some physical effect it must be at the site of injection; isonicotinamide escapes faster than the surfactant administered as a 5.0 % solution. After 6 h 10.51 ± 0.79 % of surfactant remained, while after 24 h less than 5 % of the surfactant remained in the thigh muscle. Kobayashi and his colleagues have concluded that the polysorbates exert their action by reducing the rate of transport of the drugs

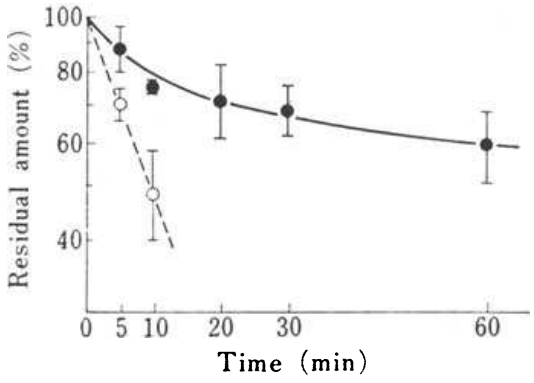



**Figure 7.31** Semilogarithmic plots of the disappearance of polysorbate 80 and isonicotinamide from the rat thigh muscle.
A 50 μl of 5.0 % polysorbate 80 containing 50 mM isonicotinamide was injected intramuscularly. Vertical bars indicate standard deviation.
—●—: polysorbate 80
—○—: isonicotinamide
From Kobayashi *et al.* [132] with permission.

through the extracellular space and connective tissue. 5.0% polysorbate reduces transport through the extracellular space by about 17%, 10 min after administration using insulin as a marker. Intradermal injection of polysorbate reduces the spread of a dye administered at the same time [133]. While this might be due to solubilization of the dye it could also be ascribed to a reduction in dermal tissue permeability.

### 7.4.4 Surfactants and percutaneous absorption

Skin permeability is increased by contact with a variety of substances, soap and detergents being deemed to be among the most damaging of all substances routinely applied to the skin [134]. The increased permeability of the human epidermis can be measured in the presence of very low concentration of anionic and cationic surfactants [135], although non-ionic surfactants are less damaging [136]. Detailed investigations of the interaction of surfactants with skin have been undertaken [137] showing that typical cationic and non-ionic surfactants are weak penetrants of skin unlike sodium lauryl sulphate which readily penetrates and destroys the integrity of the stratum corneum in hours. The addition of polyoxyethylene glycols or polyoxyethylated non-ionic surfactants to NaLS solutions reduces the rate of permeation of the ionic surfactant (see Fig. 7.32) possibly by complexing or forming mixed micelles with NaLS (see Chapter 6). Such effects are termed 'anti-irritation' phenomena and may generally be the result of three separate mechanisms [138]:

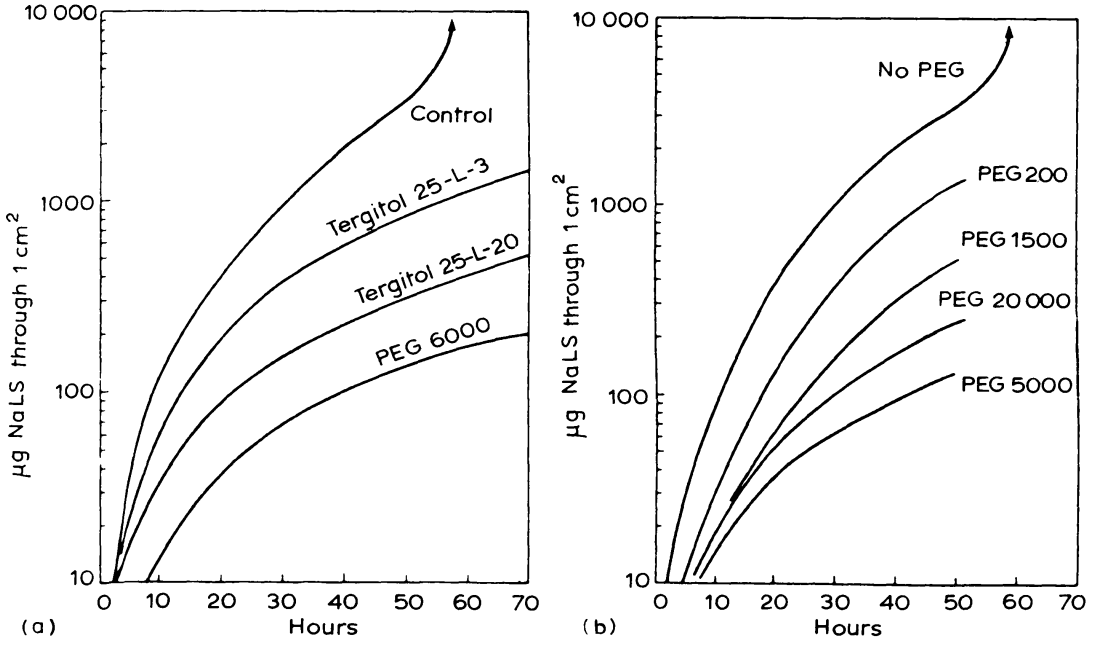



**Figure 7.32** Permeation curves for 10% sodium lauryl sulphate (control) containing (a) 5% various ethoxylated compounds, PEG6000, Tergitol 25-L-3 ($C_{11-15}E_3$) and Tergitol 25-L-20 ($C_{11}E_{20}$) and (b) 5% of a series of PEG homologues. The membranes used were neonatal rat stratum corneum membranes. From Faucher *et al.* [137].

(1) prevention of intimate physical contact of irritant and skin;
(2) complexation; and
(3) blocking of otherwise reactive sites on the skin.

The first would occur by occlusion caused by film formers. The last can only be speculated upon but it is possible that competition for sites does occur.

Provided that the surfactants used in topical formulations are not toxic a more pressing biopharmaceutical concern is the effect of surfactants on the absorption of active ingredients. The nature of topical cream and ointment formulations is such that the unravelling of surfactant influences is not easy. Surfactants will affect the stability of an emulsified vehicle, the solubility of drugs in the vehicle and the spreadability of the formulation and thus directly influence drug release. This can be demonstrated *in vitro*; for example non-ionic surfactants increase the diffusion of sulphanilamide from oily bases and solubilization of the drug in the vehicle retards its release compared to release from systems in which the drug is suspended [139]. Such effects are to be anticipated from the prediction of Poulsen and colleagues [140] of the factors affecting release of drugs from topical formulations. The problem is similar to that encountered in Fig. 7.23 with sulphonamide suspensions and solutions, but less well defined. Inhibition zones on agar plates obtained with different concentrations of solubilized and suspended sulphanilamide in ointments containing 15% surfactant are shown in Table 7.13. Increasing the sulphanilamide concentration increases the amount solubilized in both polysorbate 85 and 20; in the latter at 3% sulphonamide, inhibition zones are maximal for reasons that are not clear. Obviously in the suspension systems the base has the capacity to solubilize drug and thus the continuous phase is never saturated.

The incorporation of emulsifying agents into ointments was shown to improve the release of sulphadiazine [141]. Such findings were also obtained using other drugs such as hexetidine, and yellow mercuric oxide [142, 143].

An *in vivo* method has been developed for monitoring the effect of polysorbate 85 on epidermal permeability [144] by measurement of moisture loss over a period of several days. After treatment for this period of time with surfactant the

**Table 7.13** Inhibition zones (mm) obtained with different concentrations of solubilized and incorporated sulphanilamide (in ointments containing 15% surfactant)

| Sulphanilamide (%) | Tween 85 | | Tween 20 | |
|---|---|---|---|---|
| | Solubilized sulphanilamide | Incorporated sulphanilamide | Solubilized sulphanilamide | Incorporated sulphanilamide |
| 0.5 | 2.06 | 3.75 | 3.25 | 5.50 |
| 1 | 3.50 | 4.88 | 4.50 | 4.75 |
| 2 | 6.62 | 7.18 | 4.75 | 4.33 |
| 3 | 7.56 | 7.87 | 5.16 | 5.63 |
| 4 | — | 8.31 | 4.00 | 5.50 |
| 5 | — | 8.54 | 4.31 | 5.50 |

From [139].

skin can become irregular due to sloughing of the epidermis [145] when the surface is occluded with the vehicle.

Only sodium lauryl sulphate and sodium laurate increased the permeation of naproxen from aqueous gels through excised human abdominal skin, hexadecyl pyridinium chloride, polysorbate 60 and polyoxyethylene (23) lauryl ether decreasing permeation or having little effect [146]. Methyl decylsulphoxide, a surfactant derivative of dimethylsulphoxide (DMSO) has at 1% levels a considerable effect on flux, increasing it in excised human skin by ten times when naproxen was presented as an O/W cream formulation. Its mode of action is not known. These cationic surfactants are thought to bind to α-protein causing a reversible denaturation and uncoiling of the filaments. Membrane expansion, 'hole' formation and loss of water binding capacity are said to be consistent with the reversible $\alpha \rightleftharpoons \beta$ conversion of keratin [147] induced by surfactant binding. A more extensive range of non-ionic surfactants was incorporated into white petrolatum USP ointment base containing 10% salicylic acid or sodium salicylate (11.5% w/v) with dimethyl sulphoxide [148] (Fig. 7.33). These formulations were applied to rabbits and percutaneous absorption found to increase significantly in the presence of several of the non-ionic surfactants, even when DMSO was present. The nature of the effects is not yet clear.

Salicylic acid is absorbed faster from two ointment bases containing surfactants when applied to oral mucous membranes than from bases containing none but the complexity of the formulations used prevents detailed analysis. Some results are shown in Fig. 7.33c.

Using a more restricted range of components, an attempt has been made to optimize a steroid formulation containing propylene glycol or polyoxypropylene (15)-stearyl ether [150]. The partition coefficient between skin and vehicle, $P_s$, the solubility of the drug diflorasone diacetate in the vehicle and the percutaneous absorption were measured. Data for $P_s$ and solubility are presented in Fig. 7.34a. The solubility increases with increasing surfactant concentration, a break occurring at about 0.2 weight fraction. As the solubility in the vehicle increases, $P_s$ naturally falls. The steady state flux of $^3$H diflorasone diacetate from various formulations (Fig. 7.34b) decreases with increasing surfactant beyond 0.2 weight fraction, the results agreeing moderately with those predicted from the following analysis [150].

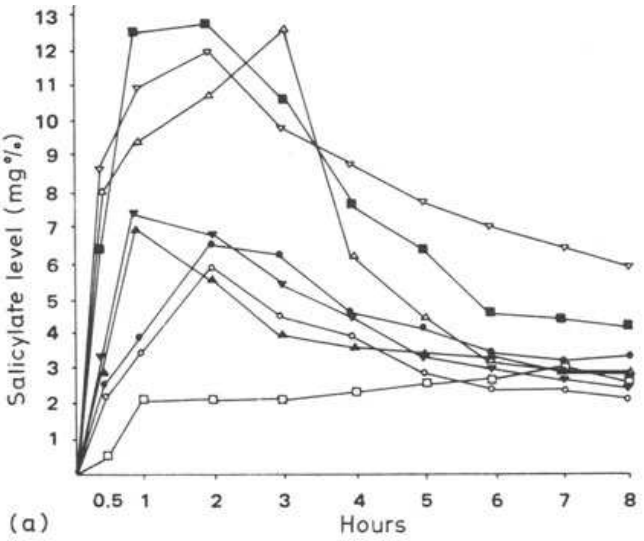
The data obtained for the *in vitro* percutaneous penetration kinetics of diflorasone diacetate in vehicles consisting of propylene glycol–water and polyoxypropylene (15)-stearyl ether–mineral oil suggest that the skin is the rate-determining barrier for this compound. In this case, the appropriate relationship is represented by:

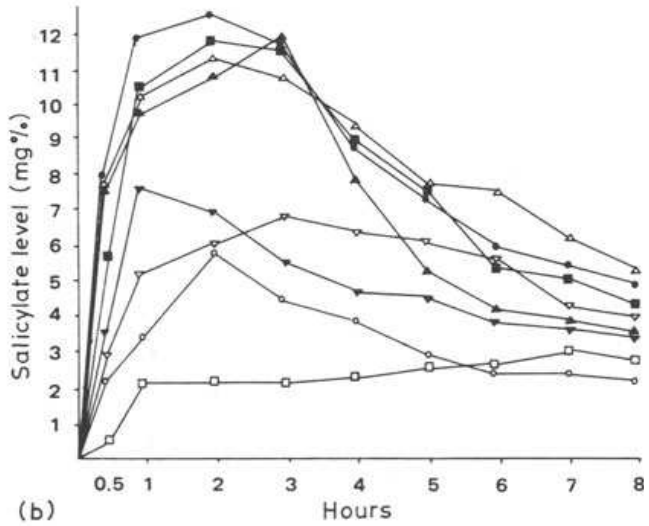
$$-\frac{dC_F}{dt} = \frac{P_s C_F D_s}{V_F h_s}, \tag{7.33}$$

where the equation refers to unit area (1 cm$^2$).

$C_F$ = concentration of dissolved diflorasone diacetate in the vehicle ($\mu g\,cm^{-3}$)

$D_s$ = diffusion coefficient of diflorasone diacetate through the skin ($cm^2\,s^{-1}$)


Salicylate level (mg%)
13
12
11
10
9
8
7
6
5
4
3
2
1
0.5 1 2 3 4 5 6 7 8
Hours
(a)


Salicylate level (mg%)
12
11
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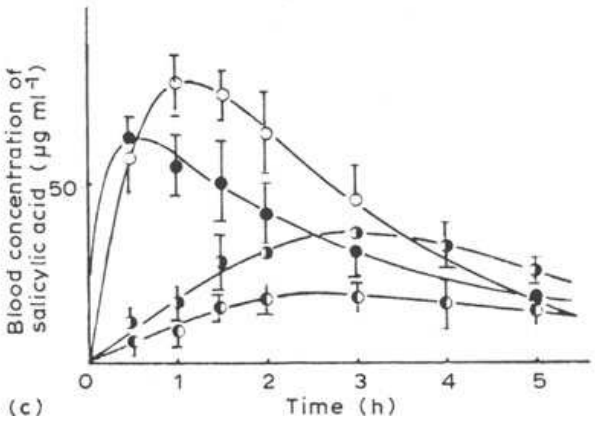
1
0.5 1 2 3 4 5 6 7 8
Hours
(b)


Blood concentration of salicylic acid (μg ml⁻¹)
50
0 1 2 3 4 5
Time (h)
(c)

$h_s$ = thickness of the skin barrier (cm)
$P_s$ = diflorasone diacetate skin-vehicle partition coefficient
$V_F$ = volume of formulation applied ($cm^3$).

The thickness of the skin barrier and the diffusion coefficient are combined and defined as a resistance, $R_s = h_s/D_s$. The resistance has units of time per length. Equation 7.33 can be simplified to:

$$-\frac{dC_F}{dt} = \frac{P_s C_F}{V_F R_s}. \tag{7.34}$$

**Figure 7.33**(a) Effect of sorbitan and polysorbate surfactants on percutaneous absorption of salicylic acid in the presence of dimethyl sulphoxide. △, 10% sorbitan monolaurate plus 10% dimethyl sulphoxide plus 10% salicylic acid; ▽, 10% sorbitan monopalmitate plus 10% dimethyl sulphoxide plus 10% salicylic acid; ■, 10% sorbitan trioleate plus 10% dimethyl sulphoxide plus 10% salicylic acid; ●, 10% polysorbate 20 plus 10% dimethyl sulphoxide plus 10% salicylic acid; ▲, 10% polysorbate 40 plus 10% dimethyl sulphoxide plus 10% salicylic acid; ▼, 10% polysorbate 60 plus 10% dimethyl sulphoxide plus 10% salicylic acid; ○, 10% dimethyl sulphoxide plus 10% salicylic acid; and □, 10% salicylic acid.
(b) Effect of poloxamer and polyoxyethylene surfactants on percutaneous absorption of salicylic acid in the presence of dimethyl sulphoxide. △, 10% poloxamer 182 plus 10% dimethyl sulphoxide plus 10% salicylic acid; ▽, 10% poloxamer 184 plus 10% dimethyl sulphoxide plus 10% salicylic acid; ■, 10% poloxamer 231 plus 10% dimethyl sulphoxide plus 10% salicylic acid; ●, 10% polyoxyethylene (2) oleyl ether plus 10% dimethyl sulphoxide plus 10% salicylic acid; ▲, 10% polyoxyethylene (4) lauryl ether plus 10% dimethyl sulphoxide plus 10% salicylic acid; ▼, 10% polyoxyethylene (20) oleyl ether plus 10% dimethyl sulphoxide plus 10% salicylic acid; ○, 10% dimethyl sulphoxide plus 10% salicylic acid; and □, 10% salicylic acid. From Shen *et al.* [148] with permission.
(c) Blood concentrations of salicylic acid following application of four different ointments to the cheek pouch of the hamster. ○ absorption ointment, ● hydrophilic ointment, ◑ macrogol ointment, ◐ white petrolatum. Each symbol represents the mean of five determinations with different animals. Bars indicate the standard error.
The formulation of the ointments is given below

| | Absorption ointment | Hydrophilic ointment | Macrogol ointment | White petrolatum |
|---|---|---|---|---|
| White petrolatum | 40.0 | 25.0 | — | 98.0 |
| Cetyl alcohol | 18.0 | — | — | — |
| Stearyl alcohol | — | 22.0 | — | — |
| Hexadecyl alcohol | — | — | — | — |
| Oleyl alcohol | — | — | — | — |
| Lanolin | — | — | — | — |
| Beeswax | — | — | — | — |
| Sorbitan monooleate | 5.0 | — | — | — |
| Sorbitan monostearate | — | — | — | — |
| Propylene glycol | — | 12.0 | — | — |
| Sodium lauryl sulphate | — | 1.5 | — | — |
| Macrogol 400 | — | — | 49.0 | — |
| Macrogol 4000 | — | — | 49.0 | — |
| Salicylic acid | 2.0 | 2.0 | 2.0 | 2.0 |

From Tanaka *et al.* [149].

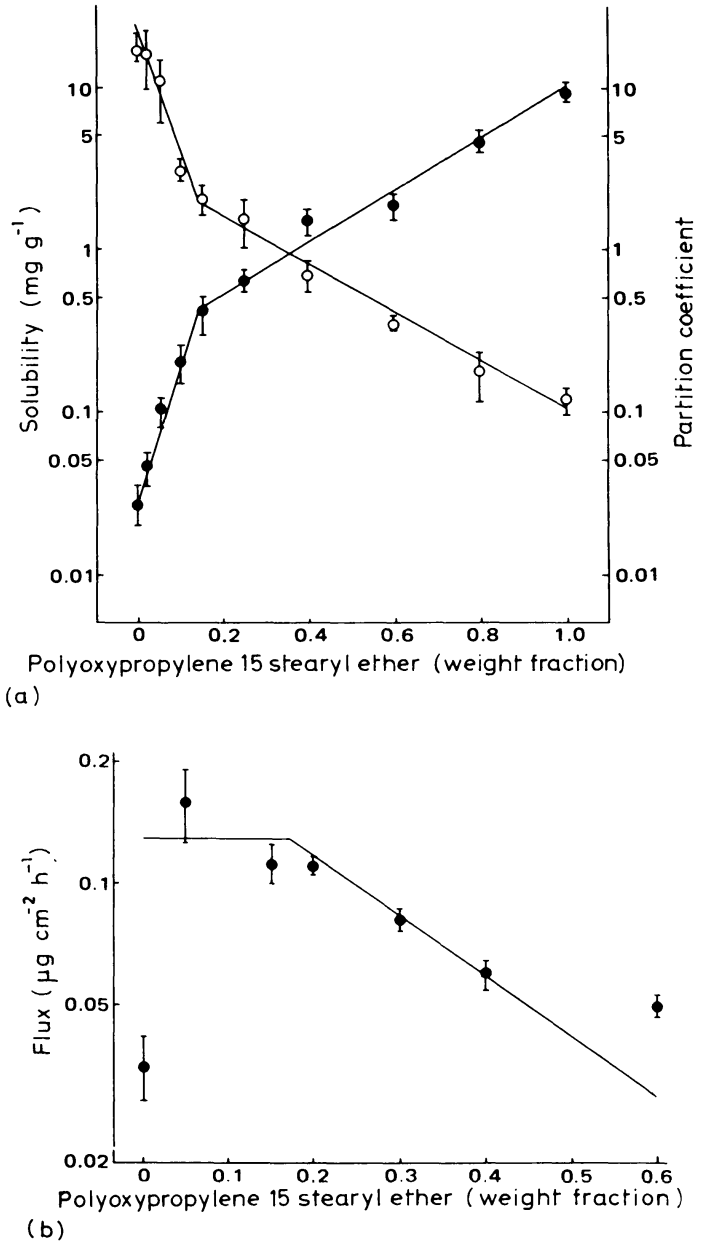



**Figure 7.34** (a) Solubility and partition coefficients of diflorasone diacetate as a function of the weight fraction of polyoxypropylene (15) stearyl ether in mineral oil; average (± S.D.) of four determinations. ●, solubility, and ○, partition coefficient. (b) Steady-state flux of 0.05% $^{3}$H-diflorasone diacetate formulations containing various weight fractions of polyoxypropylene (15) stearyl ether in mineral oil. The solid line was generated using Equation 7.33. The points are experimental values obtained from penetration studies. From Turi *et al.* [150] with permission.

The concentration of dissolved diflorasone diacetate, $C_F$, the partition coefficient, $P_s$ and possibly the resistance, $R_s$, are influenced by the quantity of solvent or surfactant in a given vehicle. Under certain conditions, the solubility of

a drug in a co-solvent system can be represented by the following expression:

$$C_F = C_0 \, e^{\alpha(f_s)} \tag{7.35}$$

where $C_0$ is the solubility of the drug in the formulation when the weight fraction of the solvent is zero, $\alpha$ is a constant, and $f_s$ is the weight fraction of the solvent.

In a similar manner, the partition coefficient of a drug between the skin and the vehicle can be expressed as:

$$P_s = P_0 \, e^{-\beta(f_s)}, \tag{7.36}$$

where $P_0$ is the partition coefficient of the drug between the skin and the vehicle when the weight fraction of the solvent is zero and $\beta$ is a constant. Inserting Equations 7.35 and 7.36 into Equation 7.34 leads to

$$-\frac{dC_F}{dt} = \frac{[P_0 \, e^{-\beta(f_s)}]\,[C_0 \, e^{-\alpha(f_s)}]}{V_F R_s}. \tag{7.37}$$

During the steady state period of penetration, the following relationship is valid:

$$V_R \frac{dC_R}{dt} = -\frac{V_F dC_F}{dt}, \tag{7.38}$$

where $C_R$ is the concentration of diflorasone diacetate in the receptor compartment of the diffusion apparatus and $V_R$ is the volume of the receptor compartment.

Equation 7.38 states that the amount of diflorasone diacetate leaving the vehicle per unit time is equal to the amount entering the receptor solution of the diffusion apparatus. With this relationship, Equation 7.37 can be written as:

$$V_R \frac{dC_R}{dt} = \frac{[P_0 \, e^{-\beta(f_s)}]\,[C_0 \, e^{\alpha(f_s)}]}{R_s}. \tag{7.39}$$

Integration of Equation 7.39 gives

$$Q_R = \frac{1}{R_s}[P_0 \, e^{-\beta(f_s)}]\,[C_0 \, e^{\alpha(f_s)}]\,t \tag{7.40}$$

where $Q_R$ is the amount of diflorasone diacetate in the receptor compartment at time $t$. Equation 7.40 predicts that the addition of a solvent to a formulation could increase, decrease, or have no effect on the amount of drug diffusing through the skin. The result depends on the magnitudes of $\alpha$ and $\beta$ and whether or not the drug solution is saturated or unsaturated.

Consideration of Equation 7.33 shows immediately that the vehicle has an influence on the absorption of the drug; if the vehicle is changed so that the drug becomes less soluble in it, $P$ increases so that permeability increases. The vehicle is more dominant in topical therapy than in most routes of administration because the vehicle remains at the site, although not always in an unchanged form. Evaporation of water from the base would leave drug molecules immersed in the oily phase. Oil-in-water emulsion systems may invert to water-in-oil systems,

such that the drug would have to diffuse through an oily layer to reach the skin. Non-volatile components of the formulation increase in concentration as the volatile components are driven off; this may alter the state of saturation of the drug and hence its activity. Drug may precipitate due to lack of *remaining solvent.* These changes mean that theoretical approaches very much represent the ideal case.

The thermodynamic activity of the drug is obviously the determinant of biological activity. If the solubility of the drug in the base is increased by addition of propylene glycol then its partition coefficient towards the skin is reduced. On the other hand, the increasing amount which can be incorporated in the base is an advantage and the concentration gradient is increased. It is apparent that there is an optimum amount of solubilizer. The optimum occurs at the level of additive which just solubilizes the medicament. Addition of excess results in desaturation of the system, and therefore a decrease in thermodynamic activity.

Other aspects of formulation such as the nature of the binary or ternary vehicle (oil–surfactant, water–surfactant or oil–water–surfactant, respectively) have been considered recently [151]. Addition of polysorbate 80 to the aqueous phase has no significant effect on the epidermal transport of ethanol, but a significant reduction in the transport of the less soluble octanol results, in line with the arguments presented above; in isopropyl myristate, octanol transport is not affected by the solubilizer while that of ethanol is decreased. In the ternary systems identified in Fig. 7.35, the results in Table 7.14 were obtained indicating a general decrease in permeability constants for ethanol, butanol and octanol. The viscosity of the vehicles was not a factor although this varied from 1 to $39 \times 10^3$ cP. In the ternary systems a surfactant will distribute itself between the aqueous and non-aqueous phase; quantitative prediction of permeation is made difficult even with data on the transport properties of the permeants in the individual phase. The results indicate that the percutaneous absorption of the

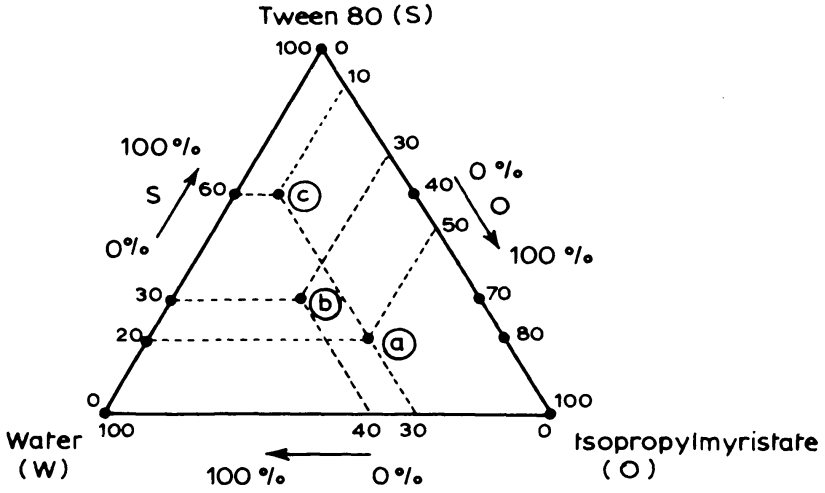



**Figure 7.35** Phase diagram of the isopropylmyristate, polysorbate 80, water system. From Garcia *et al.* [151].

**Table 7.14** Epidermal permeability constants for three alkanols in ternary vehicles

| | $K_p$ (cm h$^{-1}$ × 10$^3$) | | |
|---|---|---|---|
| *Alcohol* | a | b | c |
| Ethanol | 1.8 ± 0.36 | 1.4 ± 0.13 | 1 ± 0.3 |
| Butanol | 3.6 ± 0.21 | 3.5 ± 1.2 | 1.1 ± 0.12 |
| Octanol | 0.1 ± 0.02 | 0.1 ± 0.02 | 0.01 ± 0.001 |

a, b, c as in Fig. 7.35.
From [151].

alcohols from these two-phase mixtures is a function of their affinity for the aqueous phase in contact with the stratum corneum.

Non-ionic surfactants affect the local anaesthetic intensity and duration of tetracaine when present at 5% levels in a vehicle containing propylene glycol (10%) [152]; corroborative results on bupivacaine have been published [153] indicative of increased penetration of the anaesthetic (Table 7.15). However, an increased toxic response was observed due both to increased drug levels in the tissues and to the vasodilating effect of the surfactant (a $C_{12}$ polyoxyethylene ether). The surfactant increased the toxicity of bupivacaine when administered together into the trachea or the bladder of rabbits. The somewhat complicated relationship between solubility and toxicity in the bladder is demonstrated by the finding that racemic bupivacaine with a higher solubility than the D(+) and L(−) isomers does not precipitate in the bladder and is consequently absorbed to a greater extent.

**Table 7.15** Topical anaesthesia in man by application of test solutions on the medial part of the upper lip. The maximal pain thresholds are expressed in per cent of the normal pain thresholds (NaCl) of the individual volunteers ($n = 6$.)

| Compound | Concentration (%) | Pain threshold (%) | Duration of anaesthesia (min) ($\bar{x}$ ± S.E.M.) |
|---|---|---|---|
| Surfactant (SA) | 1.0 | 100 ± 12 | < 5 |
| Bupivacaine | 1.0 | 130 ± 9 | 8 ± 3.1 |
| Bupivacaine | 2.0 | 175 ± 10 | 18 ± 4.4 |
| Bupivacaine + SA | 2.0 + 0.25 | 190 ± 8 | 22 ± 3.2 |
| Bupivacaine + SA | 2.0 + 0.50 | 190 ± 14 | 28 ± 3.6 |
| Bupivacaine + SA | 2.0 + 1.0 | 270 ± 19 | 41 ± 6.4 |
| Tetracaine | 2.0 | 250 ± 16 | 58 ± 7.4 |
| NaCl | 0.9 | 100 | — |

From [153].

## 7.4.5 Surfactants and corneal permeability

Marsh and Maurice [154], in their paper on the influence of non-ionic detergents on human corneal permeability, list previous attempts at increasing corneal

penetration by application of surfactants, dating back to 1942. Ionic surfactants increase drug penetration in both man and animals [155–160] and in studies on non-ionic detergents [158–162], polysorbate appeared to be the most effective agent. As with many of the studies we have discussed, the range of studies of the surfactants was too wide to allow a better understanding of the processes involved. Marsh and Maurice [153], however, have attempted to relate the HLB of the surfactant to the corneal permeation of fluorescein in human subjects. No clear relationship with HLB was adduced although surfactants with HLB values in the range 16 to 17 including polysorbate 20 and Brij 35 caused the greatest increase in permeability, Myrj 52 had little effect in spite of an HLB value in this range, Brij 58 was also effective but caused 'alarming epithelial changes' [154]. The concentration dependency of the effect of polysorbate 20 and Brij 35 are shown in Fig. 7.36. Both substances are non-irritating to the rabbit eye [163]. Maximum comfortable levels are shown in Fig. 7.36.

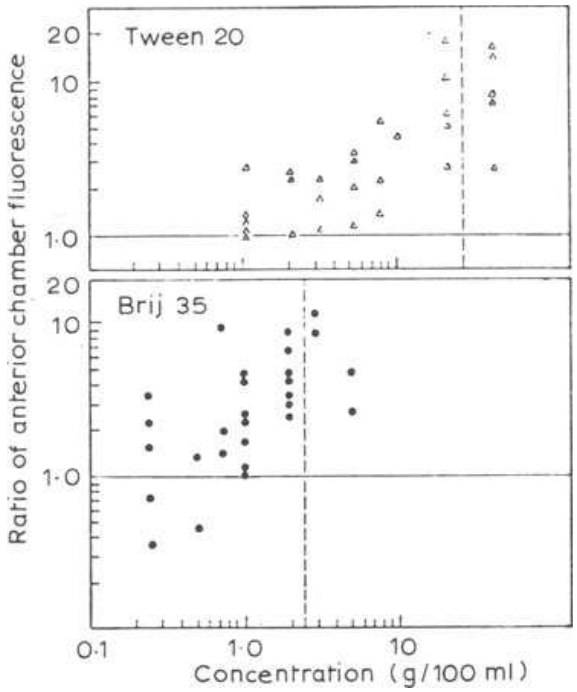



**Figure 7.36** Effect of concentration of surfactants, HLB 16-17, on penetration of fluorescein from 1 drop into the anterior chamber of the eye. Ordinate: Log ratio of fluorescein in experimental aqueous humour to that in control. Vertical line: maximum comfortable concentration. From Marsh and Maurice [154] with permission.

## 7.5 Miscellaneous formulations and the influence of surfactants

Evidence for increased transport of $^{14}$C-labelled nitrogen mustard *N*-oxide through rat ascites hepatoma cell membranes by polysorbate 80 [164] and the recent observation that this surfactant can increase methotrexate uptake into the brain [82a] gives rise to hope that surfactants can play a useful role in modification of drug action in specialized forms of treat-

ment. This is a largely unexplored field. This finding of enhanced entry of anticancer drugs into tumours is a clear indication of the influence of solubilizer but the solubilizer may have other effects which might preclude their use in medicines. At least one should be aware of the potential. Especially is this true in biochemical and pharmacological experiments when disregard of the surfactant's potential for altering pharmacological response is scientifically dangerous. As an example one can cite several papers which have discussed the difficult problem of formulating $^{9}\Delta$-tetrahydrocannabinol (THC), a very lipid-soluble molecule with a high octanol/water partition coefficient [165]. A mixed solvent system of ethanol, polyoxyethylated non-ionic surfactant, and physiological saline (5:5:90) previously used for two antineoplastic nitrosoureas [166] was evaluated as a solvent for THC. The utility of the solvent depends on its pharmacological effects in the test system and the results seemed equivocal. The more detailed study of Roth and Williams [165], in particular in relation to the interaction of THC with specific receptor sites or membrane components and the effect of solubilizers on this is valuable. The membrane/solvent partition coefficient of the THC was reduced to almost zero at levels of cremophor EL of 0.4 mg ml$^{-1}$, the effects of polysorbate 80 being qualitatively similar. Ethanol also decreased the partition coefficient but at 5% v/v the reduction was not as significant. Membrane concentrations of the THC are estimated to be considerably reduced by the presence of solubilizers although this effect can be compensated to some extent by the increased concentrations that can be applied. Nevertheless the conclusion reached by Roth and Williams [165] was that the use of solubilizers to increase the water solubility of THC did not increase the membrane concentration to levels in excess of those which would occur in the absence of solubilizer; the only apparent advantage of adding solubilizer was 'to decrease the loss by adsorption of THC on to glassware and other apparatus!' At least one recent paper [167] has acknowledged the potential biological problems with solubilizing agents and reports ethanol as a substitute in an examination of THC on contractions of the isolated rat vas deferens.

The manner in which the formulation of THC affects the biological performance has been examined by two groups [168, 169]. Polysorbate 65–sorbitan monolaurate mixtures appeared to confer a longer duration of action by the intraperitoneal or subcutaneous route when compared with a PVP suspension and polysorbate 80 dispersion. Contrary to these findings, Sofia *et al.* [169] find 1% polysorbate 80 to be a poor vehicle for oral, s.c., i.p. or i.v. administration producing inadequate results when compared to a PVP dispersion or a dispersion in propylene glycol. The most suitable vehicle did, however, contain 1% polysorbate. The divergent opinion no doubt arises from the fact that the preparations are dispersions or emulsions and their mode of manufacture differs from laboratory to laboratory. Particle size and stability will thus vary.

Propylene glycol and 20% Cremophor EL have been compared as vehicles for diazepam [170] in view of the number of reports of thrombophlebitis associated with intravenous diazepam. The Cremophor vehicle caused significantly less post-injection thrombophlebitis possibly because it prevents the precipitation of the drug substance at the site of injection by its solubilizing effect. Ease of injection

was also improved owing to the lower viscosity of the aqueous Cremophor (Table 7.16). These are relevant factors in the choice of a formulation and can override advantages which might be gained in drug absorption.

It is often assumed that drug solutions must be the most bioavailable form of the drug, but solutions of drugs poorly soluble at tissue pH will precipitate at the site of injection and subsequently release from the site might be slow. Precipitation may also occur if the drug is solubilized in a mixed solvent. In the presence of surfactant, as solubility is in most cases a linear function of surfactant

**Table 7.16(a)** Frequency (%) of thrombophlebitis after i.v. diazepam dissolved in propylene glycol or Cremophor EL

| Complication | Propylene glycol (right hand) | Cremophor (right hand) | Other anaesthetic agents (left hand) |
|---|---|---|---|
| Swelling | | | |
| None | 80.0 | 93.3 | 95.2 |
| Moderate | 20.0 { 8.9 | 6.7 { 6.7 | 4.8 { 3.8 |
| Marked | 20.0 { 11.1 | 6.7 { 0 | 4.8 { 1.0 |
| Erythema | | | |
| None | 86.7 | 98.3 | 96.1 |
| Moderate | 13.3 { 8.9 | 1.7 { 1.7 | 3.9 { 2.9 |
| Marked | 13.3 { 4.4 | 1.7 { 0 | 3.9 { 1.0 |
| Phlebitis | | | |
| None | 37.8 | 96.6 | 91.3 |
| Moderate | 62.2 { 17.8 | 3.4 { 1.7 | 8.7 { 6.7 |
| Marked | 62.2 { 44.4 | 3.4 { 1.7 | 8.7 { 2.0 |

**(b)** Symptoms after i.v. injection of diazepam dissolved in propylene glycol or Cremophor (%)

| Pain or functional disturbance | Propylene glycol (right hand) | Cremophor (right hand) | Other anaesthetic agents (left hand) |
|---|---|---|---|
| None | 34.1 | 91.5 | 91.4 |
| Moderate | 65.9 { 34.1 | 8.5 { 6.8 | 8.6 { 4.8 |
| Severe | 65.9 { 31.8 | 8.5 { 1.7 | 8.6 { 3.8 |

**(c)** Ease of injection of diazepam dissolved in propylene glycol or Cremophor (%)

| Solvent | *n* | Good | Fair | Poor |
|---|---|---|---|---|
| Propylene glycol | 82 | 35.4 | 37.8 | 26.8 |
| Cremophor | 97 | 62.9 | 32.0 | 5.1 |

From [170].

concentration, precipitation should not occur, although it will occur if the surfactant is diluted to below its CMC. A comparison of plasma levels achieved by two commercial formulations of diazepam (available in Finland) showed that diazepam solubilized in cremophor EL (Stesolid$^{R}$) produced peak levels twice those produced by a formulation in propylene glycol (Diapam$^{R}$) which is the same solvent as used in Valium$^{R}$ injection (Fig. 7.37) [171].

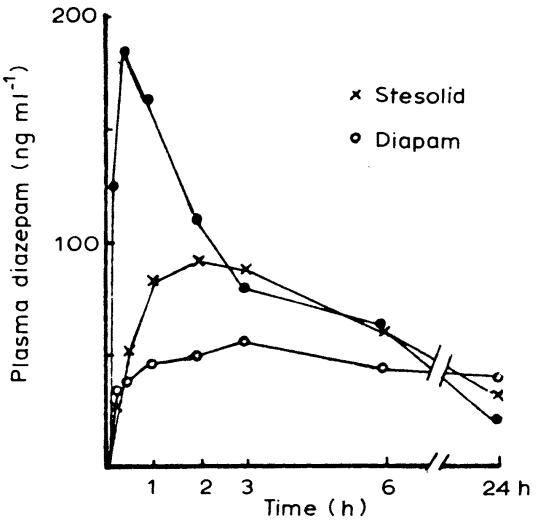



**Figure 7.37** Plasma diazepam levels following intramuscular administration of diazepam; ○ in propylene glycol vehicle; × in a Cremophor EL vehicle compared with ● intravenous administration of the propylene glycol preparation. From Kanto [171] with permission.

## 7.6 Surfactants and antibacterial activity

As surfactants alter the permeability of mammalian cells it is not too surprising that, in spite of the differences between bacterial cell walls and mammalian cell membranes, some surfactants have the ability to increase the permeability of the bacterial cell wall or to act synergistically with antibacterial agents. There are several unique facets to discussion of this topic; some surfactants have antibacterial properties and some antibacterial agents have surface-active properties. In considering the subject one has to be aware, as before, of surfactant antibacterial interactions, the influence of surfactant on the performance of the dosage form or formulation, and surfactant–cell wall interactions.

Thus the antimicrobial effectiveness of the range of substances presented in Fig. 7.38a and b at a range of surfactant concentration will not be a simple function. The inactivation that occurs is frequently preceded at lower concentrations by an enhancement of activity. This is brought out well in Fig. 7.38a and b.

Since Dubos and Davis [174] first recommended the use of a polysorbate–albumin medium for cultivation of tubercle bacilli there have been a number of reports on the effect of these compounds on antibacterial activity. Reduction in activity has been pointed out by Forrest *et al.* [175], Youmans and

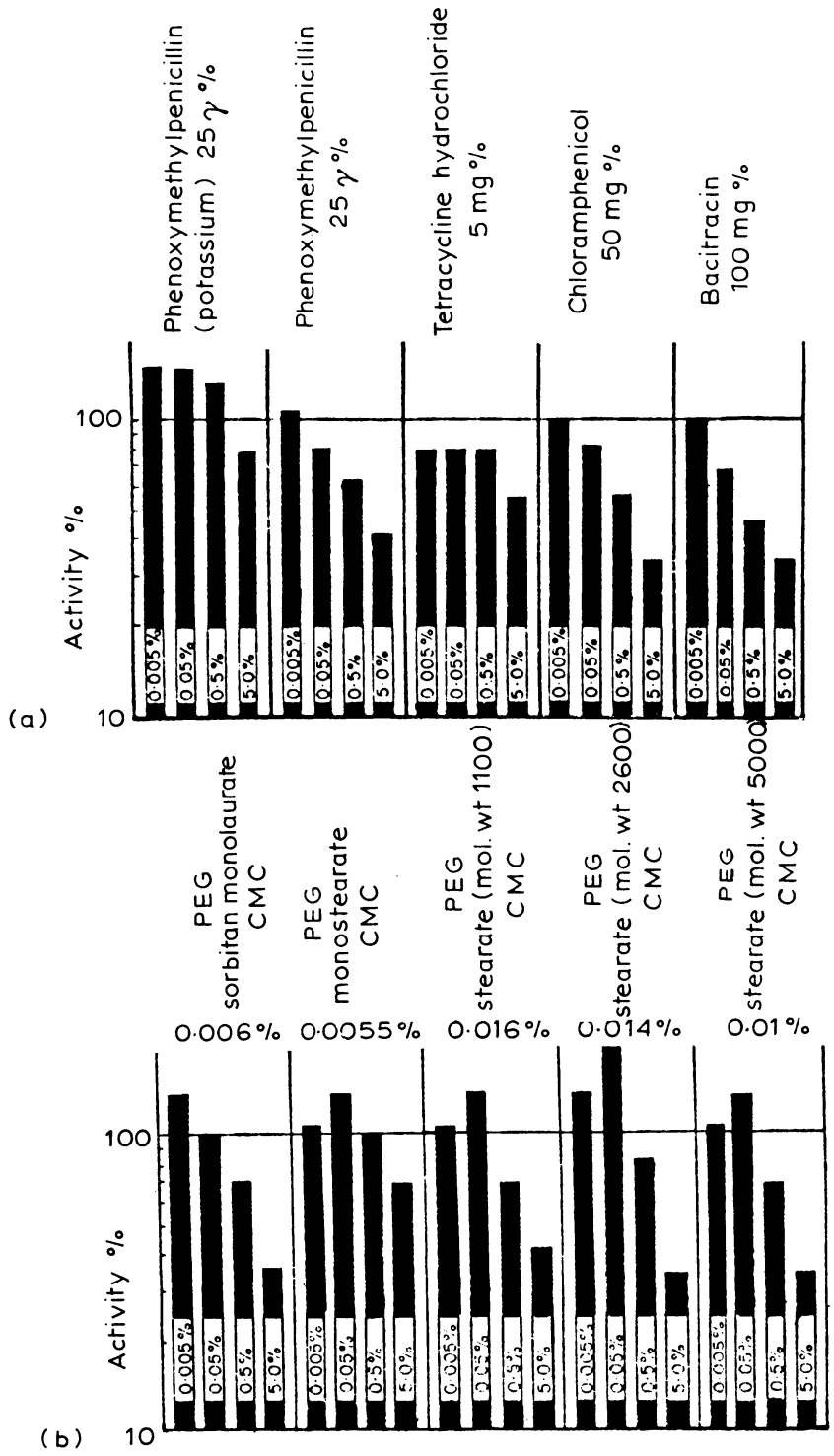



**Figure 7.38** (a) and (b) The effect of non-ionic detergents on the activity of antibiotics as shown by the effect of: (a) polyoxyethylene lauryl ether (CMC 0.011%) on penicillin, tetracycline, chloramphenicol, and bacitracin in concentrations ranging from 0.005 to 5.0%, and (b) the effect of five different non-ionics on the activity of chloramphenicol (50 mg%). The critical micellar concentrations of the detergents are shown [172].

Youmans [176], and Fenner [177]. This inactivation is utilized in microbiological tests where sterility tests are being carried out in the presence of antibacterial agents [174].

Natori [178] found that the addition of 0.05% polysorbate 80 decreased the activity of isoniazid, 4,4′-diaminodiphenylsulphone, oleic acid, and 3-aminobenzofuran, but had no significant effect on streptomycin sulphate. The activity of isoniazid and 4,4′-diaminodiphenylsulphone was, however, reported to be increased by the addition of surfactants under different conditions [176].

The decrease of antibacterial activity caused by the addition of surfactants has been broadly related to solubilization of the antibacterial in the detergent micelles. The apparent increase in solubility in the presence of surfactants, does not exactly parallel the decrease in biological activity. Undoubtedly the effect of the surfactant on bacterial permeability and viability will be one factor causing deviation from strictly mathematical relationships. Correlation of mathematically predicted preservative availability in solubilized and emulsified systems with the measured antimicrobial activity has been attempted by Kazmi and Mitchell [179]. Fig. 7.39 shows some of their results for the bacterial activity of chlorocresol against *E. coli* and theoretical estimates based on an equation relating free bactericide concentration and activity. The difference between the slopes of curves B and C in Fig. 7.39 according to Kazmi and Mitchell suggests that increasing the cetomacrogol concentration may decrease bactericidal activity. This decrease could be due to a stimulation of microbial growth or protection of the organism by the non-ionic surfactant. Although solubilized and emulsified dispersions with the same $D_i$ are equitoxic, the present results indicate that they do not have the same activity as a solution of the preservative in water with the same $D_f$. The antimicrobial activity of chlorocresol in each surfactant solution was less than that of the solution in water. However, increasing the surfactant concentration in the range shown in Fig. 7.39 is not important provided that the concentration of 'unbound' or 'free' chlorocresol is the same.

Others [180] have asserted that theories equating antimicrobial activity to the concentration of non-micellar preservatives are inadequate. Comparison of systems containing benzoic acid with and without surfactant, for their antifungal activity versus *Schizosaccharoryces pombé* at equivalent values of free benzoic acid, demonstrated a significant increase in activity in the presence of surfactant (see Table 7.17). If no synergism between surfactant and antifungal agent occurs then systems containing the same free concentration should have identical activities regardless of total active agent present.

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Figures illustrate the effect of non-ionic detergents on the activity of a range of antibiotics, showing the effect of concentration and of detergent structure on chloramphenicol activity as shown by zone-inhibition assay. Whether this mode of assay bears any relationship to actual conditions *in vivo* is a matter for debate. See also Ullmann and Moser [173].

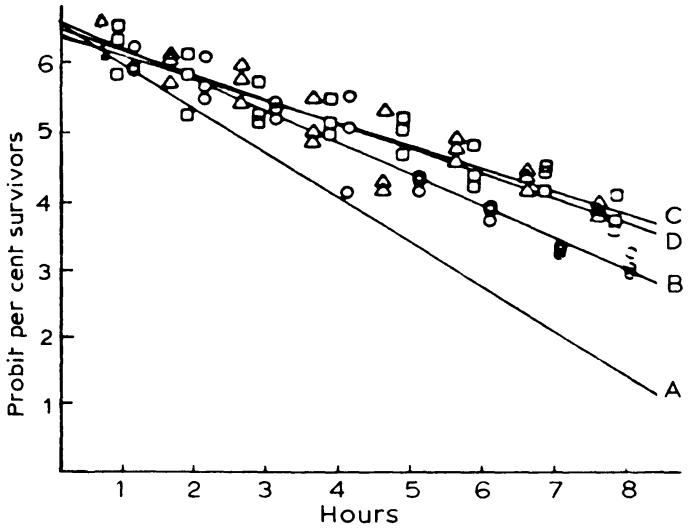


**Figure 7.39** Probit % survivors as a function of time for the bactericidal activity of chlorocresol in aqueous cetomacrogol solutions against *E. coli*. [Cetomacrogol concentration (%)]: A, 0.0; B, ○, 1.0; C, □, 3.0; and D, △, 5.0 [Total preservative concentration, $[D_t]$ (%)]: A, 0.0350; B, 0.1743; C, 0.4528; and D, 0.7314. The initial free preservative concentration, $[D_f]$, = 0.035%. The points are experimental; the lines were fitted using a linear model. The equation

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 t + \beta_5 x_1 t + \beta_6 x_2 t + \beta_7 x_3 t + \varepsilon$$

where $\beta_0$ is the intercept of curve A; $\beta_1$, $\beta_2$, and $\beta_3$ are the differences between the intercepts of curves B and A, C and A, and D and A, respectively; $\beta_4$ is the slope of curve A; $\beta_5$, $\beta_6$, and $\beta_7$ are the differences in slope between curves B and A, C and A, and D and A, respectively; $x$ are the dummy variables where $x_1 = 1$ if curve B and otherwise is zero, $x_2 = 1$ if curve C and otherwise is zero, and $x_3 = 1$ if curve D and otherwise is zero; $\varepsilon$ is a random variable; and $t$ is time. From Kazmi and Mitchell [179] with permission.

Phenylethanol and polysorbate 80 when used in combination with benzalkonium chloride show enhanced activity against *Pseudomonas aeruginosa* [181–183]. Benzalkonium-sensitive cells grown in 0.5% polysorbate 80 appear to have normal cell walls [184]. Resistant cells grown in benzalkonium chloride solutions are also normal, but when grown in the presence of polysorbate 80 (0.02%) or benzalkonium chloride plus polysorbate 80 exhibits evidence of cytoplasmic damage. At high concentrations, polysorbate 80 totally inactivates the antipseudomonal activity of the benzalkonium chloride. At lower concentrations it undoubtedly increases the permeability properties of the cell and enables the benzalkonium to reach its site of action more efficiently. No evidence of synergism between hexadecyl pyridinium chloride or dodecyl pyridinium chloride and a series of non-ionic surfactants against *E. coli* above or below the surfactant CMC, was noted [185].

Polysorbate 80 was found to be more effective as an inactivating medium for hexachlorphene than serum albumin, but the Spans were found to be devoid of inactivating activity [186]. The importance of finding inactivators for hexachlorophene arises because its greatest area of usefulness has been in soaps

**Table 7.17** Comparison of fungicidal activity of benzoic acid systems, with and without surfactant, at the same $[D_w]$*

| Mixture | Exposure time (h) | % survival in replicate determinations | | | | |
|---|---|---|---|---|---|---|
| | | 1¾ | 3½ | 3½ | 1½ | 1¾ |
| | $[D_t]$ | 26.0 mM | 26.0 mM | 26.0 mM | 29.0 mM | 29.0 mM |
| | $[D_w]$ | 13.5 mM | 13.5 mM | 13.5 mM | 15.0 mM | 15.0 mM |
| B Benzoic acid + surfactant | | 12.8 | 0.8 | 0.1 | 0.04 | 0.09 |
| | | 12.7 | 0.7 | 0.1 | 0.07 | 0.02 |
| | | 13.1 | 0.8 | 0.2 | 0.00 | 0.1 |
| | | 11.2 | 0.9 | 0.1 | 0.03 | 0.09 |
| | | 15.3 | | | 0.00 | 0.07 |
| | Mean | 13.0 | 0.8 | 0.1 | 0.03 | 0.07 |
| | $[D_t] = [D_w]$ | 13.5 mM | 13.5 mM | 13.5 mM | 15.0 mM | 15.0 mM |
| C Benzoic acid alone | | 24.9 | 5.3 | 0.2 | 0.6 | 2.8 |
| | | 23.4 | 7.5 | 0.2 | 0.9 | 3.2 |
| | | 27.2 | 6.3 | 0.2 | 0.4 | 3.0 |
| | | 26.1 | 7.5 | | 0.4 | 2.5 |
| | | | 3.8 | | 0.5 | 2.8 |
| | Mean | 25.4 | 6.1 | 0.2 | 0.6 | 2.9 |

Saturation solubility, $C_s$ (benzoic acid) in N/1000 HCl = 26.5 mM. $C_s$ (benzoic acid) in 2% w/v surfactant = 51.0 mM.* $[D_w]$ is the concentration of benzoic acid in non-micellar phase.
From [180].

and shampoos, and the consequent need to test their efficacy. Inactivation prevents false results caused by the retention of the bactericide on the bacterial cell.

An apparent potentiation of hexachlorophene by polysorbate 80 in high concentration in a hydrophilic ointment base, observed by a zone-inhibition method, agrees with the finding of Berthet [187] that the ionic Aerosol OT in a concentration of 1:2000 increased the phenol coefficient of hexachlorophene four-fold. However, the two concentration levels are different and the method of testing different. It is dangerous to rely on one method alone. The surface-active agents may, in some way, facilitate the diffusion of the antibacterial agent through the agar, yet in solution may solubilize it and reduce its activity. It is safe to assert that most drugs act in solution, so the agar plate method would give a misleading indication of surfactant effect. Certainly Anderson and Morgan [188] observed that their agar plate diffusion results for hexachlorophene–non-ionic surfactant systems bore no relationship to their solubilization or dialysis data. Attempts to determine minimum inhibitory concentrations of hexachlorophene in the presence of solubilizing agents have been prevented by the interaction of the surfactants with both components [188].

In actual use antibacterial agents will be lost from the system by interaction with bacteria, skin, foreign substances and the 'capacity' of the system to compensate for such losses has to be considered. In a solubilized system the 'capacity' would depend on the degree of saturation of the system or more precisely the change in total saturation of the system as a function of the saturation of the aqueous phase [188]. Anderson and Morgan have attempted to measure this by applying the results of dialysis experiments (Fig. 7.40). From this diagram it can be seen that if a saturated solution of hexachlorophene in 1% macrogol at pH 8 is used under conditions when the phenol is being lost, a fifth of the phenol can be removed and the residual activity is equivalent to that of an aqueous solution 85 to 90% saturated with respect to hexachlorophane; on the other hand, a similar loss of a fifth of the total phenol from a saturated solution of 1% Brij 35 reduces the activity to that of a 60% saturated aqueous solution. The uptake of antibacterial agents has been quantified. Hugo and Newton [189] when comparing the uptake of iodine by micro-organisms and serum from an iodide solution and an iodophor, found that there was a greater uptake of iodine from the former (see Fig. 7.41) which suggested that the iodine may 'be absorbed from the cetomacrogol system in the form of a complex, or that there is a greater affinity of the iodine for the cetomacrogol than for the ethanol–potassium iodide solution'. Interfacial tension will also play a part, as Freundlich considered that adsorption is greatest where the interfacial tension between solvent and substrate is high. The surfactant, of course, lowers the interfacial tension.

The uptake of hexylresorcinol by *E. coli* in the presence and absence of cetomacrogol exhibits the same trend as the uptake of iodine from aqueous solution and surfactant mixtures, with a marked reduction in the presence of detergent [190]; the rate of uptake is not affected. Beckett *et al.* [190] consider that the phenol–cetomacrogol complex probably prevents cell-wall penetration. The amount of hexylresorcinol bound per organism is less than the theoretical

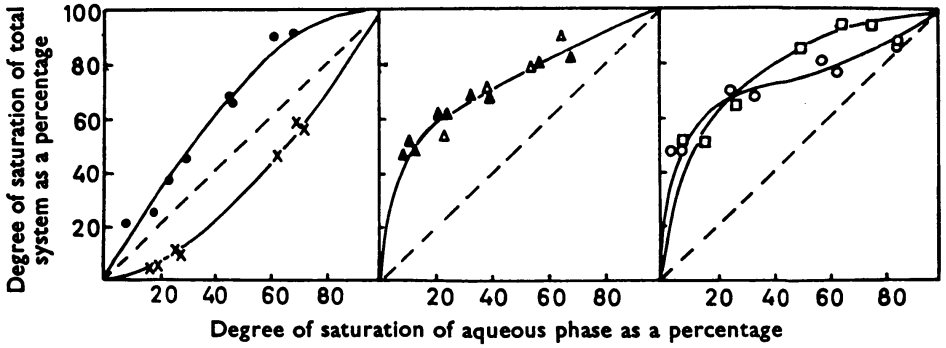


**Figure 7.40** Distribution of hexachlorophene in solutions of various agents in aqueous 0.05M *tris* buffer, pH 8.0 at 25° C. ○, sucrose laurate 1%. □, polysorbate 20 1%. △, lauromacrogol 0.1%. ▲, lauromacrogol 1%. ×, macrogol 1%. ●, poloxamer 188 1%. Lauromacrogol = Brij 35; macrogol = PEG 4000; sucrose laurate = sucrose monolaurate; poloxamer 188 = Pluronic F68.
From Anderson and Morgan [188] with permission.

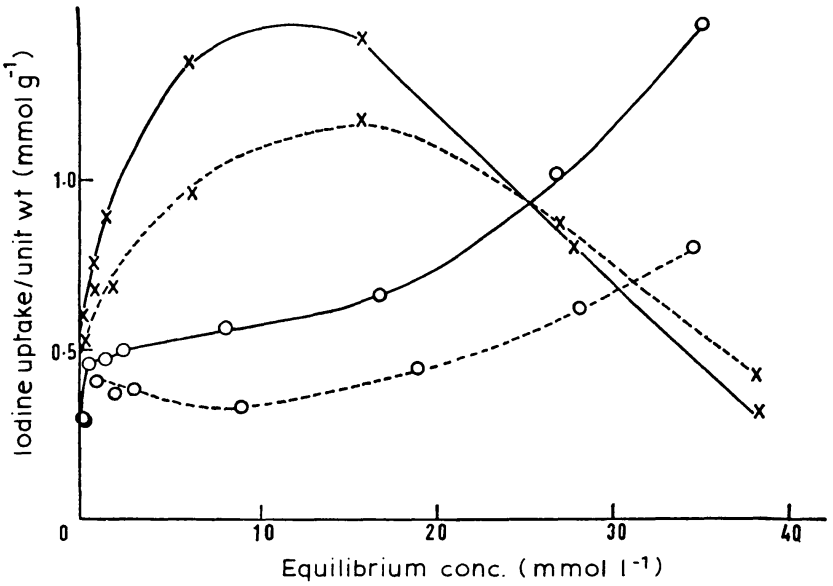


**Figure 7.41** Adsorption isotherms for the uptake of iodine by *E. coli* (—) and *Staph. aureus* (- - -) from iodine formulations, after 5 h. *E. coli*, dry weight 2690 $\mu g\,ml^{-1}$ for iodine solution and 3190 $\mu g\,ml^{-1}$ for the iodine : cetomacrogol complex. *Staph. aureus*, dry weight 3430 $\mu g\,ml^{-1}$ for iodine solution and 3060 $\mu g\,ml^{-1}$ for the iodine : cetomacrogol complex. × Iodine solution. ○ Iodine : cetomacrogol complex (iodophor). From Hugo and Newton [189] with permission. Similar differences were obtained from the adsorption isotherms when the substrate was yeast or serum [189].

amount required to form a monomolecular layer around the organism in the absence of additive. It is possible [191] that hexylresorcinol becomes bound to the bacteria in the presence of excess cetomacrogol (i.e. in micellar solutions) in the form of a phenol–non-ionic complex. When cationic antibacterials or cationic surfactant antibacterials such as cetyl pyridinium chloride are involved, the anionic groups on the surface of most cells will be implicated in the antibacterial surfactant–cell interaction [192]. In yeast suspensions at pH values between 3.5 and 6.0 the cationic surfactants cetrimide and cetyl pyridinium chloride have strong cytolytic effects above certain critical concentrations. Sodium dodecyl sulphate, on the other hand, was only cytolytically active below pH 3.2 [193]. However, the strong binding of surfactant cations by the cell surface suggests that van der Waals' interactions were also operative between the surfactant alkyl chains and hydrophobic groups on the cell surface.

Riemersma [192] suggests that phosphate groups belonging to phosphoinositides, phosphatidic acid and other anionic lipids were involved in the ionic interaction of the surfactant head groups while the alkyl chain actually penetrated the membrane bilayer. At a certain concentration the membrane would form 'mixed micelles' with the surfactant cations leading to higher permeability and cytolysis. However, both anionic and cationic surfactants induce lysis and their mode of action cannot be identical. Bradford *et al.* [194] examining the solubilization of microsomal constituents observed that both CTAB and

deoxycholate solubilized membrane protein, cholesterol phospholipid and an enzyme in a similar manner, protein and cholesterol solubilization occurring at a critical surfactant concentration (Fig. 7.42).

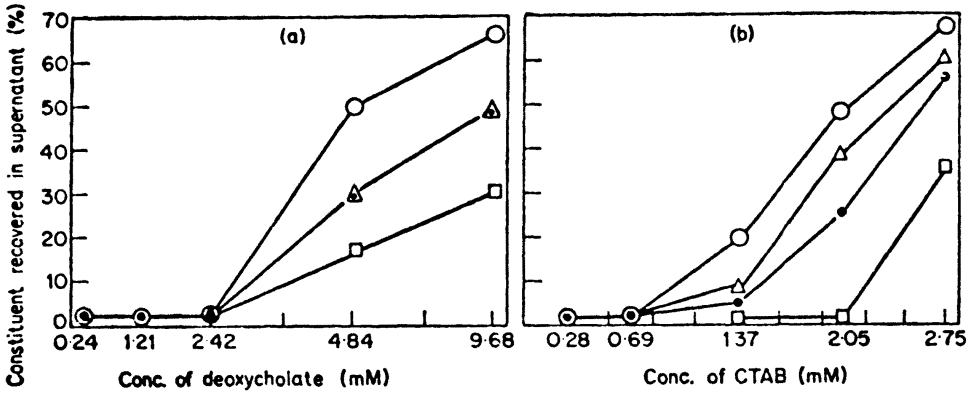


**Figure 7.42** Solubilization of microsomal constituents by increasing concentrations of: (*a*) deoxycholate (*b*) cetyltrimethylammonium bromide; Protein (○), cholesterol (△), phospholipid phosphorus (●), and $Na^+$-ion-stimulated adenosine triphosphatase (□). Diagrams show the percentage of this constituent in the supernatant of the microsomal suspensions after treatment, as described by Bradford *et al.* [194].

In relation to surfactant influences on antibacterial activity some information is required on how surfactants will influence antibacterial binding to cell components. Some interactions between surfactants and body components including proteins are discussed in Chapter 10 but here we can consider some of the effects, discussed by Alhaique *et al.* [195], which might be fundamental to our understanding of this complex problem. They had found [196] that an allosteric transition could be easily effected by reaction of surfactant monomers with a protein in the presence of a ligand, chloramphenicol. The interaction of the anionic detergent, NaDS, with the protein resulted in an increase in the free antibiotic; in diffusion experiments this complex interaction was paralleled by an increase in the transfer rate of the antibiotic [197]. NaDS and CTAB both increase the amount of chloramphenicol bound to an albumin–lecithin complex when present in concentrations below their CMCs; polysorbate has little effect (see Fig. 7.43). This is most likely to be due to the surfactant causing the dissociation of the protein–phospholipid complex into surfactant–phospholipid and serum–albumin–surfactant complexes each capable of bonding the antibiotic to a greater extent than the original complex. As polysorbate 80 had negligible effects on ligand binding the dissociative process must be associated with adsorbed surfactant ions. Such interactions have been shown by Alhaique *et al.* [197] to alter the transport of chloramphenicol across a barrier prepared from aqueous dispersions of phospholipid or phospholipid–albumin complexes. In the latter case permeability coefficients are decreased and lag times increase on addition of low concentrations of NaDS ( $< 1 \times 10^{-7}$ M) CTAB has the same effect and polysorbate 80, none.

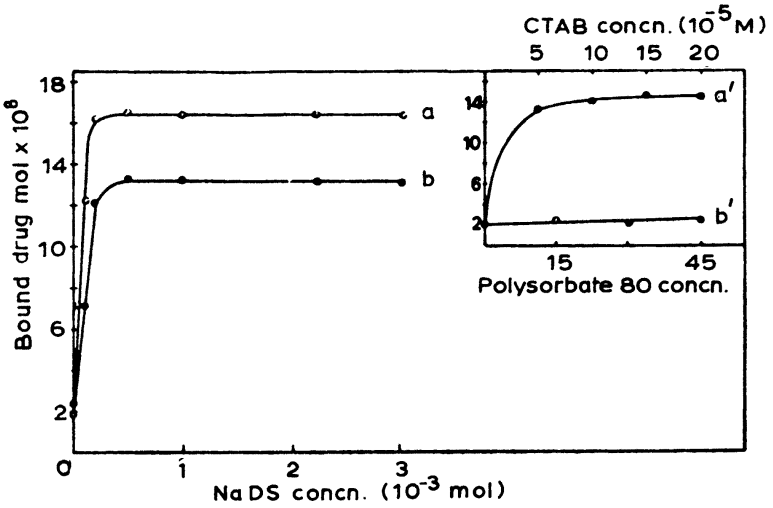


**Figure 7.43** Association curves of chloramphenicol with the albumin–lecithin complex (3% w/v) in phosphate buffer (pH = 6.8) at 25° C, in the presence of increasing amounts of sodium dodecyl sulphate (NaDS). Plots a (○)and b (●) refer to different initial concentrations of the antibiotic, i.e.—$3.1 \times 10^{-5}$ and $6.2 \times 10^{-5}$ M, respectively. Inset. Association curves of chloramphenicol with the albumin–lecithin complex (3% w/v) in phosphate buffer (pH 6.8) at 25° C, in the presence of increasing amounts of surfactants. Plots a′ and b′ refer to cetyltrimethylammonium bromide (●) (CTAB) and polysorbate 80 (○) (concn in mg $ml^{-1} \times 10^2$), respectively. In all cases, the initial concentration of the antibiotic was $3.1 \times 10^{-5}$ M. From Alhaique *et al.* [195] with permission.

While we can observe these and other effects in isolated systems they allow us, at this stage, simply to appreciate the variety of interactions that occur when foreign surfactant molecules insinuate themselves into membranes. We are probably not much further along the road to a complete understanding of the specific proteins or sites that are involved. Nor indeed has sufficient work been done to differentiate one surfactant's effects on a variety of membranes of known composition. The day of prediction is still a long way off.

### 7.6.1 Other observations on interactions of solubilizers and antibacterials

The formation of mixed micelles of quaternary ammonium compounds and non-ionic surfactants has been suggested as a possible mechanism for the association of antibacterials with polysorbate 20 [198], for such an interaction the degree of binding would be expected to increase with increasing length of hydrocarbon chain of the cation below its normal CMC. DeLuca and Kostenbauder [199] deduce that according to the treatment of the process by the law of mass-action, a maximum should occur in the concentration of monomeric long-chain ions as the total surfactant concentration is increased, and they were able to find experimentally a maximum in the adsorption isotherm for the interaction of cetyl pyridinium chloride and 0.2% polysorbate 80 at 30° C. One could regard this process as a form of solubilization where this term is taken to mean 'interaction

with micellar component'. The binding of organic electrolytes by non-ionic detergents is not limited to quaternary ammonium derivatives, as chlorpromazine, promethazine, and tetracine hydrochloride are also bound.

Ansel [200] reported that polyoxyethylene glycols prevent the haemolysis of rabbit erythrocytes by haemolytic concentrations of phenol, *m*-cresol, *p*-chlorophenol. The method is suggested as a means of appraising phenol–PEG interaction in preservative systems. A number of phenols cause leakage of the cell contents of *E. coli*. Judis [201] studying the effect of polysorbate 80 on the release of cell contents caused by the phenolics found further evidence of complexation, as the non-ionic protected the bacterium from the lethal effects of *p*-chloro-*m*-xylenol. This is interesting, as polysorbate is interfacially active and would be expected to promote the release of cell contents if no complex formation took place. Lytic effects of lysophosphatidyl choline (LPC) dispersions were reduced by saturating with progesterone, cholesterol or trioolein [202]. The lytic activity of a mixed LPC–phosphatidyl choline (PC) dispersion is completely abolished by incorporation of progesterone, suggesting that the co-operativity of the mixed micellization reduces the escaping tendency of the LPC reducing its ability to interact with the membrane. Progesterone itself is, in certain concentrations, haemolytic yet mixtures of this steroid with a haemolytic phospholipid can be devoid of such activity. Co-solubilization and mixed micelle formation can thus complicate an already complex picture. The inactivation of preservative esters in surfactant solutions in which other oil substances are solubilized has been investigated. The results are of special relevance in formulation studies. Propyl paraben was most subject to interference. For example, where its effective preservative level in the presence of surfactant is 0.162%, this rises to 1.30% when 2% of isopropyl myristate is solubilized in the same surfactant solution [203].

The results of Matsumoto and Aoki [204] have been recalculated in terms of solubilities in 0.01 M solutions. This presents a picture exactly opposite to the one obtained on a percentage basis (see Fig. 7.44). This evidence should make the selection of a preservative for use in non-ionic systems less empirical. It is suggested that where no information is available for the interaction of the preservative with the detergent the least hydrophobic compound is used to minimize solubilization, or where a compound such as the butyl paraben must be employed a surfactant with a long hydrophilic group is chosen. Often a balance between the two will have to be made.

Chlorobutanol, benzyl alcohol, and phenylethyl alcohol–non-ionic systems have been studied at two temperatures [205], as was the binding of benzoic acid by polyoxyethylene stearates [206]. The latter confirmed that solubilization was greatest in the least hydrophilic surfactant (on percentage basis) and there was no evidence of interaction below the CMC.

The results of Anderson and Slade [207] suggest that hydrogen-ion concentration has little effect on the amount of benzoic acid solubilized. In spite of the fact that they estimate that only one in every 90 ether oxygens in non-micellar glycols are associated with benzoic acid in solution, the authors conclude that solubilization takes place in the PEG region of the micelles.

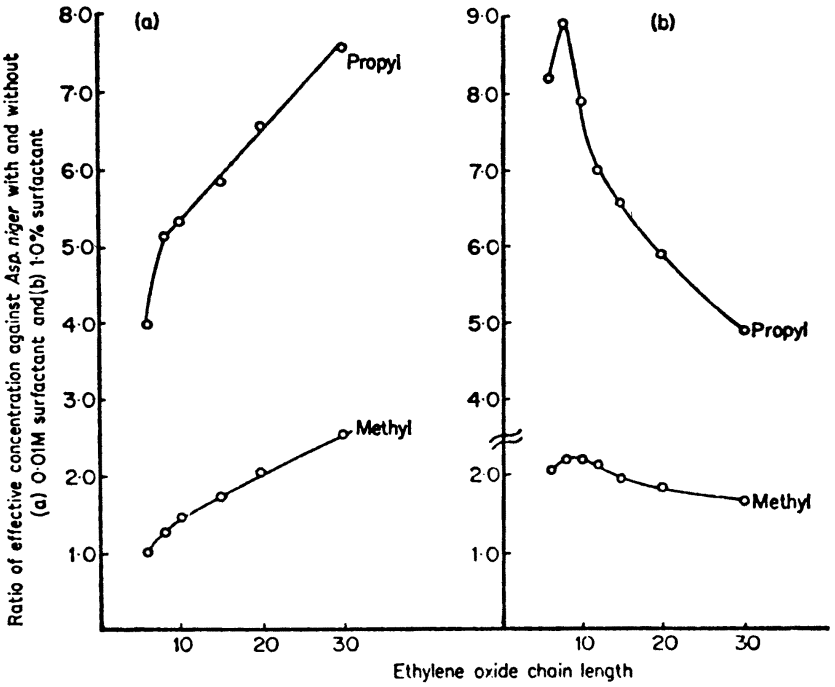


**Figure 7.44** Effect of ethylene oxide chain length on the effective concentrations of the parabens versus *Asp. niger*, shown as a ratio of the concentration with and without surfactant. The results are shown: (a) on a molar basis, and (b) a percentage basis (0.01 M and 1.0% surfactant), respectively. Drawn from data calculated from Matsumoto and Aoki [204].

The increase of solubilization (mole per mole) with increasing glycol chain length may be explained by the fact that the ethylene oxide chains in the micelle form an environment exactly like a concentrated polyoxyethylene glycol solution, and hence the solubility of the solute increases. It remains true, however, that the ratio of solubilizate to ethylene oxide is 0.011 for PEG 3000, whereas it is 0.048 to 0.057 for non-ionics of polysorbate and Myrj and Brij type [207]. It is doubtful if there is a specific interaction. A large increase in the solubility of the paraben esters has been noted in solutions of carboxymethylhydroxyethyl cellulose and PEGs 200 and 400, and inactivation was noted in a bacteriological study. This finding is contrary to earlier investigations which suggested that there was no decrease in activity in the presence of glycols [208, 209]. Bolle and Mirimanoff [210] found that Crills, Spans and Tweens, but not Carbowax 1500 inhibited the activity of antiseptics against *Asp. niger*.

Antibacterial and antifungal agents have been used increasingly in shampoos and skin-cleansing agents. Russell and Hoch [211] have discussed the solubilization of typical materials (3,4,4′-trichlorocarbanilide and diaphene) in surfactant mixtures. The presence of lanolin – a common additive – did not interfere with the solubilization of the bacteriostats and in fact appeared to increase the amount solubilized. The presence of the non-ionics added as solubilizers did not appear to reduce the antibacterial activity of the mixture; indeed, in some cases there is a suspicion of enhanced activity, e.g. 3,4,4′-trichlorocarbanilide solubilized by

Igepal CO-630 in comparison with its activity in polysorbate 80 and Nimcolan 2. Banks and Huyck [212] indeed state that hexachlorophane must be solubilized to produce its maximal germicidal effect.

The problem of inactivation in emulsions and solubilized systems has received much attention; the observation that Millipore filters contain up to 3% of their dry weight of Triton X-100 [213], and the fact that these are used to filter solutions containing bacteriostats shows that the subject has many manifes-

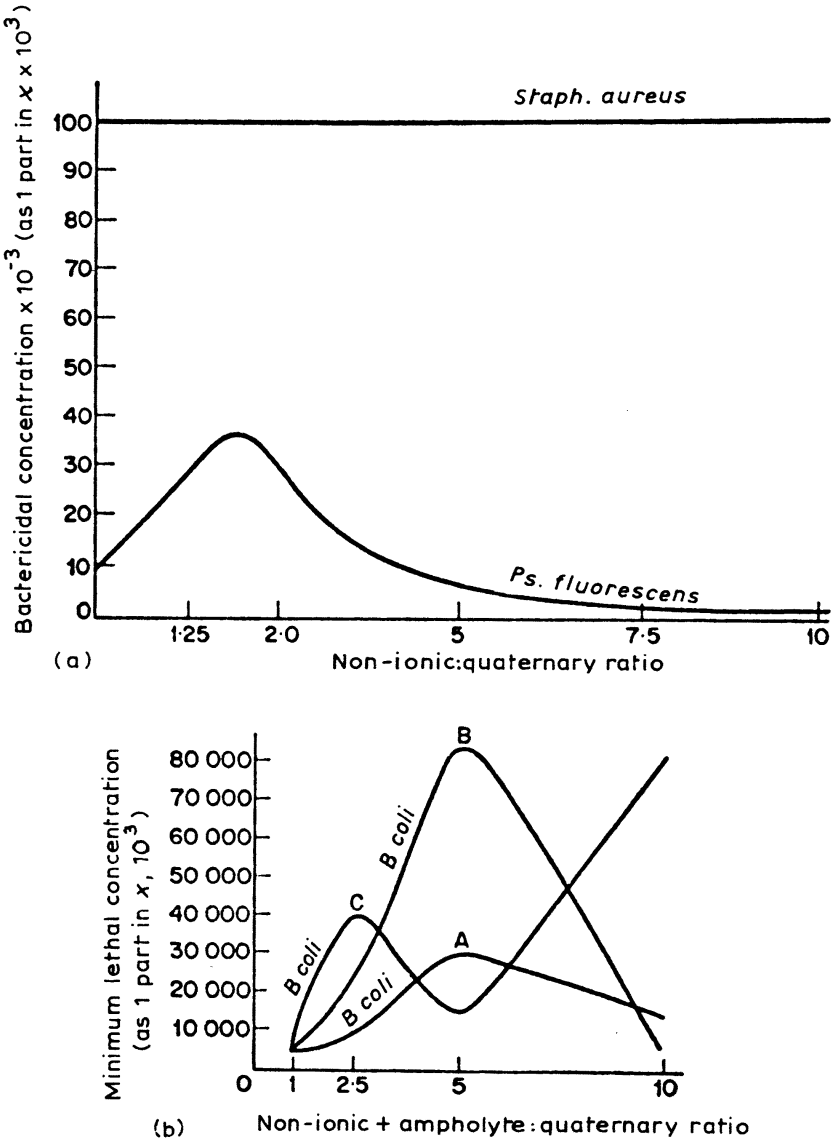


**Figure 7.45**(a) Interactions between detergents and quaternary ammonium compounds showing variation of bactericidal conentrations (1 part in $x \times 10^3$) with alteration in the ratio between non-ionic and quaternary showing initial increased activity, followed by a decrease in activity. *Staph. aureus* shows no variation, as it is so sensitive to the quaternary compound. From [220]. (b) Bactericidal activity in non-ionic:ampholyte:quaternary systems. (From [220]). A = 75% non-ionic, 25% sodium dodecyl amino propionate; B = 50% non-ionic, 50% ampholyte; C = 25% non-ionic, 75% ampholyte.

tations and is by no means exhausted. The danger of inadvertent inactivation must be avoided. A proprietary steroid cream diluted routinely to one-quarter of its strength with a cetomacrogol emulsifying wax resulted in a reduction of the chlorocresol content to 0.1%, which was, in the presence of the detergent, insufficient to prevent the growth of *Ps. aeruginosa* [214]. Not all antimicrobials interact with non-ionics of course. Phenyl mercuric nitrate is not inactivated by 2% polysorbate 80 [215]. Cases of increased activity are less apparent than cases of inactivation. Certain substances at appropriate concentrations should, in view of their membrane activity, be able to enhance activity. Polysorbate 80 has been shown to increase the action of polymixins B and D and of circulin [216]; the action of polymixin B sulphate, benzalkonium chloride, and chlorhexidine against *Ps. aeruginosa* is substantially increased in the presence of polysorbate 80. The inhibitory effect of the polymixin is enhanced at all concentrations of polysorbate from 0.004 to 0.5%, the effect increasing with increasing concentration [217].

Synergism has also been noted between dodecyl hexahydroxyethylene glycol ester (Emulgen 106) and benzoquinone, the activity of which was increased 100 times against *M. pyogenes* var. *aureus* [218]. The bactericidal action of neomycin is claimed to be increased over forty times by cationic surfactants [219]. In admixture with small amounts of a non-ionic detergent the action of some quaternary compounds is increased, but with greater concentrations the activity shows a gradual decrease. It is obvious from Fig. 7.45a that the ratio of non-ionic to quaternary compound must not be greater than 4:1 if inactivation is to be avoided. The steep rise in the activity curve indicates that synergism is possible but close control of concentration is required. Ternary mixtures of Morpans (ampholytic surfactants) and non-ionics can also be used, the interactions becoming even more critically dependent on concentration, as is shown in Fig. 7.45b.

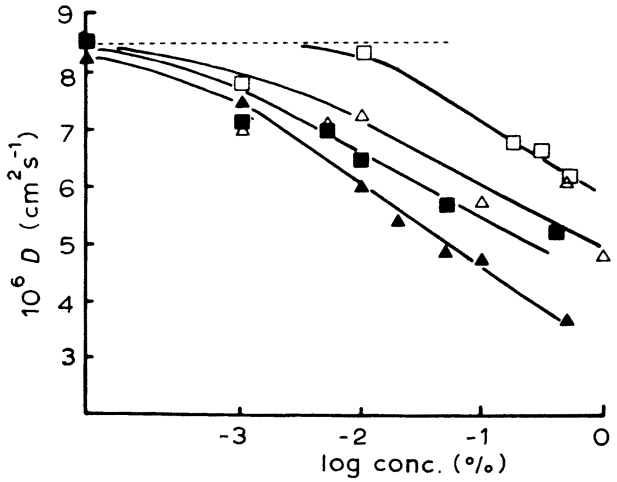


**Figure 7.46** Diffusion coefficients of thioridazine (0.4%) as a function of concentration of various non-ionic surfactants, measured by dialysis from Visking cellophane bags. ■ Cremophor EL; △ Atlas G2162; ▲ Renex 650 and □ Atlas G1295. From Florence [221].

## 7.7 Utilization of solubilization in drug delivery systems

Results of dialysis of solubilized systems using cellophane or polydimethylsiloxane membranes indicate the possibility of using the solubilized state to control transport rates of drugs from reservoirs bounded by such inert membranes, permeable to drug and impermeable to micelles. The required degree of control over the free drug concentration in the reservoir is achieved by altering the surfactant concentration or the surfactant itself (Fig. 7.46). In Fig. 7.46 the diffusion coefficient of thioridazine has been reduced from $8.3 \times 10^{-6}\,cm^2\,s^{-1}$ aqueous solution to $4 \times 10^{-6}\,cm^2\,s^{-1}$ [221] in less than 1% of the non-ionic surfactant Renex 650. Micellar solutions, emulsions and co-solvent systems have been compared for their ability to control the release of butamben from silicone capsules [222]. Micellar solutions and emulsions provide reservoirs to maintain a more constant concentration of drug on the donor side of the membrane. With simple solutions the permeation rate falls as the solution concentration decreases. Emulsions and suspensions have problems of instability. In assessing a simple model for drug release the following equation was used to calculate the release profile

$$M(t) = M_\infty[1 - \exp(-APC_s^o t/lVC_s)], \tag{7.41}$$

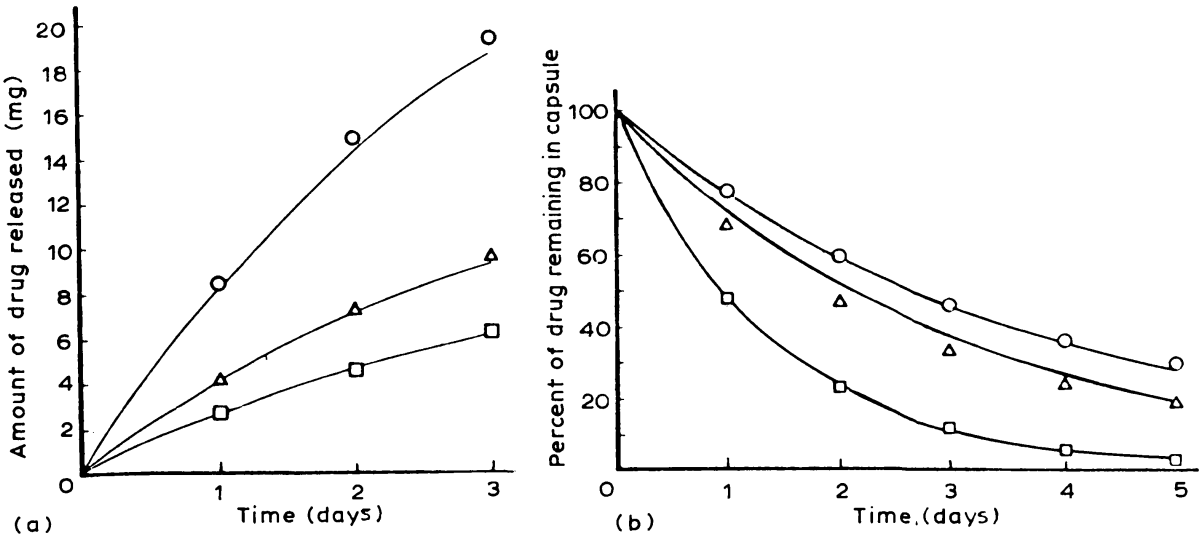


**Figure 7.47**(a) Release profiles of butamben from micellar systems in 10% sodium lauryl sulphate solution at three loading levels in a silicone capsule at 37° C. Drug loading levels were ○, 30 mg; △, 15 mg; and □, 10 mg. ——, theoretical profile predicted from Equation 7.7. (b) Effect of concentration of sodium lauryl sulphate on the release of butamben from micellar systems containing 15.5 mg butamben in silicone capsules at 37° C. Sodium lauryl sulphate concentrations were ○, 15%; △, 10%, and □, 5%. ——, theoretical profile predicted from Equation 7.41. In the theoretical calculations, the following parameters were used: $P = 1.24 \times 10^{-5}\,cm^2\,s^{-1}$ (determined from a permeation study using the same silicone rubber membrane at 37° C), $A = 6.25\,cm^2$, $l = 0.155\,cm$, $C_s^0 = 1.7\,mM$, $C_s = 227\,mM$ (solubility of butamben in 10% sodium lauryl sulphate at 37° C). From Juni *et al.* [222] with permission.

where $M_\infty$ and $M(t)$ are the amount of drug initially introduced and the cumulative amount of drug released at time $t$, respectively; $A$ and $l$ are the available area and thickness of the membrane, respectively; $P$ is the permeability; $V$ is the volume of intracapsular solution; and $C_s^\circ$ and $C_s$ are the solubilities of drug in water and surfactant solution, respectively. $P$ is dependent on the membrane used, and $A$, $l$ and $V$ depend on the size of the device. Control of release is achieved through $C_s$. The theoretical terms for release of half the drug in the silicone capsules in the system shown in Fig. 7.47b were 0.99, 2.14 and 2.74 days for the 5, 10 and 15% surfactant systems respectively [222]. The systems were tested after subcutaneous implantation in rabbits; close agreement between *in vitro* and *in vivo* release rates was found.

Mixed micelle formation and complex formation will achieve similar alterations in the transport properties of drug molecules. When the drug molecules themselves can aggregate, this will result in a reduction in permeability above their critical micelle concentration [221, 223].

### 7.7.1 Theoretical considerations of transport and release from solubilized systems

In order to evaluate the effect of micellar solubilization on the rate of transport of a solubilized drug, Matsumoto and co-workers compared experimental dialysis results with theoretical values based on an analysis of the system [224, 225] which considered the diffusion of the free drug. When the degree of interaction between drug and surfactant was low, theoretical predictions were accurate, but measured rates frequently exceeded the predicted rates of dialysis. Matsumoto ascribed the discrepancy to transport of some drug directly from the micelles following 'coalescence' with the membrane as the measured rates exceeded those predicted. A detailed analysis has been carried out by Goldberg and Higuchi [226, 227] of transport from a solubilized aqueous phase to an oil phase. They consider the possibility of transport of micellar-solubilized drug. In order for this to occur the micellar drug must diffuse 'to some point close to the oil, and then leave the micelle, unless the micelle itself enters the oil' [226]. The greater the solubilization the more important this process will be.

If the transport rate of the drug is diffusion controlled then the rate of uptake by the oil phase will be equal to the rate of transport through the aqueous phase. The steady-state rate of transport through the aqueous phase to the oil droplet, $G$, is given by

$$G = \left( AD_f \frac{dC_f}{dh} + AD_m \cdot \frac{dC_m}{dh} \right). \tag{7.42}$$

Subscripts f = free drug and m = drug in the micelle, as before. Other symbols have their usual meaning; $h$ is the diffusion layer thickness. The oil is regarded as a 'perfect sink' and the following relation assumed

$$C_m = P_m \cdot C_f \cdot C_{SA} \tag{7.43}$$

where $C_{SA}$ is the surfactant concentration. It was shown that for the planar case

$$\ln\left(\frac{\alpha}{\alpha-\beta C_0}\right)=\left(\frac{\beta A}{lv}\right)\left(\frac{D_f}{P_m C_{SA}}+D_m\right)t \tag{7.44}$$

Where $v$ is the volume of oil (ml ml$^{-1}$), $C_0$ is the concentration of drug in the oil, $\alpha$ is defined as

$$\alpha=\frac{C_t}{(1+1/P_m C_{SA})(1-v)} \tag{7.45}$$

and

$$\beta=\frac{v}{(1+1/P_m C_{SA})(1-v)}+\left(\frac{1}{P_{app}}-\frac{1}{P_{O/W}}\right) \tag{7.46}$$

where $C_t$ is the total amount of drug present and $P_{app}$ and $P_{O/W}$ being the apparent and true partition coefficients respectively. It can be shown that

$$\ln\left(\frac{\alpha}{\alpha-\beta C_0}\right)=\left(\frac{\beta A}{lv}\right)\left(\frac{D_f}{P_m C_{SA}}+D_m\right)t$$

$C_0$ = concentration of drug in oil.

The equivalent equation for the spherical case (diffusion to a sphere of oil) is

$$\ln\left(\frac{\alpha}{\alpha-\beta C_0}\right)=\frac{\beta A}{v}\left(\frac{D_f}{P_m C_{SA}}+D_m\right)t, \tag{7.47}$$

the only difference being the disappearance of the diffusion layer thickness from the equation. The equation can be rewritten to give the concentration of drug in the oil as a function of time:

$$C_0=\frac{\alpha}{\beta}\left\{1-\exp\left[-\frac{\beta A}{v}\left(\frac{D_f}{P_m C_{SA}}+D_m\right)t\right]\right\}, \tag{7.48}$$

in which every term can be independently determined so that predictions of transport can be made. The model becomes more complex with additional considerations of micellar charge and charged liquid interface. In this case the free drug and the drug in the micelle diffuse freely to some distance from the oil droplet where an electrical barrier then permits only free drug to diffuse. Interfacial barriers to transport other than electrical barriers may also exist [227], for example, as a result of adsorbed surfactant or polymer. An interfacial barrier constant, $\Gamma$, can be introduced into Equation 7.48, thus giving

$$C_0=\frac{\alpha}{\beta}\left\{1-\exp\left[-\frac{\beta\Gamma A}{v}\left(\frac{D_f}{P_m C_{SA}}+D_m\right)t\right]\right\}. \tag{7.49}$$

As $\Gamma \to 1$ the model approaches the simple diffusion model. The smaller $\Gamma$ the lower the rate of transport from the aqueous phase into the oil. The simple diffusion approach was deemed by Goldberg and Higuchi to be inadequate. Rate data for the indoxole-isopropyl myristate–polysorbate 80 system are shown in Fig. 7.48. The points are experimental, the solid lines based on Equation 7.49 when $\Gamma = 1.27 \times 10^{-4}$ for 2% polysorbate 80 and $1.85 \times 10^{-4}$ for 1% poly-

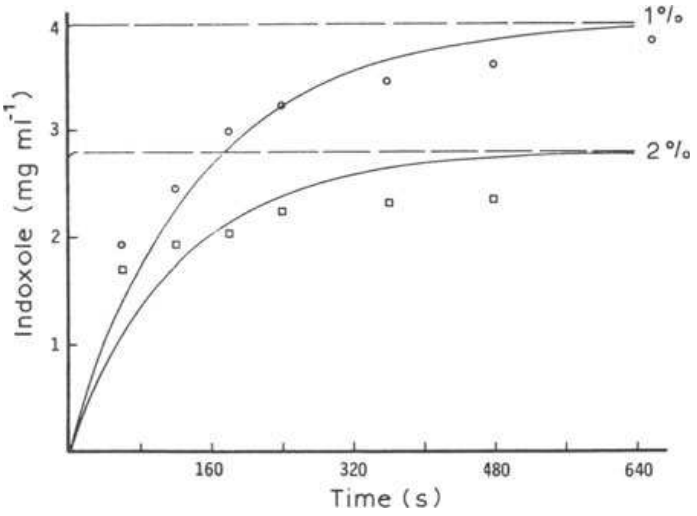


**Figure 7.48** The appearance of indoxole in the oil phase as a function of time. Points, experimental data; dashed line, the theoretical rate of transport based on diffusion theory; solid line, the theoretical rate based on the interfacial barrier theory. Results for 1% and 2% polysorbate 80 are shown. The oil phase is isopropyl myristate. From Goldberg and Higuchi [227] with permission.

sorbate 80; the dashed lines are those calculated for single diffusion. Predicted rates are too fast, the magnitude of the barrier is sufficient to reduce rates of transport by up to several thousand times according to this analysis. Such observed discrepancies could not be attributed to an electrical barrier which reduced the calculated rates by at most a factor of ten for an oil droplet with a surface potential of 100 mV. Brodin's experimental results on the influence of surfactants on mass transfer between an aqueous phase and an oil phase (discussed earlier) confirm these impressions that interfacial barriers to transport exist. Whether these considerations apply at artificial membranes is another matter. Adsorption of surfactant onto membranes (especially multilayer adsorption) is likely to influence transport of drugs considerably. Adsorption of non-ionic surfactants onto the intestinal membrane may be one of the factors contributing to the absorption inhibiting effect of high concentrations of surfactant [47] when there is little interaction between drug and micelles, a phenomenon postulated to explain reductions in transfer of substances into leaves [228] and goldfish [40].

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