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# Drug-surfactant interactions: effect on transport properties

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**Abstract**

The physico-chemical interactions between three model drugs and a variety of surfactants were characterized by measuring the apparent permeability coefficients of the drugs in the presence and absence of surfactants in vitro. The extent of interaction between the model drugs and the surfactants can best be described by the hydrophobic effect (primarily determined by the hydrophobic surface area of the drug molecule) and the electrostatic effect (primarily determined by the charge associated with the drug molecule as well as the surfactant molecules). For drugs that do not possess a significant hydrophobic surface area (timolol and cefoxitin), their interactions can best be described based on electrostatic effects (charge effects). This interaction being strong with oppositely charged surfactants. The interactions of L-692 585 (a model drug with appreciable hydrophobic surface area) in the presence of surfactants is dominated by the hydrophobic effect, with the electrostatic effect playing a minor secondary role. The apparent permeability coefficient of timolol as a function of the amount of surfactant in solution is modelled in light of micellar formation and entrapment and/or interaction of free drug with this micellar structure. Briefly, the extent of interaction as a function of amount of added surfactant for timolol indicates that initially as surfactant is added the activity of drug for transport declines significantly until a breaking point is reached, after which the drug activity available for transport remains relatively constant upon addition of more surfactant. A model is derived which is capable of describing this behavior and provides reasonable estimates for the critical micellar concentration of the surfactant, the affinity or binding constant for the interaction of drug with an equivalent micellar structure, and the loading capacity of the equivalent micellar structure. These observations are potentially significant for drug formulation of poorly bioavailable drugs. © 1997 Elsevier Science B.V.

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## 1. Introduction

Various surfactants have been utilized in their ability to enhance the permeability of drugs across

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biological membranes. Two primary considerations arise in using surfactants to enhance drug transport across biological membranes. The first concerns the effect of the surfactant on the biological membrane. These issues revolve around the alteration of the biological membrane as the rate limiting barrier in the presence of a surfactant; increased membrane fluidity, solubilization and/or extraction of lipids present in biological membranes, and alterations in tight junction properties (Attwood and Florence, 1983; Ashton et al., 1986; Cooper, 1984; Florence et al., 1984; Dominguez et al., 1977; Golden et al., 1986; Goodman and Barry, 1986; Muranushi et al., 1980).

The second consideration entails the interaction of the drug with surfactants. These latter issues revolve around physico-chemical interactions between drug molecules and surfactants in solution. These physico-chemical interactions manifest themselves in terms of enhanced solubility and/or dissolution of the drug, prevention of drug precipitation if administered in solution form, and reduction in drug activity (Barry and El Eini, 1976a,b; Corrigan et al., 1980; O'Driscoll and Corrigan, 1982; Gamesan et al., 1984; Juni et al., 1978). This reduction in drug activity is a consequence of strong interactions of the drug with higher ordered aggregates and/or micelles formed from the surfactants. These interactions can occur either at the interface or the interior of these higher ordered aggregates.

In vivo drug absorption in the presence of surfactants might be better interpreted in light of understanding the physico-chemical interactions between drugs and surfactants. To this end, a systematic study was designed to characterize the interactions of drugs with various surfactants. In particular, the apparent permeabilities of model drugs in the presence and absence of a variety of surfactants were quantitated using side-by-side diffusion cells. Regenerated cellulose dialysis membranes (MW cutoff 3500) were used as the rate limiting barrier. This membrane allows for facile diffusion of the free drug, whereas the drug interacting with micelles or higher order surfactants possessing higher molecular weights are retained (Withington and Collett, 1972, 1973). The method utilized is commonly referred to as dialysis escape kinetics (Agren and Elofsson, 1967; Connors, 1987; Meyer and Guttman, 1968, 1970; Silhavy et al., 1975). Utilizing this technique apparent permeability coefficients for the various systems can be calculated and based on the calculated apparent permeability coefficients it is possible to characterize the extent of drug-surfactant interactions.

## 2. Experimental

### 2.1. Materials

The surfactants chosen for this study fall into the four primary surfactant categories: anionic, cationic, nonionic and zwitterionic. Specifically they were: sodium dodecyl sulfate (SDS; Sigma), 1-heptanesulfonic acid, sodium salt 98% (Aldrich), cetyl trimetyl ammonium bromide (CTAB; Cal Biochem), palmitoylcholine chloride (ICN Biochemical), polyethylene oxide polymer (Polox, 600K Union Carbide), Zwittergent® 3–16 (Cal Biochem) and palmitoyl carnitine chloride (PCC; Merck).

The model drugs were timolol maleate (Merck), cefoxitin sodium (Merck) and L-692 585 (Merck). Sodium phosphate dibasic anhydrous (Mallinckrodt), sodium phosphate monobasic (Mallinckrodt), phosphoric acid (85 wt% solution in water, ACS reagent; Aldrich) and sodium chloride were used for buffer preparation. Sodium hydroxide (50% w/w; Fisher) was used to adjust to pH if necessary. The buffers prepared were pH 7.4 phosphate buffer (0.02 M; $I = 0.1$ adjusted with NaCl) and pH 2.05 phosphoric acid buffer (0.022 M phosphoric acid; $I = 0.1$ adjusted with NaCl).

### 2.2. Set up

The experimental set up consisted of water jacketed side-by-side diffusion cells which were clamped together and placed on the magnetic console provided (600 rpm; Crown Glass, Sommerville, NJ). The volume of each cell was approximately 3 ml; the exposed area for transport was 0.6936 $cm^2$. The rate limiting barrier used was

regenerated cellulose dialysis membrane tubing with molecular weight cutoff of 3500 (Spectra/por 3; Spectrum Medical Industries). These were regenerated according to manufacturer's direction and stored in distilled water at least 24 h before experiments. Non-reinforced 0.005 inches Silastic® sheeting was cut into washers and used as O-rings in between the cells to prevent leakage. A Haake water bath was used to maintain the temperature at 25°C.

The concentrations of donor solutions used were 1 mg/ml for timolol maleate and cefoxitin sodium, and 0.5 mg/ml for L-692 585. These drug concentrations were chosen in order to simplify the analytical quantitation of the drugs. The drug concentrations chosen were well below the solubility concentrations of the drugs thus avoiding the confounding problems mentioned previously. The donor solutions were prepared in pH 7.4 phosphate buffer or pH 2.05 phosphoric acid buffer. The concentration of surfactants used were 1% w/v unless otherwise specified. The experiments were initiated by placing approximately 30 mg of surfactant in the donor cell, subsequently 3 ml of the donor solution was added. The stirring action of the stirring bar was sufficient to dissolve/disperse the surfactants in a short time. The physical state of the surfactant is noted if it is in solid state. The receiver cell consisted of the respective buffer.

The absorbance in the receiver cell was monitored by flow through UV using a master flex pump (Cole Parmer, Chicago, IL) and an LKB Ultrospec II spectrophotometer (LKB Biochem, Cambridge, UK). This flow through system was used for analytical purposes only, the receiver chamber contained 3 ml of buffer at all times and the buffer in the flow through UV cell was recirculated at a flow rate of 10 ml/min ensuring accurate measurements of the drug concentration in the receiver chamber as a function of time. The wavelength used was 295 nm for timolol maleate, 235 nm for cefoxitin, 230 nm for L-692 585 at pH 7.4 and 225 nm for L-692 585 at pH 2.05. There was a slight shift in $\lambda_{max}$ due to pH change for L-692 585. A CompuAdd 286 computer was used to collect the absorbance measurements as a function of time. The absorbance data was collected every 2 min for 6 h. The absorbance versus time profiles were linear, however, minor lag times were observed in some instances.

After the experimental run was completed, the pH of both the receiver and donor cell were measured to ascertain the effect of the surfactant on the pH of the solutions, if any (Orion Model 601A digital ionanalyzer with Corning semi-micro combination electrode). The pH of both donor and receiver solutions were consistent with the initial buffer pH, except in the case of palmitoyl carnitine chloride (PCC) wherein the 7.4 phosphate buffer was not strong enough to maintain the pH at 7.4. Additional sodium hydroxide (50% w/w) was used to adjust the pH of the resulting solution/suspension to 7.4 at the beginning of the experiment. The adjusted pH remained stable during the experiment.

### 2.3. Data analysis

The absorbance versus time profiles obtained were linear indicating that the process is zero order with respect to time. This is indicative of the fact that the driving force for the transport of the drug across the membrane remains constant during the course of the experiment. The slope of the absorbance versus time profiles were determined using least squares linear regression. Time points of 1–4 or 1–6 h were used to calculate the slopes in order to avoid the initial minor lag phase observed in some of the systems. The apparent permeability coefficients (Cussler, 1984) for drug transport were calculated using Eq. (1) which is based on the definition of apparent permeability:

$$P_{app} = \frac{\text{Amount}}{\text{Time Area } C_{Donor}} \quad (1)$$

In this equation, the amount of drug transported per unit time is normalized with respect to surface area available for transport. $C_{Donor}$ is the initial concentration of the donor solution. In all cases in the course of an experiment less than 5% of the donor compound was transported; therefore, sink conditions were assumed.

The Amount/Time quantity in the above expression can be represented by Eq. (2):

$$\frac{\text{Amount}}{\text{Time}} = \frac{\text{Slope } V_{\text{Receiver}}}{Eb} \quad (2)$$

where slope refers to the slope of the absorbance versus time profiles. $V_{\text{Receiver}}$ is the volume of the receiver cell (including the volume of flow through UV line and cell). $E$ is the molar absorbitivity of the drug and $b$ is the cell path length. The concentration of donor solution ($C_{\text{Donor}}$) can be represented by Eq. (3):

$$C_{\text{Donor}} = \frac{A_{\text{Donor}}}{Eb} \quad (3)$$

Where $A_{\text{Donor}}$ is the initial absorbance of the donor solution. Substituting Eqs. (2) and (3) into Eq. (1) and making the appropriate cancellations an expression for apparent permeability coefficient can be obtained in Eq. (4):

$$P_{\text{app}} = \frac{\text{Slope } V_{\text{Receiver}}}{\text{Area } A_{\text{Donor}}} \quad (4)$$

Appropriate units were chosen so that the apparent permeability coefficient had the units of cm/sec. The percent permeability (%$P$) was defined as the apparent permeability coefficient of the drug in the presence of surfactant divided by the permeability coefficient of the drug in the absence of surfactant.

## 3. Results and discussion

The primary concept of dialysis escape kinetics is related to the ability of the free drug to cross or escape through the membrane whereas the bound drug is not capable of crossing the membrane due to its increased size as a result of complexation with the substrate molecule (Agren and Elofsson, 1967; Connors, 1987; Meyer and Guttman, 1968, 1970; Silhavy et al., 1975). The complexation kinetics process (association/dissociation) is much more rapid than transport kinetics process (diffusion of the free drug across the membrane), therefore the complexation equilibria is always maintained in the donor chamber as a result of dissociation of the drug from the substrate (Silhavy et al., 1975). The half-life of the complexation process is dependent on the individual substrate and ligand species involved, however this process is usually so fast that NMR relaxation times have been used to study this phenomenon and most systems have half-lives of less than a few seconds (Becker, 1969; Silhavy et al., 1975). Therefore, the complexation equilibria is always maintained during the course of the experiment, furthermore, the transport of the drug across the membrane is dependent on the free drug concentration on the donor side. If the free drug concentration on the donor side is relatively constant as a function of time the rate of appearance of the drug on the receiver side as a function of time will also be constant (zero order escape kinetics). In this case a plot of concentration of the drug in the receiver chamber as a function of time will be linear and the slope of this line will be the zero order rate constant (Agren and Elofsson, 1967). The zero order rate constant is directly related to the free drug concentration in the donor chamber. This zero order rate constant can be utilized to calculate permeabilites of the free drug across the membranes studied. This is preferred since the cell geometry factors such as surface area of membrane available for transport, volume of donor and acceptor solution is normalized with respect to these variables yielding apparent permeability values. The apparent permeability values can be readily used for comparative purposes with other systems reported in the literature (Cussler, 1984).

If the concentration of the free drug changes as a function of time then the escape kinetics observed across the membrane is not zero order. In these cases the kinetics of transport is usually first order (Meyer and Guttman, 1968, 1970; Silhavy et al., 1975). The interpretation of first order systems is rather complicated since the free drug concentration changes as a function of time. Finally some systems do not fall into the simple zero order or first order escape kinetics. These latter systems are almost impossible to interpret since the free drug concentration does not follow any particular behavior (Kanfer and Cooper, 1976). These latter systems are a result of poor experimental design in which the system has not been well defined and the conditions have not been well optimized in order to simply the phenomenon under investigation. In short, in these

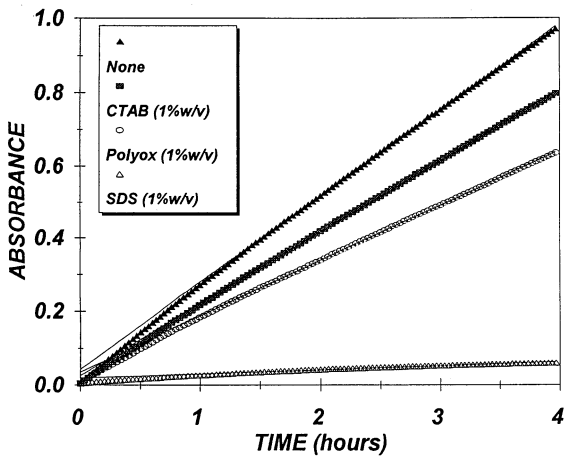


Fig. 1. Timolol maleate transport across Spectrapor® dialysis membrane in the presence and absence of approximately 1% w/v surfactant. The symbols represent the absorbance data obtained, the fitted least squares lines are superimposable on the data indicating zero order escape kinetics across the membrane.

latter systems too many variables are changing as function of time thus changing the free drug concentration as a function of time in an incomprehensible fashion. In our systems we have optimized the conditions under investigation in order to obtain zero order kinetics since the interpretation of these systems are relatively straight forward.

### 3.1. Timolol maleate transport

The absorbance versus time plots for timolol maleate transport across spectrapor dialysis membrane were linear (Fig. 1) indicating a zero order escape kinetics. Based on the calculated slope and the geometry of the diffusion cell, Eq. (4) was used to calculate the apparent permeability coefficients for the various systems studied. The apparent permeability for the transport of timolol across the membrane in the absence and presence of the surfactants (1% w/v level) at pH 7.4 and 2.05 appear in Table 1. The %$P$ values were calculated by using the apparent permeability coefficient value in absence of the surfactant as the reference (i.e. 100%) value. These values allow for easier comparison of the effect of surfactant on the transport property of timolol across the membranes.

In the absence of surfactants, the apparent permeability coefficients calculated for timolol at both pH values are comparable. From the %$P$

Table 1
Timolol maleate transport through Spectrapor® MW cutoff 3.5 K in the presence of various surfactants at approximately 1% w/v

| Surfactant added | pH 7.4 phosphate buffer | | $I = 0.1$ NaCl | pH 2.05 phosphoric acid | | $I = 0.1$ NaCl |
|---|---|---|---|---|---|---|
| | Permeability $10^5 \times P$ (cm/s) | %$P$ | Surfactant charge | Permeability $10^5 \times P$ (cm/s) | %$P$ | Surfactant charge |
| None | 2.80 (0.2) | 100 (8) | NA ($n = 2$) | 2.54 (0.1) | 100 (4) | NA ($n = 2$) |
| CTAB | 2.50 | 89 | Positive | 2.48 | 98 | Positive |
| Palmitoylcholine chloride | 2.96 | 106 | Positive | 2.56 (0.1) | 101 (4) | Positive ($n = 2$) |
| PCC | 2.69[a,b] (0.01) | 96 (0.5) | Zwitterionic ($n = 2$) | 2.50[a,c] (0.01) | 99 (0.05) | Positive ($n = 2$) |
| Zwittergent 3–16 | 3.04[a] | 109 | Zwitterionic | 2.35[a] | 93 | Zwitterionic |
| Polyox® 600 K | 1.94 | 69 | Neutral | 1.88 (0.3) | 74 (11) | Neutral ($n = 2$) |
| 1-Heptane sulfonic acid | 2.62 | 94 | Negative | 2.17 | 85 | Negative |
| SDS | 0.140 | 5 | Negative | 0.086 | 3 | Negative |

Standard deviations appear in parenthesis.
Timolol is positively charged at pH 7.4 and 2.05 ($pK_a \approx 9.2$).
[a] Indicates that the surfactant is in the precipitated state.
[b] Sodium hydroxide was initially used to adjust the pH to 7.4.
[c] PCC dissolves as a function of time.

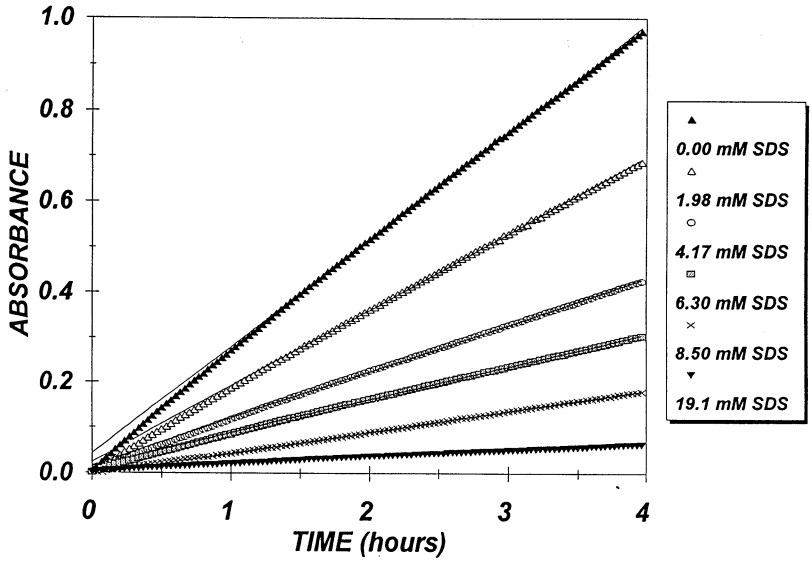


Fig. 2. The effect of added sodium dodecyl sulfate (SDS) on timolol maleate transport across Spectrapor® dialysis membrane. The symbols indicate the absorbance data obtained which is indicative of zero order escape kinetics across the membrane. As more SDS is added the free drug concentration available for transport across the membrane decreases due to binding with SDS micelles.

values (Table 1), it is apparent that there is little to no interaction between timolol which is positively charged at both pH values (Mazzo and Loper, 1987) and the following surfactants: CTAB, palmitoylcholine chloride, palmitoyl carnitine chloride and Zwittergent 3–16. These surfactants are either positively charged or zwitterionic at the pH values studied. On the other hand, timolol interacts strongly with SDS, which is negatively charged.

The interaction of timolol with SDS was further characterized by studying the transport behavior of timolol as a function of SDS concentration whereas the amount of timolol added to the donor chamber was fixed at a concentration of 1 mg/ml. This study was conducted by varying the amount of SDS added to the donor chamber. Representative absorbance versus time profiles appear in Fig. 2. Once again these plots are linear indicating a zero order escape kinetics across the membranes which is directly related to the free drug concentration in the donor chamber. In all the systems studied the plots were linear indicating that in all systems the free drug concentration in the donor chamber as a function of time was constant through the entire course of the experiment. As is evident the slope of the lines decrease as function of increasing amount of SDS added to the donor chamber indicating that the free drug concentration available for transport across the membrane decreases as the amount of surfactant added increases. The apparent permeability coefficients based on the zero order escape kinetics were calculated. These values are reported as a function of the amount of SDS added to the donor solution in Table 2. The decline in the apparent permeability coefficients as a function of the added surfactant is a result of entrapment and/or interaction of the drug with the formed SDS micelles on the donor side. This interaction effectively reduces the free drug concentration available for transport across the membrane.

A potential consideration is the fact that the surfactant which is placed in the donor solution is also capable of diffusing across the dialysis membrane during the course of the experiment thus changing the underlying driving force for transport. However, this effect is minor since any change in the driving force would manifest itself in terms of non-linear transport kinetics across the membrane (Agren and Elofsson, 1967). This was not observed for any of the systems under

investigation. The linearality in the escape kinetics in our system is not unexpected particularly if one assumes that the surfactant molecules cross the membrane at the same rate as the drug molecules since the molecular weights of the individual surfactant molecules studied are in the same range as the molecular weights of drug molecules investigated. Therefore, less than 5% of surfactant is expected to cross the membrane during the course of the experiment.

The apparent permeability coefficient observed can be expressed in terms of Eq. (5):

$$P_{app} = F_f P_f + F_b P_b \quad (5)$$

where $F_f$ represent the free drug fraction, $F_b$ represent the bound drug fraction, $P_f$ represent the permeability of free drug across the membrane, and $P_b$ is the permeability of the bound drug across the membrane. Since the bound fraction cannot traverse the membrane given the size of the aggregate; we assume that $P_b = 0$. Therefore, the above expression can be represented by the following simplified Eq. (6):

$$P_{app} = F_f P_f \quad (6)$$

The free drug fraction in presence of the surfactant can be modelled using equilibrium binding since the time frame for the binding process (association/dissociation) is much faster than the time frame for transport across the membrane (Agren and Elofsson, 1967; Silhavy et al., 1975). In this equilibrium binding model, assume $m$ molecules of surfactant forming a micellar structure with which $n$ molecules of drug are capable of interacting or complexing with. By further assuming, identical, distinguishable, independent sites, without interactions between the bound drugs we can in effect assume that the drug molecule interacts with $(m/n)$ molecules of surfactant. This $(m/n)$ ratio is presumed to be a fixed quantity indicative of number of binding sites available. The above assumptions have been made previously by others (Agren and Elofsson, 1967; Connors, 1987) and simplify the mathematical analysis of the system at the expense of some information; namely quantities $m$ and $n$. This confounding problem cannot be resolved regardless of approach taken. Therefore the simplified model has been adopted and can be viewed as an equivalent micellar structure interacting with a single drug molecule.

$$\mathrm{EMS} + \mathrm{D} \overset{K_{\text{interaction}}}{\rightleftarrows} \mathrm{DEMS}$$

where EMS stands for the equivalent micellar structure which is composed of $(m/n)$ surfactant molecules, D stands for free drug, and DEMS represents the bound drug. The $K_{\text{interaction}}$ is the affinity constant of the drug for the equivalent micellar structure. The free drug fraction can be represented by Eq. (7):

$$F_f = \frac{1}{1 + K_{\text{interaction}}[\mathrm{EMS}]} \quad (7)$$

where the concentration of the equivalent micellar structure present can be expressed in terms of Eq. (8):

$$[\mathrm{EMS}] = \frac{[\mathrm{SDS}] - [\mathrm{CMC}]_{\mathrm{SDS}}}{(m/n)} \quad (8)$$

where [SDS] is the concentration of SDS present in the solution, $[\mathrm{CMC}]_{\mathrm{SDS}}$ is the critical micellar concentration for SDS, and $(m/n)$ is the number of surfactant molecules in the equivalent micellar structure. Substituting this expression in the preceding equation we obtain Eq. (9):

Table 2
Timolol maleate transport through Spectrapor® MW cutoff 3.5 K in the presence of various concentrations of sodium dodecyl sulfate, pH 7.4 phosphate buffer $I = 0.1$ (NaCl)

| mg of SDS added | SDS mM | Apparent permeability $10^5 \times$ cm/s | %$P$ |
|---|---|---|---|
| 0 | 0.00 | 2.63 | 94 |
| 0 | 0.00 | 2.97 | 106 |
| 1.71 | 1.98 | 2.15 | 77 |
| 3.61 | 4.17 | 1.31 | 47 |
| 5.45 | 6.30 | 0.938 | 34 |
| 7.35 | 8.50 | 0.590 | 21 |
| 16.5 | 19.1 | 0.177 | 6.3 |
| 31.26 | 36.1 | 0.140 | 5.0 |
| 60.06 | 69.4 | 0.0822 | 2.9 |

$$F_f = \frac{1}{1 + \frac{K_{interaction}}{(m/n)}([SDS] - [CMC]_{SDS})} \quad (9)$$

Finally substituting this into Eq. (6) above we can model the apparent permeability coefficients obtained in presence of various amounts of SDS added.

$$P_{app} = \frac{1}{1 + \frac{K_{interaction}}{(m/n)}([SDS] - [CMC]_{SDS})} P_f \quad (10)$$

using this Eq. (10) and non-linear regression the apparent permeability coefficients data obtained can be modelled. In this equation the quantity $P_f$ (the permeability coefficient for the free drug) is known experimentally, therefore there are only two fitting parameters. The first parameter is the $[CMC]_{SDS}$ which is the critical micellar concentration of SDS and the other parameter is the $(K_{interaction}/(m/n))$ term. This term is an indication of not only the affinity ($K_{interaction}$) of the drug for the surfactant but also of the capacity of the micelle for the drug $(m/n)$. The affinity and capacity quantities cannot be readily resolved based on the model equation derived; therefore, the composite quantity will be fitted.

The apparent permeability values determined experimentally along with the fitted lines using the model Eq. (10) appears in Fig. 3. As is evident the simple model derived here is capable of fitting the data very well. The fitted parameter value obtained for $[CMC]_{SDS}$ using this model is $1.34 \times 10^{-3}$ M; the reported critical micellar concentration for SDS ($I = 0.1$ M NaCl) is $1.49 \times 10^{-3}$ M (Mukerjee and Mysels, 1971). The fitted parameter value for the critical micellar concentration of SDS is in excellent agreement with the published literature value lending credibility to the experimental and theoretical approach taken. The fitted parameter value obtained for the other term in our model, namely $(K_{interaction}/(m/n))$, is 447 $M^{-1}$. This parameter value is an indication of the affinity and the capacity of the drug for the surfactant. An estimate for the capacity, $(m/n)$ quantity can be deduced based on the following argument.

A visual examination of the plot of SDS concentration added (mol/l) versus apparent permeability

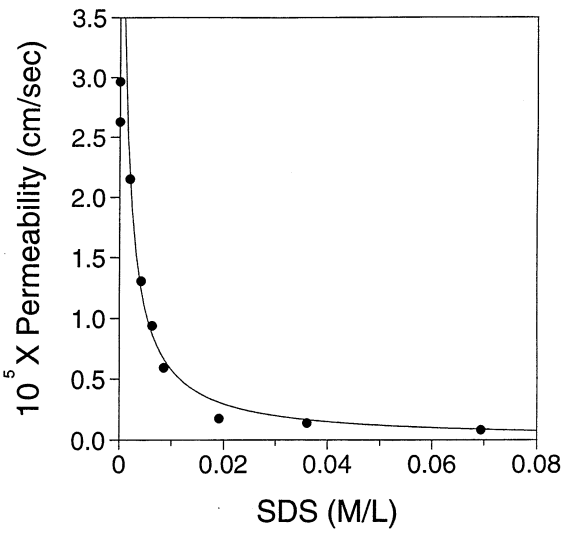


Fig. 3. The apparent permeability coefficients calculated for Timolol maleate as a function of added SDS concentration. The curve is the fitted line using the model equation derived (Eq. 10).

coefficients (Fig. 3) indicates a break in the curve in the range of $8.5 \times 10^{-3}$ to $2 \times 10^{-2}$ mol/l. A manual interpolation indicates a value of approximately $1.5 \times 10^{-2}$ mol/l. It is assumed that this break in the curve is as a result of attainment of full capacity at which time sufficient number of micelles have been formed to provide enough binding sites for the timolol maleate in solution (1 mg/ml or $2.31 \times 10^{-3}$ M). Then an estimate for $(m/n)$ can be determined by subtracting the critical micellar concentration of SDS from the SDS concentration at the intrapolated break value and dividing by the timolol maleate concentration in solution $((1.5 \times 10^{-2} - 1.34 \times 10^{-3})/2.31 \times 10^{-3})$. This gives a value of 5.91 for $m/n$ indicating that on average approximately six molecules of surfactant are interacting with each drug molecule at the point at which full capacity is attained which a reasonable value. Using this value we calculate a value of 2642 $M^{-1}$ for the $K_{interaction}$ term which is the affinity constant for the drug interacting with the equivalent micellar structure. This value is also reasonable since a typical range for complexation constant of small molecules is $1–10^4$ $M^{-1}$, which corresponds to a free energy change value of 0 to $-5.5$ kcal $mol^{-1}$

Table 3
L-692,585 transport through Spectrapor® MW cutoff 3.5 K in the presence of various surfactants at approximately 1% w/v

| Surfactant added | pH 7.4 phosphate buffer | | $I = 0.1$ NaCl | pH 2.05 phosphoric acid | | $I = 0.1$ NaCl |
|---|---|---|---|---|---|---|
| | Permeability$10^5 \times P$ (cm/s) | $\%P$ | Surfactant charge | Permeability$10^5 \times P$ (cm/s) | $\%P$ | Surfactant charge |
| none | 1.23 (0.1) | 100 (8) | NA ($n = 4$) | 1.40 (0.08) | 100 (5) | NA ($n = 4$) |
| CTAB | 0.099 (0.001) | 8 (1) | Positive ($n = 2$) | 0.5 | 36 | Positive |
| Palmitoylcholine chloride | 0.019 | 1.5 | Positive | 0.23 | 17 | Positive |
| PCC | 1.07[a,b] (0.05) | 87 (5) | Zzwitterionic ($n = 2$) | 0.49[a,c] (0.01) | 35 (1) | Positive ($n = 2$) |
| Zwittergent 3–16 | 0.034[a] | 2.8 | Zwitterionic | 0.086[a] (0.009) | 6.2 (0.6) | Zwitterionic ($n = 2$) |
| Polyox® 600 K | 0.81 | 66 | Neutral | 0.80 | 57 | Neutral |
| SDS | 0.091 | 7.4 | Negative | 0.055 | 4 | Negative |

Standard deviations appear in parenthesis.
L-692 585 is zwitterionic at pH 7.4 and positively charged at pH 2.05.
[a] Indicates that the surfactant is in the precipitated state.
[b] Sodium hydroxide was initially used to adjust the pH to 7.4.
[c] PCC dissolves as a function of time.

or $-23$ kJ mol$^{-1}$ on a molar basis at 25°C (Connors, 1987). This range is anticipated to include most non-covalently bound complexes of small molecules, with higher values being associated with more stable complexes as in the case of macromolecular systems such as enzyme-inhibitor and antigen-antibody systems where more specificity between the binding sites exist. In our system we have hypothesized a macromolecular structure composed of $(m/n)$ surfactant molecules interacting in a non-specific manner with the drug molecule; the complexation constant obtained in our model is consistent with typical values anticipated for such systems.

The simple model derived here is capable of describing the interaction between timolol and SDS as a function of the added surfactant. Furthermore, the model provides reasonable estimates for the critical micellar concentration of the surfactant, the affinity or binding constant for the interaction of drug with an equivalent micellar structure, and the loading capacity for the equivalent micellar structure. The extent and nature of these interactions however are highly dependent on the physico-chemical properties of the drug and the surfactant under study. The study of the interaction of the next two model drugs and the surfactants as well as some of the timolol data presented in this section aims to shed some light on the nature of these interactions and the physico-chemical properties determining the extent of these interactions.

### 3.2. L-692 585 transport

The absorbance versus time plots for these systems were linear and the apparent permeability and $\%P$ values for transport of L-692 585 in presence and absence of a variety of surfactants at 1% w/v concentration were calculated as mentioned earlier, these values are presented in Table 3. In the absence of surfactants there is no significant difference in transport of the drug at the two pH values studied which is consistent with the behavior observed with Timolol. L-692 585 is zwitterionic at pH 7.4 and positively charged at pH 2.05. In absence of surfactants no charge effects are observed which indicates that no charge effects are associated with the use of the Spectrapor® membranes.

The permeability data indicate that at pH 7.4 the zwitterionic drug interacts very strongly with the positive, negative and zwitterionic surfactants, with the exception of palmitoylcarnitine chloride.

Table 4
Cefoxitin transport through Spectrapor® MW cutoff 3.5 K in the presence of various surfactants at approximately 1% w/v

| Surfactant added | pH 7.4 phosphate buffer | | $I = 0.1$ NaCl |
|---|---|---|---|
| | Permeability $10^5 \times P$ (cm/s) | $\%P$ | Surfactant charge |
| none | 1.87 (0.14) | 100 (8) | NA ($n = 4$) |
| CTAB | 0.43 (0.05) | 23 (3) | Positive ($n = 2$) |
| Palmitoylcholine chloride | 0.38 (0.07) | 21 (4) | Positive ($n = 2$) |
| PCC | 1.81[a,b] (0.2) | 97 (10) | Zwitterionic ($n = 2$) |
| Zwittergent 3–16 | 1.33[a] (0.06) | 71 (3) | Zwitterionic ($n = 3$) |
| Polyox® 600 K | 1.52 (0.04) | 82 (2) | Neutral ($n = 2$) |
| SDS | 2.02 (0.04) | 108 (2) | Negative ($n = 2$) |

Standard deviations appear in parenthesis.
Cefoxitin is negatively charged at pH 7.4 ($pK_a \approx 2.2$).
[a] Indicates that the surfactant is in the precipitated state.
[b] Sodium hydroxide was initially used to adjust the pH to 7.4.

This exception is due to the fact that the majority of PCC exists in the precipitated form, therefore, solution state interactions with PCC are at a minimum.

At pH 2.05 the apparent permeability data along with the calculated $\%P$ values indicate that the positively charged drug interacts strongly with the positive, negative and zwitterionic surfactants. Although, the extent of these interactions are not as strong with positive and zwitterionic surfactants as observed with the zwitterionic drug at pH 7.4. The converse is true in describing the drug interaction with SDS. This is highly suggestive that there is a great driving force for interaction between this drug and the surfactants studied. Furthermore, this driving force is modulated by presence of a minor role from charge or electrostatic effects.

### 3.3. Cefoxitin transport

Once again the absorbance versus time plots for these systems were linear indicating a zero order escape kinetics. The apparent permeability coefficients and $\%P$ values calculated based on these slopes appear in Table 4. From the $\%P$ values it is apparent that the negatively charged cefoxitin ($pK_a \approx 2.2$; Brenner, 1982) does not interact with SDS which is also negatively charged. The interaction of cefoxitin with Zwittergent 3–16 is moderate. However, it interacts rather strongly with the positively charged surfactants. Similar transport studies for cefoxitin were not conducted at pH 2.05 since the drug would not have been completely neutralized at this pH ($pK_a \approx 2.2$).

The interaction of polyox with the drugs studied were not discussed thus far. However, looking at the $\%P$ values for polyox in Tables 1, 3 and 4 it is evident that rather similar values appear for $\%P$ ($\approx 70\%$) in all the systems investigated. This consistent effect of polyox on transport of drug indicates that this compound exerts its effect by non-specifically binding the various drugs studied to the same extent which is unlikely or alternatively it exerts its effect through its viscosity inducing ability.

## 4. Conclusion

Zero-order escape kinetics was found to be a useful model in characterizing drug surfactant interactions. These specific interactions can be characterized in terms of electrostatic and hydrophobic effect.

Specifically, for cefoxitin and timolol the charge state of the drug and the corresponding charge state of the surfactant are the predominant deter-

mining factors as to the extent of interaction between the drug and the surfactant. That is, the interaction is described based on simple electrostatic principles.

In case of L-692 585, there is a strong drug interaction with all surfactants studied (except polyox). The electrostatic effect mentioned previously plays a minor role in describing the interaction of L-692 585 with the surfactants. In this case the hydrophobic effect is the predominant determining factor since L-692 585 possess a significant hydrophobic surface area. Cefoxitin and timolol molecules do not possess significant hydrophobic surface area. Therefore, for molecules possessing significant hydrophobic area the predominant determining factor is the hydrophobic driving force with the electrostatic effect playing a minor secondary role.

In the case of timolol and SDS, where the transport property of timolol was characterized as a function of added surfactant. The activity of timolol was reduced significantly until a breaking point was observed during which a sufficient number of micelles were formed to provide enough binding sites for the timolol in solution. Beyond the break in the curve additional surfactant had minimal effect on the activity of timolol and hence its transport property. The entire transport property of timolol as a function of added SDS was successfully modelled using the model equation derived. The critical micellar concentration calculated based on the data and model equation derived was in excellent agreement with the published literature value. Furthermore, the affinity constant and the capacity constant calculated for the equivalent micellar structure were reasonable. The success of the model equation derived in describing the data and yielding reasonable parameter values in excellent agreement with the literature values indicates the validity of the experimental and theoretical approach taken.

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