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Mathematical Modelling of Drug Transport in Emulsion Systems

KYUNG AE YOON AND DIANE J. BURGESS

Department of Pharmaceutical Science, School of Pharmacy, University of Connecticut, Box U-92, 372 Fairfield Road, Storrs, CT 06269-2092, USA

Abstract

Two mathematical models for the prediction of drug transport in triphasic (oil, water and micellar) emulsion systems as a function of micellar concentration have been developed and these models were evaluated by comparing experimental and simulated data. Fick's first law was used to derive a transport model for hydrophilic drugs, assuming that the oil/water (o/w) partitioning process was fast compared with membrane transport and therefore drug transport was limited by the membrane. Consequetive rate equations were used to model transport of hydrophobic drugs in emulsion systems assuming that the o/w interface acts as a barrier to drug transport.

Benzoic acid and phenol were selected as hydrophilic model drugs. Phenylazoaniline and benzocaine were selected as hydrophobic model drugs. Transport studies at pH 3·0 and 7·0 were conducted using side-by-side diffusion cells. According to the hydrophilic model, an increase in micellar concentration is expected to decrease drug transport rates. The effective permeability coefficients (P_{eff}) of drugs were calculated using an equation relating P_{eff} and the total apparent volume of drug distribution (determined experimentally using drug/membrane permeability and partition coefficient values). The hydrophobic model was fitted to the experimental data for the cumulative amount of model drug in the receiver cells using a weighted least-squares estimation program (PCNONLIN). The oil/continuous phase partitioning rates (k_1) and the membrane transport rates (k_2) were estimated.

The goodness of fit was assessed from the correlation coefficients of plots of predicted versus experimental data. The predicted data were consistent with the experimental data for both the hydrophilic and hydrophobic models.

It has been shown that transport in emulsion systems is affected by the presence of excess surfactant (Yoon & Burgess 1996, 1997). Surfactants alter drug transport kinetics by modifying the partitioning process between the oil and aqueous phases as a result of micellar solubilization and by change in the dispersed phase interfacial film barrier properties (Bikhazi & Higuchi 1970; Ghanem et al 1970a,b; Yoon & Burgess 1996, 1997). To determine the rate of drug appearance in the continuous phase, it is necessary to separate the dispersed and continuous phases. Separation processes such as ultracentrifugation and filtration result in change in emulsion droplet size, size distribution and micellar concentration and consequently the effect of micellar phase on drug transport cannot be evaluated (Menon & Wasan 1985). Therefore the models reported here are for transport measured using side-by-side diffusion cells mounted with membranes.

Correspondence: D. J. Burgess, Department of Pharmaceutical Science, School of Pharmacy, University of Connecticut, Box U-92, 372 Fairfield Road, Storrs, CT 06269-2092, USA.
E-Mail: dburgess@uconnvm.uconn.edu

Several models have been developed for drug transport in emulsion systems (Goldberg et al 1967; Ghanem et al 1969, 1970a,b; Lostritto et al 1987; Levy & Benita 1990). Goldberg et al (1967) derived a theoretical model for interfacial transport between an aqueous and oil environment based on Fick's first law of diffusion. The effects of interfacial area, charge and continuous-phase ionic strength were included in this model. Ghanem et al (1969, 1970a,b) studied the effect of interfacial barriers on transport in emulsion systems and concluded that the presence of an adsorbed layer may alter transport rates across an interface. Bikhazi & Higuchi (1970) reported that the transport of cholesterol in o/w emulsion systems decreased in the presence of an interfacial barrier. The effect of drug/surfactant interfacial

interactions on drug transport in emulsion systems was investigated by Lostritto et al (1987). These authors developed a theoretical transport model assuming monolayer surfactant coverage at the interface and that the charged and neutral drug species have different partitioning behaviour.

The transport models reported here differ from previous theoretical models in that the present models include the effect of micellar concentration on drug transport in emulsion systems.

Theory

A physical model of the transport process in triphasic (oil, water and micellar) emulsions has been developed and is shown schematically in Figure 1. It is assumed that transport rates are first order. The rate equations for each phase (oil, aqueous donor, micelle in donor and receiver phases) are expressed as follows:

$$\frac{dQ_e}{dt} = -k_1 C_e + k_{-1} C_w \quad (1)$$

$$\frac{dQ_w}{dt} = k_1 C_e - k_{-1} C_w + k_{-3} C_m - k_3 C_w + k_{-2} C_r - k_2 C_w \quad (2)$$

$$\frac{dQ_m}{dt} = k_3 C_w - k_{-3} C_m + k_{-4} C_r - k_4 C_m \quad (3)$$

$$\frac{dQ_r}{dt} = k_2 C_w - k_{-2} C_r + k_4 C_m - k_{-4} C_r \quad (4)$$

where Q and C represent the amount and concentration of drug; subscripts e, w, m and r denote oil, aqueous donor, micelle in donor and receiver phases, respectively; k is the rate constant; and subscripts 1, 2, 3 and 4 represent oil/aqueous donor, aqueous donor/receiver, aqueous donor/micellar donor and micellar donor/receiver phase rate constants, respectively. The positive and negative signs represent the forward and reverse transport processes. Two mathematical models were developed based on drug hydrophobicity.

Mathematical model for hydrophilic drug transport in emulsion systems

In general hydrophilic drugs have low o/w partition coefficient values and consequently the o/w

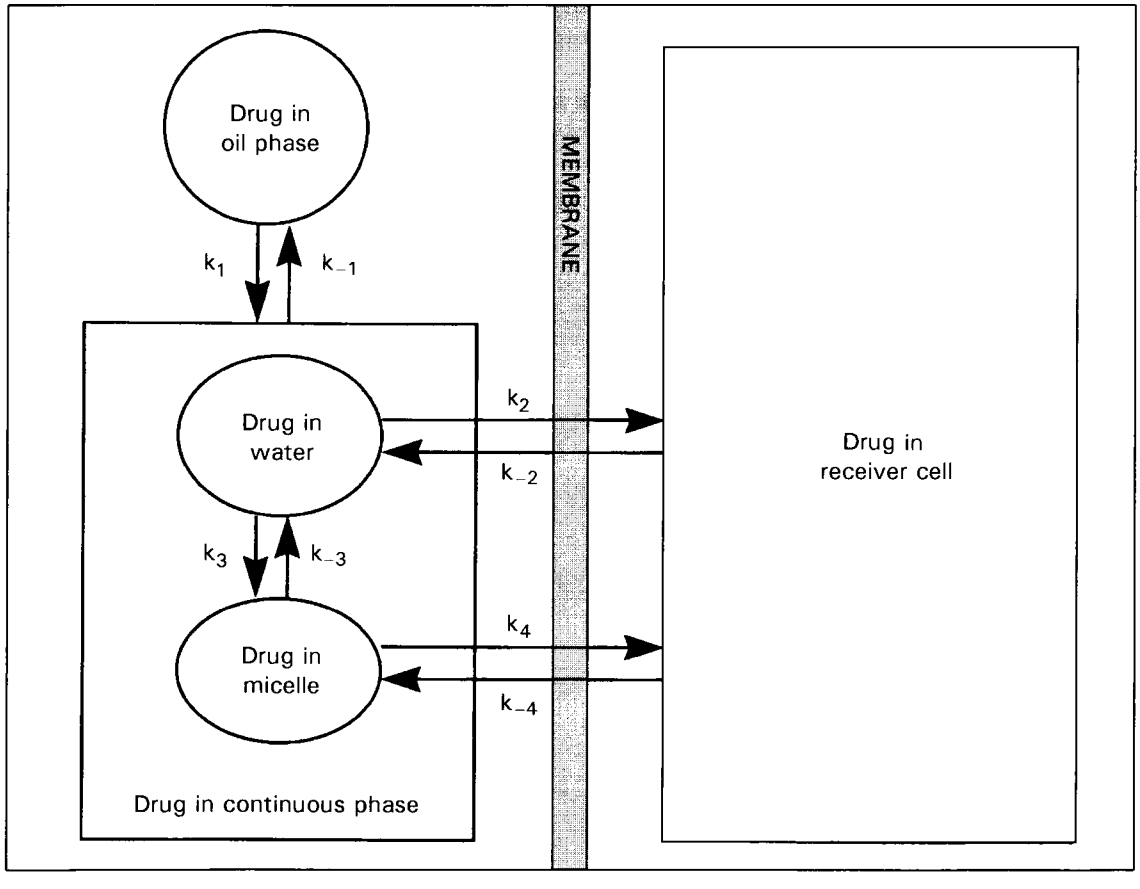

Figure 1. Schematic diagram of drug transport in triphasic emulsion systems using side-by-side diffusion cells.

interfacial resistance to transport can be neglected. Therefore, the proposed physical model is based on the hypothesis that drug transport in emulsion systems is limited by membrane transport from the donor to the receiver phase and consequently, is dependent on membrane characteristics.

Kinetic analysis of drug transport using a low molecular-weight cut-off membrane. Drug transport rates from the donor to receiver phases, using a membrane with a pore size smaller than the micellar size are assumed to be dependent on the concentration of free drug available in the aqueous phase. The rate of drug appearance in the receiver compartment in the quasi steady state can be expressed using Fick's first law as follows (Lostritto et al 1987):

$$\frac{dQ_r}{dt} = A_m P_d C_w \quad (5)$$

where A_m is the area of membrane available for diffusion, P_d is the drug permeability coefficient. C_w depends on the oil/water and micelle/water partitioning processes as well as o/w interfacial adsorption.

Mass balance of drug in the donor compartment is expressed as:

$$Q_d = Q_e + Q_w + Q_i + Q_m \quad (6)$$

where subscripts d and i denote the donor compartment and the o/w interface, respectively.

Q_e, Q_w and Q_m are expressed as:

$$Q_e = C_e V_e \quad (7)$$

$$Q_w = C_w V_w \quad (8)$$

$$Q_m = C_m V_m \quad (9)$$

where V is the phase volume.

Drug/surfactant interfacial complexation and drug interfacial activity may play a significant role in drug release from submicron-sized emulsion systems as a result of the large interfacial area. The amount of drug located at the oil droplet/water interface is related to drug-surfactant complexation and free drug interfacial activity.

Q_i was expressed by Lostritto et al (1987) as follows:

$$Q_i = Q_{id} + Q_{as} \quad (10)$$

where Q_{id} and Q_{as} are the amount of drug at the o/w interface due to the free drug interfacial activity and the amount of drug complexed to surfactant at the o/w interface, respectively. Drug/surfactant interfacial complexation is dependent on drug and surfactant characteristics. In preliminary data analysis, a one-to-one complexation can be assumed and this can be modified for a given drug, after drug/surfactant complexation has been analysed. Accordingly, equation 10 is rewritten as follows:

$$Q_i = C_w A_s (K_i + K_b S_i) \quad (11)$$

where K_i is the interfacial activity of drug oriented at the o/w interface, A_s is the total interfacial area in the donor emulsion, S_i is the surfactant concentration at the o/w interface, and K_b is the equilibrium distribution coefficient of drug bound to surfactant.

On substitution of equations 7, 8, 9 and 11 into equation 6, Q_d is expressed as:

$$Q_d = C_e V_e + C_w V_w + C_w A_s \times (K_i + K_b S_i) + C_m V_m \quad (12)$$

The partition coefficients of both the ionized and unionized drug must be considered for ionizable drugs. The o/w partition coefficient (K_e), the micellar distribution coefficient (K_m), the drug interfacial activity at the o/w interface (K_i) and the equilibrium distribution coefficient of drug bound to surfactant (K_b) are expressed as:

$$K_e = F_n K_{en} + (1 - F_n) K_{ec} \quad (13)$$

$$K_m = F_n K_{mn} + (1 - F_n) K_{mc} \quad (14)$$

$$K_i = F_n K_{in} + (1 - F_n) K_{ic} \quad (15)$$

$$K_b = F_n K_{bn} + (1 - F_n) K_{bc} \quad (16)$$

where the subscripts n and c denote the un-ionized and ionized drug, respectively. F_n is the neutral fraction of drug in the aqueous phase.

On substitution of equations 13, 14, 15 and 16 into equation 12, Q_d (the amount of drug in the donor compartment) is expressed as follows:

$$\begin{aligned} Q_d = {} & C_w V_e [F_n K_{en} + (1 - F_n) K_{ec}] \\ & + C_w V_w + C_w V_m [SAA] \\ & \times [F_n K_{nm} + (1 - F_n) K_{mc}] \\ & + C_w A_s [F_n (K_{in} + K_{bn} S_i) \\ & + (1 - F_n)(K_{ic} + K_{bc} S_i)] \end{aligned} \quad (17)$$

where [SAA] is the micellar concentration in the emulsion systems. Assuming that the value of the oil, micellar and water phases and the emulsion droplet size are constant during the experimentation, C_w is the only time-dependent variable.

The total apparent volume of drug distributed in the emulsion (V_{TE}), is expressed as:

$$V_{TE} = V_e[F_nK_{en} + (1 - F_n)K_{ec} + V_w + V_m[SAA][F_nK_{mn} + (1 - F_n)K_{mc}] + A_s[F_nK_{in} + K_{bn}S_i) + (1 - F_n)(K_{ic} + K_{bc}S_i)] \quad (18)$$

Substituting equation 18 into equation 17, equation 19 is obtained:

$$C_w = \frac{Q_d}{V_{TE}} = \frac{Q_o - Q_r}{V_{TE}} \quad (19)$$

where Q_o is the initial amount of drug in the donor compartment.

Substituting equation 19 into equation 5, equation 20 is obtained:

$$-\frac{dQ_d}{dt} = \frac{dQ_r}{dt} = \frac{A_mP_d}{V_{TE}}(Q_o - Q_r) \quad (20)$$

Using the initial condition ($Q_r = 0$ at $t = t_l$, where t_l is the lag time) and the quasi steady-state approximation, equation 20 can be integrated as follows:

$$\ln(Q_d) = \ln(Q_o) - \frac{A_mP_d}{V_{TE}}(t - t_l) \quad (21)$$

Using Equation 21, V_{TE} may be calculated from the slope of ln (Q_d) versus time ($t-t_l$) when the values of A_m and P_d are known. The effect of individual parameters (partition coefficient, micellar distribution coefficient, drug interfacial activity and equilibrium distribution coefficient of drug bound to surfactant) on drug transport may be determined by analysis of the V_{TE} parameter.

Kinetic analysis of drug transport using a high molecular-weight cut-off membrane. Drug transport rates using a membrane with a pore size large enough for micelles to pass through are assumed to be dependent on both the free-drug concentration in the aqueous phase and that entrapped in the micellar phase. The quasi steady-state rate of drug appearance into the receiver compartment from a submicron emulsion donor compartment may be defined using Fick's first law as follows:

$$\frac{dQ_r}{dt} = A_m(P_d + P_m\{F_nK_{mn} + (1 - F_n)K_{mc}\}[SAA])C_w \quad (22)$$

where P_m is the permeability coefficient of micelles through a high molecular-weight cut-off membrane, K_m is the equilibrium distribution coefficient between the micellar and aqueous phases, and [SAA] is the amount of micelles in the emulsion.

By substituting equation 19 into equation 22, equation 22 can be rewritten as:

$$\frac{dQ_r}{dt} = \frac{A_m(P_d + P_m\{F_nK_{mn} + (1 - F_n)K_{mc}[SAA])}{V_{TE}} \times (Q_o - Q_r) \quad (23)$$

Using the initial condition ($Q_r = 0$ at $t = t_l$) and the quasi steady-state approximation, equation 23 can be integrated as follows:

$$\ln(Q_d) = \ln(Q_o) - \frac{A_m(P_d + P_m\{F_nK_{mn} + (1 - F_n)K_{mc}[SAA])}{V_{TE}} \times (t - t_l) \quad (24)$$

Equation 24 is used in the calculation of the total apparent volume of drug distributed between different phases in the donor compartment (V_{TE}). As mentioned in the previous section, V_{TE} can be used to determine the effect of individual parameters on drug transport kinetics.

Mathematical model for hydrophobic drug transport in emulsions

Hydrophobic drugs have high o/w partition coefficients resulting in a low driving force for oil/continuous phase transport. Consecutive rate equations were used to develop a mathematical model for hydrophobic drug transport. The model is based on the assumption that the o/w interface behaves as a membrane to drug transport. In this model it is assumed that drug transport through the o/w interface is governed by the drug concentration gradient across the interface and that reverse transport from the continuous to the dispersed phases approximates zero, since the aqueous-phase drug concentration is low (Figure 1). At surfactant concentrations above the critical micelle concentration (CMC) it is assumed that drug micellar solubilization is faster than oil/continuous phase drug transport. Therefore free drug and micelle-solubilized drug are in equilibrium in the continuous phase.

The rate equations for each phase are expressed as follows:

$$\frac{dQ_e}{dt} = -k_{1app}A_sC_e \quad (25)$$

$$\frac{dQ_{wm}}{dt} = k_{1app}A_sC_A - k_{2app}A_mC_{wm} \quad (26)$$

$$\frac{dQ_r}{dt} = k_{2app}A_mC_{wm} \quad (27)$$

where subscript wm denotes the continuous phase in emulsion systems. k_{1app} and k_{2app} are the

apparent oil/continuous phase partitioning rate coefficient and the apparent membrane transport rate coefficient, respectively.

The oil/continuous phase transport rate is proportional to the partition coefficient and the emulsion droplet interfacial area, according to the assumption that the o/w interface behaves as a transport barrier, similar to a membrane. The micellar concentration affects the oil/continuous phase partition coefficient (K_s) and consequently alters the oil/continuous phase partitioning rate (k_{1app}), as follows:

$$K_s = \frac{K_e}{1 + K_m[SAA]} \tag{28}$$

$$k_{1app} = \frac{k_1}{K_s} \tag{29}$$

where k_1 is the oil/continuous phase partitioning rate coefficient. Micellar concentration also affects the apparent membrane transport rate (k_{2app}), assuming that free-drug concentration in the continuous phase only passes through the membrane, as follows:

$$k_{2app} = \frac{k_2}{1 + K_m[SAA]} \tag{30}$$

where k_2 is the membrane transport rate coefficient.

On substitution of equations 29 and 30 into equations 25, 26 and 27, the following are obtained:

$$-\frac{dQ_e}{dt} = \frac{k_1 A_s Q_e}{K_s V_e} \tag{31}$$

$$\frac{dQ_{wm}}{dt} = \frac{k_1 A_s Q_e}{K_s V_e} - \frac{k_2 A_m Q_{wm}}{V_w(1 + K_m[SAA])} \tag{32}$$

$$\frac{dQ_r}{dt} = \frac{k_2 A_m Q_{wm}}{V_w(1 + K_m[SAA])} \tag{33}$$

Equations 31, 32 and 33 integrated with respect to time, are written as:

$$Q_e = Q_o \exp\left(-\frac{k_1 A_s t}{K_s V_e}\right) \tag{34}$$

$$Q_{wm} = \frac{k_1 A_s Q_e}{K_s V_e\left(\frac{k_2 A_m}{V_w(1 + K_m[SAA])} - \frac{k_1 A_s}{K_s V_e}\right)} \left[\exp\left(-\frac{k_1 A_s t}{K_s V_e}\right) - \exp\left(-\frac{k_2 A_m t}{V_w(1 + K_m[SAA])}\right)\right] \tag{35}$$

and

$$Q_r = Q_o\left[1 + \frac{1}{\left(\frac{k_1 A_s}{K_s V_e} - \frac{k_2 A_m}{V_m(1 + K_m[SAA])}\right)} \times \left(\frac{k_2 A_m}{V_w(1 + K_m[SAA])} \exp\left(-\frac{k_1 A_s t}{K_s V_e}\right) - \frac{k_1 A_s}{K_s V_e} \exp\left(-\frac{k_2 A_m t}{V_w(1 + K_m[SAA])}\right)\right)\right] \tag{36}$$

The cumulative amount of drug in the receiver cells (Q_r) is dependent on the oil/continuous phase partitioning rate coefficient (k_1) and the membrane transport rate coefficient from the donor to the receiver phases (k_2). The k_1 and k_2 values must be obtained to evaluate whether the rate-determining step is the partitioning process, membrane transport, or both.

In the present study, these models were evaluated by comparing simulated and experimental data. Mineral oil was selected as the oil phase, since it does not contain any surface-active impurities. Polyoxyethylene (10) oleyl ether (Brij 97) and cetyltrimethylammonium bromide (CTAB) were selected as nonionic and cationic surfactants, respectively. Benzoic acid and phenol were selected as hydrophilic model drugs, and PAA and benzocaine were selected as lipophilic model drugs. The effective permeability coefficients (P_{eff}) of model drugs in emulsion systems using side-by-side diffusion cells were reported previously to be controlled by several mechanisms, such as the partitioning process between the oil, water and micellar phases and membrane transport (Yoon & Burgess 1996, 1997).

Materials and Methods

Materials

Mineral oil, phenol, sodium chloride, monobasic sodium phosphate, and hydrophilic Spectrapor 7 dialysis membranes (molecular-weight cut-offs, 1 kD and 50 kD) were purchased from Fisher Scientific (Springfield, NJ). Hydrophobic polydimethylsiloxane membranes (PDMS, 0·005-inch) were purchased from Cardiovascular Instrument Corporation (Wakefield, MA). Phenylazoaniline (PAA) was purchased from Aldrich Chemical Company Inc. (Milwaukee, WI). Benzocaine and benzoic acid were purchased from Sigma (St Louis, MO). Cetyltrimethylammonium bromide was purchased from Eastman Kodak (Rochester, NY). Polyoxyethylene (10) oleyl ether (Brij 97) was a gift from ICI (Rochester, NY). All chemicals were

used as received without further purification. Deionized water obtained from a NANOpure ultrapure water system (D4700, Barnstead, Dubuque, IW) was used in all experiments.

Emulsion preparation

Mineral oil-in-water emulsions (20% v/v) were prepared as follows: initial surfactant concentrations of Brij 97 and CTAB were 6·2 and 2% w/v, respectively; surfactant was added to 80 mL pH 7·0 phosphate buffer (0·05 M, ionic strength I = 0·2) and mixed. Benzoic acid emulsions were also prepared with pH 3·0 phosphate buffer. A known amount of model drug (PAA, 65·7 mg; benzocaine, 40·0 mg; benzoic acid, 61·7 mg; phenol, 51·5 mg) was dissolved in 20 mL mineral oil. The two phases were mixed to form coarse emulsions and passed through a microfluidizer (Model 110T, Microfluidics, Newton, MA) five times using an external pneumatic pressure of approximately 80 psi. The resultant emulsions were diluted 1 : 1 with buffer or surfactant/buffer solution to yield 10% v/v oil phase and different surfactant concentrations.

Model drug solubility

Model drug solubilities were measured at 37°C using excess drug in phosphate buffer (0·05 M, ionic strength 0·2, pH 7·0) containing Brij 97 or CTAB at concentrations of 0–2% w/v. After equilibration for 48 h, the model drug suspensions were filtered and analysed spectrophotometrically (Milton Roy Spectronic 3000 Array, Rochester, NY). The absorbance peak values of PAA, benzocaine and phenol occurred at 377 nm, 286 nm and 271 nm, respectively, in the buffer solution, at 398 nm, 294 nm and 273 nm, respectively, in the presence of Brij 97 solution and at 398 nm, 296 nm and 273 nm, respectively, in the presence of CTAB solution. Since the benzoic acid absorbance peak occurred on the shoulder of the CTAB absorbance peak, benzoic acid in CTAB/buffer solutions was analysed spectrophotometrically, from 210 nm to 300 nm, using a deconvolution program (Perkin-Elmer 7300). Benzoic acid in Brij 97/buffer solution was analysed by HPLC (Waters Assoc. Model 440, Milford, MA) equipped with a UV detector (Waters Assoc. Model 441) set at 226 nm and a reversed phase column (μ Bondapak C_{18}, 10 μm, 30 cm × 3·9 mm i.d.; Waters Assoc.). The mobile phase, a mixture of 0·005 M monobasic sodium phosphate (pH 3·0) and methanol (1 : 1, v/v), was operated at a flow rate of 1·3 mL min^{-1}.

Oil/buffer partition coefficient determination

Two millilitres of oil containing model drug were kept in contact with 2 mL pH 7·0 phosphate buffer solution at 37 ± 0·1°C for 48 h. After equilibrium, the phases were separated, collected and analysed for model drug content using UV and FTIR (Nicolet 66) spectrophotometers.

Model drug transport

Water-jacketed diffusion cells (glass chambers, 4-mL volume and 11-mm diameter available for diffusion) mounted with either dialysis (molecular-weight cut-offs 1 kD and 50 kD) or hydrophobic (PDMS) membranes were used for kinetic studies of model drug transport in emulsions at 37 ± 0·1°C. The dialysis membranes were hydrated in receiver solution for 30 min before use. Drug-loaded emulsions, diluted 1:1 with different surfactant/buffer solutions, were placed into the donor cells. The receiver cells contained drug-free surfactant/buffer solution at the same concentration as the emulsion micellar phase. Each chamber was stirred using a magnetic stirrer. Samples (2 mL) were withdrawn at intervals from the receiver cells and analysed. Sink conditions were maintained by replacing cell samples with surfactant/buffer solutions. Control studies to determine model drug transport rates in buffer and surfactant/buffer solutions were conducted as above.

All the above experiments were repeated three times. Mean values and standard deviations were calculated.

Results and Discussion

Data analysis for hydrophilic model drugs

In the hydrophilic model, drug transport in emulsion systems is rate limited by membrane transport as a consequence of instantaneous equilibrium of drug partitioning between the oil and continuous phases. The effective permeability coefficient (P_{eff}) for hydrophilic drugs is related to the total apparent volume of drug distributed between different phases in the donor compartment (V_{TE}) as follows:

$$\begin{aligned} P_{eff} &= \frac{P_d}{V_{TE}} \\ &= P_d/\{V_e[F_n K_{en} + (1 - F_n)K_{ec}] \\ &\quad + V_w + A_s[F_n(K_{in} + K_{bn}S_i) \\ &\quad + (1 - F_n)(K_{ic} + K_{bc}S_i)] + V_m[SAA] \\ &\quad \times [F_n K_{mn} + (1 - F_n)K_{mc}]\} \end{aligned} \quad (37)$$

Therefore, P_{eff} of hydrophilic drugs in emulsion systems is expected to decrease with increase in the micellar concentration.

The expected P_{eff} values of benzoic acid and phenol can be calculated according to equation 37. The P_d, K_e, K_m, V_e, V_w and A_s values for benzoic acid and phenol are listed in Table 1. The model drug interfacial activity (K_i) and the model drug–surfactant interactions at the o/w interface (K_bS_i) cannot be determined experimentally and consequently these two parameters were assumed to be constant. The permeability coefficient (P_d) of benzoic acid in the buffer system was used in the calculation of the effective permeability coefficient (P_{eff}) for samples measured using the 1-kD molecular-weight cut-off dialysis membrane, since the micelles are too large to pass through this membrane. Although micelles can pass through the 50-kD molecular-weight cut-off dialysis membrane, the benzoic acid permeability coefficient (P_d) was used instead of $P_d + P_m$ [SAA] in the calculation of P_{eff}, since micellar permeability was low compared to that of free benzoic acid due to hindered diffusion of micelles through the membrane.

The P_{eff} values calculated using equation 4 were compared with the P_{eff} values determined experimentally (Table 2). The predicted cumulative amounts of benzoic acid in the receiver cells (Q_r) were calculated using the P_{eff} values. The predicted and experimental cumulative amounts of benzoic acid in the receiver cells at pH 3·0 are compared in Figure 2. The experimental P_{eff} values of benzoic acid in both Brij 97 and CTAB emulsions at pH 3·0 decreased with increase in micellar concentration. The predicted data of benzoic acid at pH 3·0 are in agreement with the experimental data. Univariate analysis of variance was employed to test for differences in the effective permeability coefficients among different micellar concentrations. The significance levels (*P* values) are lower than 0·01, indicating statistical significance. The calculated values for benzoic acid interfacial activity and benzoic acid-surfactant interaction, A_s ($K_i + K_bS_i$), for CTAB and Brij 97 emulsions are 4·2027 and 0·2553, respectively. Benzoic acid (pH 3·0) is considered to have greater interfacial interaction with CTAB compared to Brij 97 due to the higher interaction activity value.

The solubility of phenol at pH 7·0 was not influenced by the presence of Brij 97 and CTAB, and therefore the micellar distribution coefficients of phenol are zero for both surfactants. The calculated P_{eff} value of phenol using Equation 4 was unaffected by Brij 97 and CTAB micellar phases and this is in agreement with the experimental data (Table 3). A similar trend was observed for benzoic acid transport in Brij 97 emulsions at pH 7·0, since benzoic acid does not interact with Brij 97. However, at pH 7·0 benzoic acid complexes with CTAB as a result of ionic interaction and this complex apparently affects both drug partitioning and membrane transport rates. This benzoic acid-/CTAB interfacial complexation influenced the P_{eff} value. These data are not in agreement with the hydrophilic model, since this model does not take into account the effects of model drug-surfactant complex permeability, interfacial interaction and micellar shape on the transport process. Consequently, this model did not predict the transport rate of benzoic acid in CTAB emulsions at pH 7·0.

Data analysis for hydrophobic model drugs

The appearance rates of hydrophobic drugs in the receiver cells are dependent on both the oil/continuous phase partitioning rates (k_1) and membrane transport rates (k_2), since the oil/continuous phase partitioning process is not instantaneous for these molecules. The k_1 and k_2 values can be obtained by fitting the hydrophobic drug model to the experimental data (cumulative amount of drug in the receiver cells vs time) using PC Nonlin, according to

Table 1. The K_e, K_m, V_e, V_w, A_s and P_d values of benzoic acid, phenol, benzocaine and PAA determined experimentally for Brij 97 and CTAB emulsion systems (pH 3·0 and pH 7·0, I = 0·2, at 37°C).

Parameters	Benzoic acid (pH 3·0)		Benzoic acid (pH 7·0)		Phenol (pH 7·0)		PAA (pH 7·0)		Benzocaine (pH 7·0)	
	Brij 97	CTAB	Brij 97	CTAB	Brij 97	CTAB	Brij 97	CTAB	Brij 97	CTAB
K_e	0·23	0·23	0·25	0·25	0·11	0·11	120	120	1·19	1·19
K_m ($cm^3g^{-1} \times 10^2$)	0·20	0·45	*	*	0	0	58	110	0·25	2·56
V_e (cm^3)	0·4	0·4	0·4	0·4	0·4	0·4	0·4	0·4	0·4	0·4
V_w (cm^3)	3·6	3·6	3·6	3·6	3·6	3·6	3·6	3·6	3·6	3·6
A_s ($cm^2 \times 10^3$)	218	136	218	136	218	136	218	136	218	136
P_d ($cm\,h^{-1}$) (MW 1 kD)	0·15	0·15	0·14	0·14	0·29	0·29	0·675	0·675	0·561	0·561
P_d ($cm\,h^{-1}$) (MW 50 kD)	0·18	0·18	0·14	0·14	0·38	0·38	1·25	1·25	0·761	0·761

*Not determined.

Table 2. The effective permeability coefficients of benzoic acid predicted using the hydrophilic model and determined experimentally in emulsion systems at pH 3·0 at 37°C.

Surfactant	Concn (% w/v)	Effective permeability coefficients (cm h^{-1}) using different membranes			
		MW 1 kD		MW 50 kD	
		Predicted value	Experimental value	Predicted value	Experimental value
Brij 97	0	0·038	0·038±0·001	0·044	0·044±0·001
	1	0·033	0·033±0·001	0·037	0·038±0·002
	2	0·027	0·026±0·001	0·032	0·030±0·001
CTAB	0	0·020	0·020±0·001	0·025	0·025±0·001
	0·5	0·017	0·017±0·001	0·0230	·021±0·001
	1·0	0·017	0·016±0·001	0·021	0·020±0·001

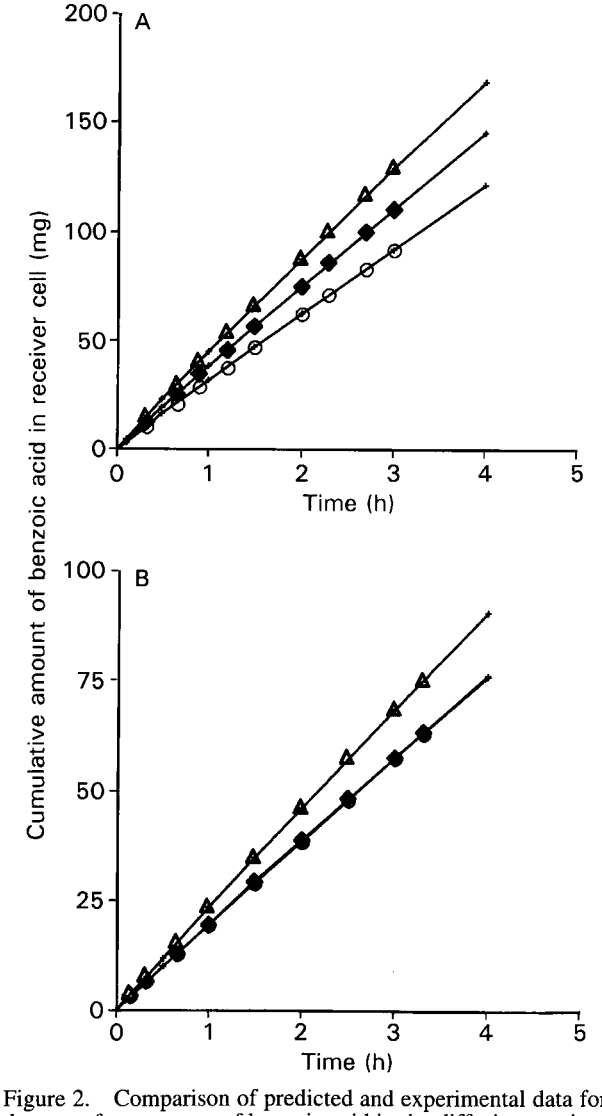

Figure 2. Comparison of predicted and experimental data for the rate of appearance of benzoic acid in the diffusion receiver cells using 1-kD molecular-weight cut-off membrane. Lines represent predicted data and symbols represent experimental data. A. The donor cells contain Brij 97 emulsions and the receiver cells contain Brij 97 buffer (△ 0 %, ◆ 1 %, ○ 2 %). B. The donor cells contain CTAB emulsions and the receiver cells contain CTAB buffer (△ 0 %, ◆ 0.5 %, ○ 1 %).

equation 36. The transport rates of PAA and benzocaine in Brij 97 and CTAB emulsions were predicted using this model. The values of the constants (the initial amount of drug [Q_o], total o/w interfacial area [A_s], membrane area [A_m], oil phase volume [V_e] and continuous phase volume [V_w]) used in this model are listed in Table 3. The predicted values of k_1 and k_2 represent the o/w interfacial barrier for drug transport and the drug permeability coefficient through the membrane, respectively (Table 4). However, the calculated k_1 values are approximate due to a limitation of the model, since the drug concentration in the continuous phase can not be determined experimentally.

The predicted amounts of PAA and benzocaine in the receiver cells (Q_r) were calculated using the values of k_1 and k_2 and compared with the experimental data of PAA and benzocaine in emulsion systems (Figures 3 and 4). The predicted data are in agreement with the experimental data. *P* values for different micellar concentrations are lower than 0·01 and therefore the differences in the k_1 and k_2 values are statistically significant. In Brij 97 and CTAB emulsions, the o/w interfacial barrier (k_1) did not depend on the molecular-weight cut-off of the membranes, since the calculated k_1 values were similar for both the 1-kD and the 50-kD membranes. The o/w interfacial barrier (k_1) increased slightly with increase in Brij 97 and CTAB micellar concentrations. This may be due to alteration of the interfacial film characteristics as a result of micellar adsorption.

The apparent partitioning rate (k_{1app}) of model drugs from the oil to the continuous phases is expressed using equation 29.

The k_{1app} values of PAA and benzocaine in Brij 97 and CTAB emulsions increased with increase in the micellar concentration (Table 4). This was thought to be due to the effect of micelles on K_s, since increase in micellar concentration decreased

Table 3. The effective permeability coefficients (P_{eff}) of benzoic acid and phenol predicted using the hydrophilic model and determined experimentally in emulsion systems at pH 7·0 at 37°C.

Surfactant	Micellar concn (% w/v)	Effective permeability coefficients (cm h^{-1}) using 1-kD MW membrane			
		Benzoic acid		Phenol	
		Predicted value	Experimental value	Predicted value	Experimental value
Brij 97	0	0·072	0·072 ± 0·001	0·050	0·049 ± 0·01
	1	0·072	0·071 ± 0·001	0·050	0·050 ± 0·002
	2	0·072	0·072 ± 0·001	0·050	0·050 ± 0·001
CTAB	0		0·024 ± 0·001	0·050	0·050 ± 0·002
	0·5		0·048 ± 0·001	0·050	0·050 ± 0·002
	1·0		0·029 ± 0·001	0·050	0·050 ± 0·002

Table 4. The calculated partitioning rates (k_1) and the membrane permeability coefficients (k_2) of PAA and benzocaine through molecular-weight cut-offs 1-kD and 50-kD membranes in Brij 97 and CTAB emulsion systems using the PC Nonlin program.

Surfactant	Concn (% w/v)	PAA		Benzocaine	
		Partitioning rates (k_1, cm h^{-1})		Membrane permeability coefficient (P_d, cm h^{-1})	
		MW 1 kD	MW 50 kD	MW 1 kD	MW 50 kD
Brij 97	0·5	0·0105	0·0107	0·0724	0·0957
	1·0	0·0117	0·0112	0·1609	0·2169
	1·5	0·0117	0·0119	0·2128	0·2897
	2·0	0·0122	0·0121	0·2258	0·3907
CTAB	0·1	0·0118	0·0121	0·0155	0·0758
	0·3	0·0126	0·0128	0·0535	0·0760
	0·5	0·0123	0·0120	0·1153	0·1380
	0·8	0·0149	0·0150	0·1163	0·1432
	1·0	0·0121	0·0158	0·1190	0·1751
	3·0	0·0190	0·0199	0·3680	0·5218

K_s (Yoon & Burgess 1996, 1997). The k_2 values increased with increase in micellar concentration. This was thought to be due to the effect of micelles on drug transport across the aqueous boundary layer (Amidon et al 1982). The P_{eff} values of PAA and benzocaine increased with increase in surfactant concentration up to 1% w/v Brij 97 and 0·5% w/v CTAB and decreased at higher surfactant concentrations.

Conclusions

Mathematical models were developed according to drug hydrophobicity. The model developed for hydrophilic drugs is based on Fick's first law. Consecutive rate equations were used in the hydrophobic drug model. These transport models are useful in describing drug release from emulsions in the presence of a micellar phase, where a membrane barrier method is used to determine release.

The P_{eff} values of hydrophilic drugs calculated using parameters such as drug/membrane permeability and partition coefficient values were consistent with the experimental data validating the hydrophilic model. An exception was benzoic acid in CTAB emulsions at pH 7·0. This was considered to be due to the ionic interaction between benzoic acid and CTAB at pH 7·0 and consequent micellar shape change which affects the partitioning and membrane transport process. The transport of benzoic acid at pH 3·0 did follow the hydrophilic model (no ionic interaction with surfactant). Hydrophobic drug transport calculated using partitioning o/w interfacial barrier and membrane transport rates was consistent with the hydrophobic model.

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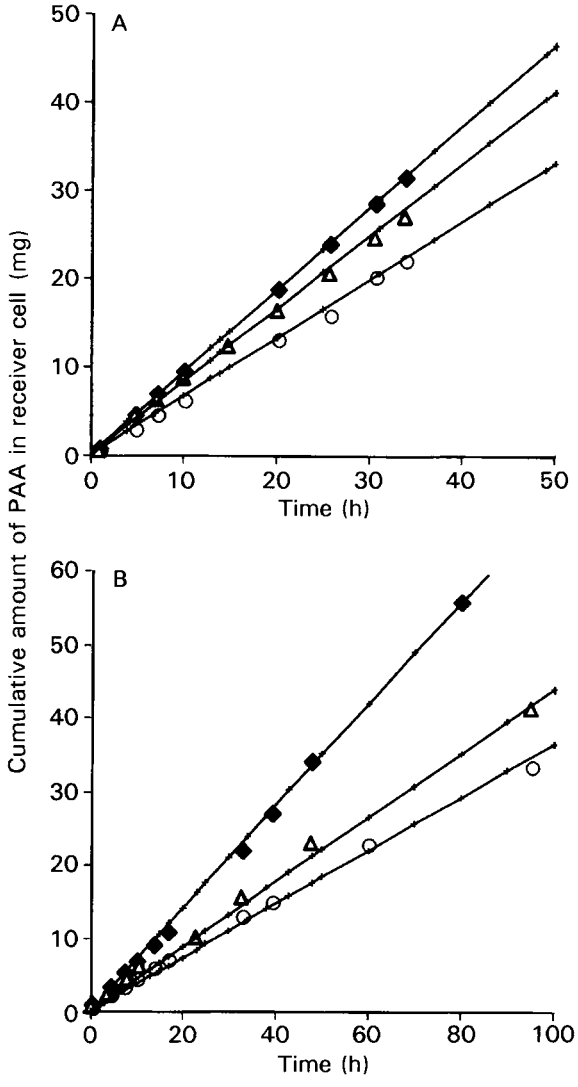

Figure 3. Comparison of predicted and experimental data for the rate of appearance of PAA in the diffusion receiver cells using 1-kD molecular-weight cut-off membrane. Lines represent predicted data and symbols represent experimental data. A. The donor cells contain Brij 97 emulsions and the receiver cells contain Brij 97 buffer (△ 0·5%, ◆ 1%, ○ 2%). B. The donor cells contain CTAB emulsions and the receiver cells contain CTAB buffer (△ 0·1%, ◆ 0·5%, ○ 1%).

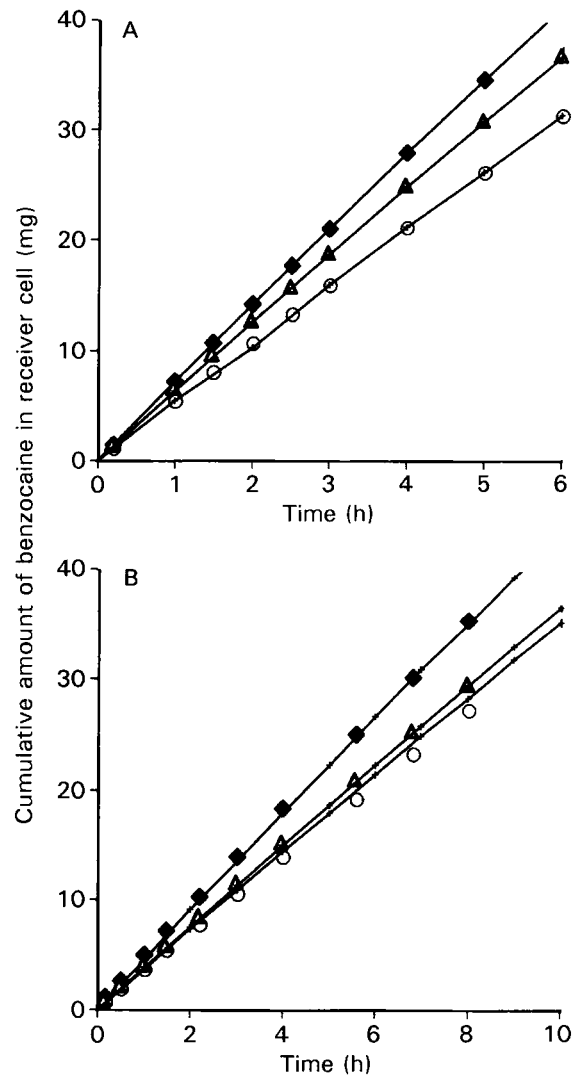

Figure 4. Comparison of predicted and experimental data for the rate of appearance of benzocaine in the diffusion receiver cells using 1-kD molecular-weight cut-off membrane. Lines represent predicted data and symbols represent experimental data. A. The donor cells contain Brij 97 emulsions and the receiver cells contain Brij 97 buffer (△ 0%, ◆ 1%, ○ 2%). B. The donor cells contain CTAB emulsions and the receiver cells contain CTAB buffer (△ 0%, ◆ 0·5%, ○ 1%).

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