Mathematical Modeling of Surface-Active and Non-Surface-Active Drug Transport in Emulsion Systems

Submitted: June 29, 2000; Accepted: September 8, 2000; Published: September 20, 2000.

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ABSTRACT Mathematical models were developed for the prediction of surface-active and non-surface-active drug transport in triphasic (oil, water, and micellar) emulsion systems as a function of micellar concentration. These models were evaluated by comparing experimental and simulated data. Fick's first law of diffusion with association of the surface-active or complexation nature of the drug with the surfactant was used to derive a transport model for surface-active drugs. This transport model assumes that the oil/water (O/W) partitioning process was fast compared with membrane transport and therefore drug transport was limited by the membrane. Consecutive rate equations were used to model transport of non-surface-active drugs in emulsion systems assuming that the O/W interface acts as a barrier to drug transport. Phenobarbital (PB) and barbitol (B) were selected as surface-active model drugs. Phenylazoaniline (PAA) and benzocaine (BZ) were selected as non-surface-active model drugs. Transport studies at pH 7.0 were conducted using side-by-side diffusion cells and bulk equilibrium reverse dialysis bag techniques. According to the surface-active drug model, an increase in micellar concentration is expected to decrease drug-transport rates. Using the Microsoft EXCEL program, the non-surface-active drug model was fitted to the experimental data for the cumulative amount of the model drug that disappeared from the donor chamber. The oil/continuous phase partitioning rates (k_1) and the membrane transport rates (k_2) were estimated. The predicted data were consistent with the experimental data for both the surface-active and non-surface-active models.

INTRODUCTION

The phenomenon of mass transport has been extensively reviewed and is important in the understanding of drug transport processes (1-3). Drug transport through membranes may be described by Fick's first law of diffusion (4). The permeability coefficient of a permeant through a membrane can be affected by micelle formation, complex formation, and the presence of cosolvents because they can affect the thermodynamic activity of the permeant either in the medium or in the barrier (5-7). If the permeant has no affinity for the micelle, the micellar phase has no significant effect on membrane transport. As the affinity of the permeant for the micellar phase increases, the fraction of unassociated diffusing species will be depleted and the flux will decrease proportionally. When the permeant has high micellar affinity, transport is limited by the rate of micellar diffusion and/or the driving force to transfer the diffusant from the micellar phase and into the membrane.

The simplest theoretical model for drug transport in emulsion systems was developed by Madan (8). This model was based on the drug partition coefficient between the two phases and used mass balance to determine the drug concentration in the two phases. Three other theoretical models have been developed by Goldberg et al (9), Ghanem et al (10-12), and Lostritto et al. (13). These models include the effect of interfacial film characteristics on emulsion transport. Goldberg et al. (9) derived a theoretical model for interfacial transport between an aqueous and oil environment based on Fick's first law of diffusion. They included the effects of interfacial area, interfacial charge, and continuous phase ionic strength on drug transport in oil/water (O/W) emulsion systems. Ghanem et al. (10,11) studied the effect of interfacial barriers on transport in emulsion systems. They also reported that the transport rates of

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diethyl phthalate and cholesterol were increased in the presence of surfactants such as sodium lauryl sulfate and dodecylpyridinium chloride and were decreased by electrolytes (12). These researchers developed a theoretical model for drug transport in emulsions, which included the effect of an adsorbed gelatin interfacial film. Bikhazi and Higuchi (14) reported that the transport of cholesterol in O/W emulsion systems decreased because of the interfacial barrier. The effect of interfacial interactions between drugs and surfactants on drug transport in emulsion systems was investigated by Lostritto et al. (13), who developed a theoretical model assuming monolayer surfactant coverage at the interface.

Yoon and Burgess (15) were the first to consider the effect of the micellar phase on drug transport in emulsion systems. However, their model did not include the effect of the micellar phase on surface-active model drugs, where the drug may compete with the surfactant for the interface and consequently can affect emulsion stability and the transport phenomenon of the model drug. The model proposed in this research is an extension of the Yoon and Burgess model (15) to surface-active model drugs. In addition, the Yoon and Burgess model and other previous models are limited because they are based on the use of side-by-side diffusion cell technique to determine the release rates of the model drugs from the emulsion systems. It has been shown that the side-by-side diffusion cell technique can lead to violation of sink conditions because of the limited membrane surface area available for transport compared with the interfacial area (16).

Theory

Model drug transport in emulsion systems can be affected by the presence of excess surfactant, as described elsewhere (16-18). The effective permeability coefficients of model drugs in emulsion systems are controlled by several mechanisms, such as the partitioning process between the oil, water, and micellar phases and membrane transport. A physical model of this transport process is shown schematically in Figure 1. The rate equation for each phase (oil, aqueous, micelle, and receiver phases) can be expressed using the following equations:

$$\frac{dQ_A}{dt} = -k_1C_A + k_{-1}C_B \quad (1)$$

$$\frac{dQ_B}{dt} = k_1C_A - k_{-1}C_B + k_{-3}C_M - k_3C_B + k_{-2}C_R - k_2C_B \quad (2)$$

$$\frac{dQ_R}{dt} = k_2C_B - k_{-2}C_R - k_4C_M + k_{-4}C_R \quad (3)$$

$$\frac{dQ_M}{dt} = k_3C_B - k_{-3}C_M - k_{-4}C_R + k_4C_M \quad (4)$$

Where Q_A , Q_B , Q_M , and Q_R are the amounts of the drug in the oil, aqueous, micellar, and receiver phases, respectively and C_A , C_B , C_M , and C_R are the concentrations of the drug in the oil, aqueous, micellar, and receiver phases, respectively. Subscripts 1, 2, 3, and 4 represent rate constants for transfer from oil to the aqueous phase in the donor chamber, from the continuous aqueous phase in the donor chamber to the receiver, from the aqueous phase in the donor chamber to the micelles in the donor chamber, and from the micelles in the donor chamber to the receiver phases, respectively. The positive and negative signs represent the forward and reverse transport processes. Two mathematical models were developed based on model drug lipophilicity.

Mathematical Model for Hydrophilic Drug Transport in Triphasic Systems

Most hydrophilic drugs will reside in the continuous phase because of low O/W partition coefficients, and therefore resistance across the O/W interface can be neglected. Consequently, the proposed physical model is based on the hypothesis that drug release rates from emulsion systems are limited by membrane transport. A major difference between this model and previous models is that the micellar phase and surface-active nature of the model drugs are accounted for in this model. The transport rates of model drugs using the molecular weight (MW) cutoff of 1 kd membrane depend on the concentration of free drug available to the aqueous

Figure 1. Schematic diagram for drug transport in triphasic emulsion systems.

phase because micelles are unable to permeate this membrane. The transport rates of model drugs using an MW cutoff of 50 kd membrane depend on the concentration of free drug available in the aqueous phase and on the concentration of drug trapped in the micellar phase. Therefore, Equation 3 can be expressed by Fick's first law equation.

Kinetic Analysis for Drug Transport

This analysis is applicable for hydrophilic model drugs. The quasi-steady-state rate of appearance of drug mass into the receiver compartment (Q_R) from a submicron emulsion donor compartment separated by a semipermeable membrane (such as an MW cutoff 1 kd dialysis membrane) may be defined using Fick's first law as

$$\frac{dQ_R}{dt} = A_m P_d C_W \quad (5)$$

where A_m is the area of membrane available for diffusion, P_d is the permeability coefficient of the drug, and C_W is the drug concentration in the aqueous phase of the donor compartment at a specific time, t . C_W depends on the O/W and micelle/water partitioning processes as well as O/W interfacial adsorption in the donor compartment.

Mass balance of the drug in the donor compartment (Q_d) is expressed as

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

where Q_d , Q_e , Q_W , Q_i , and Q_m are the amount of drug in the donor compartment, the emulsion droplets, the aqueous phase, the O/W interface, and the micellar phase, respectively.

Q_e (the amount of drug in the emulsion droplets) is expressed as

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

where C_e and V_e are the drug concentrations in the emulsion droplets and the volume of the oil phase, respectively.

Q_W (the amount of the drug in the aqueous phase) is expressed as

$$Q_W = C_W V_W \quad (8)$$

where C_W and V_W are the drug concentrations in the aqueous phase and volume of the aqueous phase.

Drug complexation to the surfactants at the interface and the interfacial activity of the drug may play a significant role on drug release from submicron-sized emulsion systems due to their large interfacial area. Therefore, the amount of drug located at the oil droplet/water interface is related to drug-surfactant complexation and the interfacial activity of the free drug.

Q_i (the amount of drug at the O/W interface) is expressed as

$$Q_i = Q_{id} + Q_{as} \quad (9)$$

where Q_{id} and Q_{as} are the amount of the drug at the O/W interface due to the interfacial activity of the free drug and the amount of the drug complexed to the surfactant at the O/W interface, respectively.

The interfacial activity of the free drug can be expressed as

$$C_W \xrightleftharpoons{K_i} C_i \quad (10)$$

and K_i is expressed as

$$K_i = \frac{C_i}{C_W} \quad (11)$$

where C_i and k_i are the drug concentration at the O/W interface and the interfacial activity of drug oriented at the O/W interface due to the free energy, respectively.

Q_{id} (the amount of drug at the O/W interface due to interfacial activity of free drug) can be expressed as

$$Q_{id} = A_s k_i C_w \quad (12)$$

where A_s is the total interfacial area in the donor emulsion.

Complexation of drug with surfactant at the O/W interface is dependent on the characteristics of both the drug and the surfactant. However, for preliminary data analysis, one-to-one complexation of drug with surfactant is assumed. The complexation equation can be modified for each drug. Complexation of drug with surfactants at the O/W interface (assuming one-to-one complexation) can be expressed as

and K_0 is expressed as

$$K_0 = \frac{C_{is}}{C_w S_i} \quad (14)$$

where S_i is the surfactant concentration at the O/W interface, C_{is} is the concentration of drug bound to surfactant at the O/W interface, and K_0 is the equilibrium distribution coefficient of drug bound to surfactant.

Q_{as} (the amount of drug complexed to the surfactant film at the O/W interface) can be expressed as

$$Q_{as} = A_s k_0 S_i C_w \quad (15)$$

By substituting Equations 12 and 15 into Equation 9, Equation 16 is obtained:

$$Q_i = C_w A_s (k_i + k_0 S_i) \quad (16)$$

Q_m (the amount of drug in the micellar phase) can be expressed by

$$Q_m = C_m V_m \quad (17)$$

where C_m is the drug concentration in the micellar phase and V_m is the volume of the micellar phase.

By substituting Equations 7, 8, 16, and 17 into Equation 6, Q_d can be expressed by

$$Q_d = C_e V_e + C_w V_w + C_w A_s (k_i + k_0 S_i) + C_m V_m \quad (18)$$

K_e (the partition coefficient of drug between the oil and water phases) can be expressed by

$$K_e = \frac{C_e}{C_w} \quad (19)$$

Micellar solubilization of drug can be expressed as Equation 19a:

where SAA is the amount of micellar phase in the emulsion and K_m is the partition coefficient of drug between the micellar and water phases.

By substituting Equation 19 and 4 into Equation 18, Equation 18 can be rewritten as

$$Q_d = K_e C_w V_e + C_w V_w + C_w A_s (k_i + k_0 S_i) + K_m [SAA] C_w V_m \quad (20)$$

In the above equation, C_w is the only time-dependent variable. The other variables (V_e , V_w , V_m , K_e , K_m , $[SAA]$, A_s , k_i , k_0 , and S_i) are independent of time because the volume of the oil, micellar, and water phases and the emulsion droplet size are kept constant during the experiments.

By rearrangement of Equation 20, Q_d is expressed as

$$Q_d = C_w (K_e V_e + V_w + A_s (k_i + k_0 S_i) + K_m [SAA] V_m) \quad (21)$$

If Z_n is defined as the total apparent volume of drug distributed between different phases in the donor compartment, this can be expressed by

$$Z_n = K_e V_e + V_w + A_s (k_i + k_0 S_i) + K_m [SAA] V_m \quad (22)$$

Then Equation 21 can be rewritten as

$$C_W = \frac{Q_d}{Z_n} = \frac{Q_0 - Q_R}{Z_n} \quad (23)$$

where Q_d and Q_0 represent the initial amount of drug in the donor and receiver compartments.

By substituting Equation 5, Equation 24 is obtained as follows:

$$\frac{dQ_d}{dt} = \frac{dQ_r}{dt} = \frac{A_m P_d}{Z_n} (Q_0 - Q_R) \quad (24)$$

Using the initial condition ($Q_R = 0$ at $t = t_1$, where t_1 is the lag time) and quasi-steady-state approximation, the solution of Equation 24 is

$$\ln(Q_d) = \ln(Q_0) - \frac{A_m P_d}{Z_n} (t - t_1) \quad (25)$$

From the above equation, we can calculate the Z_n value from the slope of $\ln(Q_d)$ versus time ($t - t_1$) when the values of A_m and P_d are given. We can determine the effect of individual parameters on drug release from analysis of the Z_n parameter.

Using a dialysis membrane with an MW cutoff of 50 kd, both free drug in the aqueous phase and drug trapped in the micellar phase can diffuse across the membrane. The quasi-steady-state rate of appearance of drug mass into the receiver compartment (Q_R) from a submicron emulsion donor compartment may be defined using Fick's first law as follows:

$$\frac{dQ_R}{dt} = A_m (P_d + P_m K_m [SAA]) C_W \quad (26)$$

where P_m is the permeability coefficient of micelles through the MW cutoff 50 kdD membrane, K_m is the equilibrium distribution coefficient between the micellar and aqueous phases, and $[SAA]$ is the amount of micellar phase in the emulsion.

By substituting Equation 23 into Equation 26, Equation 26 can be rewritten as

$$\frac{dQ_R}{dt} = \frac{A_m (P_d + P_m K_m [SAA])}{Z_n} (Q_0 - Q_R) \quad (27)$$

Using the initial condition ($Q_R = 0$ at $t = t_1$) and the quasi-steady-state approximation, the solution of Equation 27 is obtained as follows:

$$\ln(Q_d) = \ln(Q_0) - \frac{A_m (P_d + P_m K_m [SAA])}{Z_n} (t - t_1) \quad (28)$$

As mentioned above, Equation 28 is used in the calculation of Z_n , and Z_n can be used to determine the effect of individual parameters on the drug release.

Mathematical Model for Hydrophobic Drug Transport in Emulsions

Hydrophobic drugs have O/W partition coefficients resulting in a low driving force from the discontinuous oil phase to the continuous phase in an O/W emulsion. Consecutive rate equations were used to develop the 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 concentration gradient of drug across the interface. There is essentially no reverse transport from the continuous phase to the dispersed phase because of the low concentration of hydrophobic drug in the aqueous phase (Figure 1). The transport of hydrophobic model drugs in emulsions can be considered to be a consecutive first order process.

The rate equation for each phase can be expressed as follows:

$$\frac{dQ_A}{dt} = k_{1app} C_A \quad (29)$$

$$\frac{dQ_B}{dt} = k_{1app} C_A - k_{2app} C_B \quad (30)$$

$$\frac{dQ_R}{dt} = k_{2app} C_B \quad (31)$$

where Q_A , Q_B , and Q_R represent the amount of drug in the oil, continuous, and receiver phases, respectively; C_A , C_B , and C_R are the concentrations of drug in the oil, continuous, and receiver phases,

respectively; and k_{1app} is the apparent rate constant from the oil phase to the continuous phase, and k_{2app} is the apparent rate constant from the continuous phase to the receiver phase.

The transport rate between the phases is proportional to the partition coefficient and the interfacial area according to our model of the O/W interface at a transport barrier, similar to a membrane. Thus Equations 29–31 can be modified to account for the micellar concentration in the continuous phase and the interfacial area (which is relatively large for emulsion systems).

At surfactant concentrations above the critical micelle concentration (CMC), it is assumed that micellar solubilization of drug is faster than drug transport from the oil to the continuous phase, and therefore free drug and micelle-solubilized drug will be in equilibrium in the continuous phase. This was described in Equations 19a and 19b as follows:

$$K_m = \frac{[C_m]}{[C_W][SAA]} \quad (19b)$$

The total bulk concentration of the drug (C_{BT}) and the surface concentration of the drug (C_{BST}) in the aqueous compartment can be written as Equation 19c:

$$C_{BT} = C_W + C_m = C_W(1 + K_m[SAA]) \quad (19c)$$

$$\frac{Q_{BT}}{V_B} = \frac{Q_B + Q_M}{V_B} = \frac{Q_B}{V_B}(1 + K_m[SAA]) \quad (32)$$

$$C_{BST} = C_{BS} + C_{MS} = C_{BS}(1 + K_m[SAA]) \quad (33)$$

$$\frac{Q_{BST}}{V_B} = \frac{Q_{BS} + Q_{MS}}{V_B} = \frac{Q_{BS}}{V_B}(1 + K_m[SAA]) \quad (34)$$

C_{BT} is assumed to be identical to C_{BST} when the effect of the aqueous diffusion layer on transport is neglected. The rate equation from the oil (phase A) to the continuous phase (phase B) in the presence of the micellar phase is expressed by Equation 35, which is

$$\frac{dQ_A}{dt} = \frac{k_1 S_0 Q_A}{K_s V_A} \quad (35)$$

The rate equation from the donor phase (phase B) to the receiver phase (phase C) can be expressed by Equation 36, which is

$$\frac{dQ_{BT}}{dt} = \frac{k_1 S_0 Q_A}{K_s V_A} - \frac{k_2 S_m Q_{BT}}{V_B(1 + K_m[SAA])} \quad (36)$$

The rate equation for drug appearance in the receiver phase (phase C) can be expressed by

$$\frac{dQ_R}{dt} = \frac{k_2 S_m Q_{BT}}{V_B(1 + K_m[SAA])} \quad (37)$$

Upon integration of Equations 35–37 with respect to time, they can be written as

$$Q_A = Q_0 \exp \frac{k_1 S_0 t}{K_s V_A} \quad (38)$$

$$Q_B = \frac{k_1 S_0 Q_0}{K_s V_A} \frac{k_2 S_m}{V_B(1 + K_m[SAA])} \frac{k_1 S_0}{K_s V_A} \exp \frac{k_1 S_0 t}{K_s V_A} \exp \frac{k_2 S_m t}{V_B(1 + K_m[SAA])} \quad (39)$$

$$Q_R = Q_0 \left(1 + \frac{1}{\frac{k_1 S_0}{K_s V_A} \frac{k_2 S_m}{V_B W}} \right) \exp \frac{k_1 S_0 t}{K_s V_A} \frac{k_1 S_0}{K_s V_A} \exp \frac{k_2 S_m t}{V_B W} \quad (40)$$

respectively, where

$$W = 1 + K_m[SAA] \quad (41)$$

Equations 35, 36, and 37 can be correlated to Fick's first law of diffusion. Transport rates are dependent on the thickness of the diffusion layer and the membrane. It is important that these parameters do not vary. Variations in stirring speed can affect the diffusion layer thickness, and therefore the same stirring rate was used for all experimental work. It is assumed that the drug is homogeneously dispersed within the oil droplets and that drug diffusion within the oil droplets is much faster than its interfacial transport from the oil to the continuous phase.

Therefore, the concentration gradient in phase A is the rate-determining step. Accordingly, Equation 35 can be written as

$$\frac{dQ_A}{dt} = \frac{DS_0 dQ_A}{V_A dl} \quad (42)$$

where D is the diffusivity of the drug through the interfacial barrier and $dQ_A/V_A dl$ is the concentration gradient of the solute.

If sink conditions are maintained in phase B (reverse dialysis bag method), Equation 42 can be written as

$$\frac{dQ_A}{dt} = \frac{DS_0}{V_A l} \ddot{A}Q_A = \frac{DS_0}{l} \frac{Q_A}{V_A} \frac{Q_B}{V_B} = \frac{DS_0 Q_A}{V_A l} 1 - \frac{1}{K_0} \quad (43)$$

where l is the thickness of the interfacial barrier, K_0 is the oil/water partition coefficient, V_A is the volume of phase A, and V_B is the volume of phase B.

Equation 36 can be written as

$$\frac{dQ_B}{dt} = \frac{DS_0}{l} \frac{Q_A}{V_A} 1 - \frac{1}{K_0} S_m P_{app} \frac{Q_B}{V_B} \frac{Q_R}{V_R} \quad (44)$$

where S_m is the diffusional area of the membrane and P_{app} is the apparent permeability coefficient of the drug through the membrane. P_{app} is influenced by the diffusivity of the drug through the aqueous diffusion layer, the diffusivity of the drug through the membrane, the aqueous diffusion layer thickness, and the membrane thickness. If sink conditions are maintained for phase C, Equation 44 can be written as

$$\frac{dQ_B}{dt} = \frac{DS_0}{l} \frac{Q_A}{V_A} 1 - \frac{1}{K_0} S_m P_{app} \frac{Q_B}{V_B} \quad (45)$$

and Equation 37 can be written as

$$\frac{dQ_R}{dt} = S_m P_{eff} \frac{Q_B}{V_B} \quad (46)$$

Therefore, Equations 35, 36, and 37 are related to Equations 43, 45, and 46. Because Equations 43, 45,

and 46 contain a large number of unknown parameters compared with Equations 35, 36, and 37, it is more statistically acceptable to use Equations 35, 36, and 37 to calculate the values of k_1 and k_2 . The k_1 and k_2 values must be obtained to evaluate whether the rate-determining step is the partitioning process or membrane transport.

MATERIALS AND METHODS

Cetyltrimethylammonium bromide (CTAB; CMC value in buffer: 21.1 mg/L) was purchased from Eastman Kodak (Rochester, NY). Polyoxyethylene-10-oleyl-ether (Brij 97, CMC value in buffer: 15.4 mg/L) was a gift from ICI (Rochester, NY). Mineral oil, sodium chloride, sodium phosphate monobasic, and hydrophilic Spectrapor® 7 dialysis membranes and dialysis bags (MW cutoffs 1 kd and 50 kd) were purchased from Fisher Scientific (Springfield, NJ). Phenylazoaniline (PAA) was purchased from Aldrich Chemical Company, Inc (Milwaukee, WI). Benzocaine (BZ), phenobarbital (PB), and barbitol (B) were purchased from Sigma (St Louis, MO). All chemicals were used as received without further purification. Deionized water obtained from a NANO-pure ultrapure water system (D4700, Barnstead, Dubuque, IA) was used for all experiments.

Emulsion Preparation

Emulsions were prepared with initial surfactant concentration of either 6.2% wt/vol Brij 97 or 2% wt/vol CTAB (17,18). Emulsions were collected and immediately used in stability and transport studies. Emulsions were diluted 1:1 with buffer or surfactant/buffer solutions prior to the stability and transport studies. Emulsions containing CTAB concentrations higher than 1% wt/vol were prepared by addition of extra CTAB dissolved in buffer following emulsification, resulting in a 1:1 dilution. Emulsion systems, where no excess surfactant was added, were diluted 1:1 with buffer only. Consequently, all final emulsions contained 10% vol/vol oil phase.

Model Drug Solubility

Model drug solubilities were measured in phosphate buffer U.S.P. (0.05 mol/L, ionic strength 0.2, pH 7.0)

at 37° C. CTAB or Brij 97 was added to the buffer in concentrations of 0%–2% wt/vol to determine the effect of the micellar phase on solubility. The model drug (PAA and BZ)/surfactant buffer suspensions were equilibrated at 37° C for 48 hours, then filtered and analyzed spectrophotometrically using a Spectronic 3000 Array (Milton Roy, Rochester, NY). Buffer solution and CTAB or Brij 97 buffer solutions were used as reference solutions in the absence and presence of CTAB or Brij 97, respectively. The maximum absorbance for solutions of PAA and BZ occurred at 377 nm and 286 nm, respectively, in the absence of CTAB or Brij 97 solutions, and at 398 nm and 296 nm, respectively, in the presence of CTAB or Brij 97 solutions. PB and B were analyzed as described elsewhere (17) using high-performance liquid chromatography (HPLC) with an ultraviolet (UV) detector. All solubility determinations were repeated 3 times. Mean values and standard deviations were calculated.

Oil/Buffer Partition Coefficient Determination

Two mL of oil containing model drug was kept in contact with 2 mL of pH 7.0 phosphate buffer solution in a 5 mL vial at 37° C $\pm$ 0.1° C for 48 hours to allow equilibration. Preliminary experiments were conducted to determine the time to reach equilibrium. Samples were analyzed at 24 hours, 48 hours, 72 hours, and 168 hours, and it was determined that equilibrium was achieved within 48 hours. After equilibrium, the two phases were separated, collected, and analyzed for model drug content. Aqueous samples were assayed for drug content using UV and HPLC. These experiments were repeated 3 times. Mean values and standard deviations were calculated.

Model Drug Transport

Model drug transport rates in emulsion systems were investigated using the bulk equilibrium reverse dialysis bag and side-by-side diffusion cells technique described elsewhere (16).

Side-by-Side Diffusion Cell Technique

Briefly, water-jacketed side-by-side diffusion cells (glass chambers with a 4 mL volume and an 11-mm-diameter circular opening available for diffusion)

mounted with dialysis membranes (MW cutoffs: 1 kd or 50 kd) were used for kinetic studies of model drug release from emulsions (16). Samples were withdrawn from the receiver cells (2 mL) and analyzed spectrophotometrically at given intervals as described elsewhere (17,18) (surfactant solution—PAA: 398 nm, BZ: 294 nm; Buffer solution—PAA: 377 nm, BZ: 286 nm). PB and B were analyzed by HPLC as described elsewhere (17,18). The same volume of buffer or surfactant solution as withdrawn for each sample was replaced into the receiver cells to maintain volume and sink conditions.

Control Studies

(i) *Transport study of model drugs from buffer solution to buffer solution*—Model drugs in buffer solution were placed in the donor cells and buffer solutions placed in the receiver cells. Sampling and assays were performed as previously described elsewhere (17,18). This study allows determination of the permeability coefficients of model drugs through the dialysis membranes.

(ii) *Transport study of model drugs from surfactant solution to surfactant solution*—Model drugs in surfactant solution were placed in the donor cells and surfactant solutions placed in the receiver cells. Sampling and assays were performed as previously described (17,18). This study allows determination of micellar effect on permeability coefficients of model drugs through the dialysis membranes. Both control studies were repeated 3 times. Mean values and standard deviations were calculated.

Bulk Equilibrium Reverse Dialysis Bag Technique

Briefly, dialysis bags containing the continuous phase (receiver phase) alone are suspended in a vessel containing the donor phase (diluted emulsion), and the system is stirred. At predetermined time intervals, each dialysis bag is removed and the contents are analyzed for released drug. The model drug submicron-sized emulsions (5 mL) were directly placed into 500 mL of a stirred sink solution where numerous dialysis sacs containing 2 mL of the same sink solution were previously immersed. The dialysis sacs were equilibrated with the sink solutions for about 30 minutes before experimentation. At predetermined time intervals,

the dialysis bags were withdrawn and the contents assayed spectrophotometrically for model drug concentration. The release studies were performed at a fixed temperature of $37^{\circ}\text{C} \pm 0.1^{\circ}\text{C}$ under constant stirring. Measurements were conducted 3 times per sample; mean values and standard deviations were calculated.

RESULTS AND DISCUSSION

Data Analysis for Hydrophilic (Surface-Active)

Model Drug

Drug transport in emulsion systems is rate-limited by membrane transport due to instantaneous equilibration 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 (Z_n) as follows:

$$P_{\text{eff}} = \frac{P_d}{Z_n} = \frac{P_d}{K_e V_e + A_s (k_i + k_0 S_i) + (1 + K_m [SAA]) V_w} \quad (46)$$

PB and B at pH 7.0 are relatively hydrophilic and surface-active in nature compared with the other model drugs. According to Equation 46, the effective permeability coefficients (P_{eff}) of PB and B obtained experimentally (17,18) can be calculated using the following parameters: model drug permeability coefficient values (P_d), model drug partition coefficient values between the oil and water phases (K_m), volumes of the oil and water phases (V_e and V_w), O/W interfacial area (A_s), the interfacial interaction between the model drug and surfactant ($k_0 S_i$), and the model drug interfacial activity (k_i). The P_d , K_e , K_m , V_e , V_w , and A_s values for PB, B, PAA, and BZ are listed in Table 1.

The permeability coefficient (P_d) of PB and B in the buffer system was used in the calculation of the P_{eff} for samples measured using the MW cutoff 1 kd dialysis membrane, because micelles could not pass through this membrane. Although micelles can pass through the MW cutoff 50 kd dialysis membrane, the PB and B permeability coefficients (P_d) were used instead of $P_d + P_m[SAA]$ in the calculation of P_{eff} because the permeability of micelles was low

Table 1. The K_e , K_m , V_e , V_w , A_s and ($K_i + K_0 S_i$) values of phenobarbital, barbital, benzocaine and pheylazoaniline determined experimentally for Brij 97 and CTAB emulsion systems (pH 7.0, $I = 0.2\text{ M}$, at 37°C).

Parameters	Pheno barbital		Barbital		Phenylazo aniline		Benzo caine	
	Brij 97	CTABBrij 97	CTABBrij 97	CTAB	Brij 97	CTAB	Brij 97	CTAB
K_e	0.9	0.9	0.6	0.6	120	120	1.2	1.2
K_m ($\text{cm}^3 \text{g}^{-1}$) $\times 10^2$	0.24	0.51	0.10	0.11	57	109	0.24	5.51
V_e (cm^3)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
V_w (cm^3)	360	360	360	360	360	360	360	360
A_s (cm^2)	2.18×10^5	1.36×10^5	2.18×10^5	1.36×10^5	2.18×10^5	1.36×10^5	2.18×10^5	1.36×10^5
$K_i + K_0 S_i$	0.27	4.81	1.12	6.93	0.03	0.05	0.01	0.02

Table 2. The effective permeability coefficients (P_{eff}) of phenobarbital (PB) and barbital (B) predicted using the surface-active hydrophilic model and determined experimentally in emulsion systems at pH 7.0 at 37°C .

Surfactant	Micellar Concentration (%wt/vol)	Effective permeability coefficients (cm h^{-1}) using 1KD membrane			
		Phenobarbital		Barbital	
		Predicted value	Experimental value	Predicted value	Experimental value
Polyoxyethylene-10- oleyl-ether (Brij 97)	0	0.058	0.060 ± 0.001	0.041	0.039 ± 0.001
	1	0.064	0.062 ± 0.001	0.043	0.042 ± 0.002
	2	0.059	0.060 ± 0.001	0.042	0.042 ± 0.001
Cetyltrimethyl- ammonium bromide (CTAB)	0	0.021	0.022 ± 0.001	0.048	0.046 ± 0.002
	0.5	0.034	0.036 ± 0.001	0.049	0.048 ± 0.001
	1.0	0.022	0.022 ± 0.001	0.048	0.046 ± 0.002

compared with that of free PB and B because of hindered diffusion of micelles through the membrane.

The effective permeability coefficients calculated using Equation 46 were compared with the experimental values for side-by-side diffusion cell techniques in Table 2. The predicted amounts of PB and B in receiver cells (Q_R) were calculated from P_{eff} values. The predicted data and the experimental data of PB and B in emulsion systems are compared for the bulk equilibrium reverse dialysis bag technique in Figure 2. The experimental effective permeability

Figure 2. Comparison of predicted and experimental data for the $\ln$ (rate of disappearance of PB, B, PAA, and BZ) from the donor chamber using 1kd membrane. Lines represent predicted data, and symbols represent experimental data. Donor chamber contains 0.5% CTAB emulsions, and receiver chamber contains 0.5% CTAB buffer. Brij 97 = polyoxyethylene-10-oleyl-ether, CTAB = cetyltrimethylammonium bromide, PAA = phenylazoaniline, BZ = benzocaine, P_d = permeability coefficient, kd = kilodalton.

coefficients of PB and B in both the Brij 97 and CTAB emulsion systems decreased with increase in micellar concentration (17,18). The predicted data are in good agreement with the experimental data.

The solubility of B was not influenced by the presence of Brij 97 or CTAB, and therefore the micellar distribution coefficients of B are zero for both Brij 97 and CTAB (17,18). Based on Equation 46, the calculated P_{eff} of B was not affected by either Brij 97 or CTAB micellar phase; this is in agreement with the experimental data (17,18). This model does not take into account the effects of the permeability of model drug-surfactant complexes and micellar shape changes on the transport process.

Data Analysis for Hydrophobic Model Drug

The appearance rate of hydrophobic drugs in the receiver cells is dependent on the partitioning rates (k_1) of hydrophobic drugs between the oil and the continuous phases and membrane transport rates (k_2), because the drug partitioning process from the oil and the continuous phase is not instantaneous.

Table 3. The calculated partitioning rates (k_1) and the membrane permeability coefficients (k_2) of PAA and BZ through molecular weight cutoff 1kd and 50kd membranes in polyoxyethylene-10-oleyl-ether (Brij 97) and cetyltrimethylammonium bromide (CTAB) emulsion systems using the EXCEL program. Conc = concentration, PAA = phenylazoaniline, BZ = benzocaine, P_d = permeability coefficient, MW = molecular weight, kd = kilodalton.

Surfactant	Conc (% wt/vol)	PAA		BZ	
		Partitioning rates (k_1 , cm h ⁻¹)		Membrane permeability coefficient (k_2 , P_d , cm h ⁻¹)	
		MW 1 kd	MW 50 kd	MW 1 kd	MW 50 kd
Brij 97	0.5	0.0101	0.0105	0.069	0.092
	1.0	0.0112	0.0110	0.158	0.212
	2.0	0.0113	0.0118	0.223	0.388
CTAB	0.1	0.0115	0.0118	0.016	0.072
	0.5	0.0125	0.0127	0.115	0.138
	1.0	0.0120	0.0154	0.120	0.183
	3.0	0.0185	0.0198	0.372	0.542

Therefore, the k_1 and k_2 values can be obtained by fitting the hydrophobic drug model to the experimental data (cumulative amount of drug disappeared in the donor cells versus time).

The transport rates of PAA and BZ in Brij 97 and CTAB emulsion systems were predicted using this model. PAA and BZ are relatively hydrophobic compared with the other model drugs (PB and B) (17,18). The values of the constants (the initial amount of drug [Q_0], total O/W interfacial area [S_0], membrane area [S_m], volume of the oil phase [V_A], and volume of the continuous phase [V_B]) used in this model are listed in Table 1. 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 (Table 3). However, the calculated k_1 values are approximate because a limitation of the model is that the drug concentration in the continuous phase cannot be determined experimentally. The predicted amount of PAA and BZ disappearance from the donor cells was

calculated using the values of k_1 and k_2 and compared with the experimental data of PAA and BZ in emulsion systems. The effective permeability coefficients of PAA and BZ increased with increase in surfactant concentration up to 1% wt/vol of Brij 97 and 0.5% wt/vol CTAB and decreased at higher surfactant concentrations. The predicted data are in good agreement with the experimental data (deviation of about 5%). In Brij 97 and CTAB emulsion systems, the O/W interfacial barrier (k_1) did not depend on the MW cutoff of the membranes, because the calculated k_1 values for MW cutoff 1 kd membranes are similar to those for MW cutoff 50 kd membranes. The O/W interfacial barrier (k_1) increased slightly with increase in Brij 97 and CTAB micellar concentrations (Table 3). This may be a result of an alteration of the interfacial film characteristics caused by micellar adsorption.

Limitations

The effect of change in micellar shape on partitioning and membrane transport processes is not included in this model. Therefore, decrease in transport rate with increase in Brij 97 (beyond 1% wt/vol) or CTAB (beyond 0.5% wt/vol) did not fit the experimental value. Predicted data are in good agreement with the experimental data (deviation of about 5%) (Figures 2 and 3) until 1% wt/vol Brij 97 or 0.5% wt/vol CTAB within the study period of 2 hours. Beyond the study period of 2 hours, the experimental data did not follow the predicted logarithmic linear pattern with time.

CONCLUSION

Mathematical models were developed according to model drug lipophilicity and surface activity. The model developed for the surface-active hydrophilic model drugs is based on Fick's first law. This model was developed with the assumption that the partitioning rates of surface-active hydrophilic drugs are much faster than membrane diffusion and consequently the drug concentration is in equilibrium between oil, water, and micellar phases. Consecutive rate equations were used in the development of the model for the lipophilic drugs because of the slow partitioning processes of the oil phase.

The P_{eff} values of surface-active hydrophilic drugs,

Figure 3. Comparison of predicted and experimental data for the $\ln$ (rate of disappearance of PB, B, PAA and BZ) from the donor chamber using 1 kd membrane. Lines represent predicted data and symbols represent experimental data. Donor chamber contains 1% Brij 97 emulsions and receiver chamber contains 1% Brij 97 buffer.

calculated using parameters such as drug/membrane permeability and partition coefficient values, were consistent with the experimental data, thus validating the model. An exception was that the model could not predict the decrease in the permeability coefficient beyond 0.5% CTAB and 1% Brij 97, precisely. This was considered to be due to change in the micellar shape. The effect of change in micellar shape on partitioning and membrane transport processes is not included in this model. Lipophilic drug transport calculated using partitioning, O/W interfacial barrier, and membrane transport rates was consistent with the lipophilic model.

ACKNOWLEDGMENTS

The authors wish to thank Boehringer Ingelheim Pharmaceuticals, Inc, and the Parenteral Drug Association Foundation for partial support of this research and Dr Kyung Ae Yoon for technical assistance.

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