Effect of Nonionic Surfactant on Transport of Model Drugs in Emulsions

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Purpose. To investigate the influence of excess surfactant on transport kinetics in emulsions, using phenylazoaniline (PAA), benzocaine, benzoic acid and phenol as model drugs. Mineral oil was chosen as the oil phase and the nonionic surfactant, polyoxyethylene oleyl ether (Brij 97) as the emulsifier.

Methods. Model drug transport in emulsions was investigated using side by side diffusion cells mounted with hydrophilic dialysis or hydrophobic membranes. A novel method, involving a combination of a membrane equilibrium technique and surface tension measurement (Wilhelmy plate method), was developed to determine surfactant critical micelle concentration (CMC) in the presence of O/W emulsions. Emulsion stability was determined by droplet size analysis as a function of time, temperature and dilution using photon correlation spectroscopy and a light blockage technique. Model drug mineral oil/water partition coefficients and aqueous solubilities were determined in the presence of surfactant.

Results. The emulsion CMC value was used to calculate micellar phase concentration. The transport rates of PAA and benzocaine in emulsions increased with increase in Brij 97 micellar concentration up to 1.0 % w/v and then decreased at higher surfactant concentrations. The transport rates of the more hydrophilic compounds, benzoic acid (ionized form, pH 7.0) and phenol, were not affected by the presence of micellar phase.

Conclusions. Excess surfactant affected the transport rates of the model drugs in the emulsions depending on drug lipophilicity. Transport rates measured using side by side diffusion cells appeared to be governed by model drug partitioning rates from the oil to the continuous phases and by membrane type.

KEY WORDS: model drug transport; micellar phase; emulsion; surface tension; lipophilicity; CMC determination.

INTRODUCTION

Surfactants are usually present in emulsions at concentrations in excess of that necessary to form a monolayer coverage of the dispersed phase droplets (1). This excess surfactant may be present in the form of monomers or micelles dispersed in the continuous phase or adsorbed at the emulsion droplet interface (2,3). In addition to improving emulsion stability excess surfactant has the potential to effect transport.

Transport characteristics of drugs in emulsions have been shown to be affected by the following factors: drug diffusion coefficient, drug partition coefficient, interfacial barriers, droplet charge, and average droplet size and size distribution (4–10). Theoretical mechanisms of interfacial transport based on Fick's first law of diffusion have been used to predict drug release rates from an aqueous into an oil environment (5). Ghanem et al. (6–8) reported that an adsorbed surfactant layer may alter transport rates in emulsions as a result of changes in partitioning rates and apparent permeability coefficients. A theoretical model of drug transport in emulsions, which included interfacial reactions was developed by Lostritto et al. (9). However, the effect of excess surfactant on transport in emulsions has neither been investigated experimentally nor considered in the existing models. It is our hypothesis that excess surfactant may affect drug transport kinetics in emulsions by micellar solubilization, alteration of the partitioning process, and drug-surfactant complexation.

In the present study, transport rates in model emulsions are investigated in the presence of excess surfactant. Mineral oil was selected since it does not contain surface active impurities. The nonionic surfactant, polyoxyethylene-10-oleyl ether (Brij 97), was selected as it forms relatively stable mineral oil-in-water emulsions. Phenylazoaniline (PAA), benzocaine, benzoic acid, and phenol were selected as model drugs since they have similar structures, all contain a benzene moiety, and different lipophilicities (PAA > benzocaine > benzoic acid > phenol). The pKa values of benzocaine, benzoic acid and phenol are 2.5, 4.2 and 10, respectively.

MATERIALS AND METHODS

Materials

Mineral oil, phenol, sodium chloride, sodium phosphate monobasic, and hydrophilic Spectrapor® 7 dialysis membranes (molecular weight (MW) cutoffs 1KD and 50KD) were purchased from Fisher Scientific (Springfield, NJ). Hydrophobic polydimethylsiloxane membranes (PDMS, 0.005 inch) were purchased from Cardiovascular Instrument Corporation (Wakefield, MA). Polyoxyethylene-10-oleyl ether (Brij 97) was a gift from ICI (Rochester, NY). Phenylazoaniline (PAA) was purchased from Aldrich Chemical Company Inc. (Milwaukee, WI). Benzocaine and benzoic acid were purchased from Sigma (St. Louis, MO). All chemicals were used as received without further purification. Deionized water obtained from a NANOpure ultrapure water system (D4700, Barnstead, Dubuque, IO) was used for all experiments.

Emulsion Preparation

Emulsions were prepared in 100 ml batches. An initial surfactant concentration of 6.2% w/v was used for emulsions prepared for transport and stability studies. Surfactant was added to 80 ml of 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 of mineral oil. The model drug concentrations selected were their maximum solubilities in mineral oil at 37°C with the exception of phenol. 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 of oil phase and a surfactant concentration varrying from 3.1 to 5.1% w/v. Emulsion preparation for the CMC

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determination study was as above except the initial surfactant concentration varried from 1 and 6.2% w/v.

Emulsion Stability Determination

Immediately following emulsion preparation, 0.5 ml samples were sealed in 1 ml ampules and placed in temperature controlled water baths ±0.05°C at 5, 25, 37, and 60°C. Mean droplet diameters and size distributions were determined at intervals over a 3 week period using an Accusizer Optical Particle Sizer (size range 1–500 μm, Model 770, Particle Sizing Systems Inc., Santa Barbara, CA) and a Nicomp Submicron Particle Sizer (size range 0.01–1 μm, Model 370, Particle Sizing Systems, Inc., Santa Barbara, CA). The instruments were used in series to cover the entire size range.

CMC Determination

CMC Determination of Brij 97 in Buffer

Surface tension measurements were conducted at 37 ± 0.1°C using a microbalance surface tensiometer (K12, Krüss, USA, Charlotte, NC) in the Wilhelmy plate mode. The tensiometer was equipped with a Dosimat (automatic burette) for CMC determinations (Model 665, Metrohm, Switzerland). Surface tension values were determined from the measured force as follows (11):

$$F = \gamma P \cos \theta \quad (1)$$

where γ is the surface tension, F is the measured force, P is the wetted length of the plate, and θ is the contact angle. The CMC value of Brij 97 was determined from a plot of surface tension versus surfactant concentration, obtained using the K12CMC program (version 1.1, Krüss USA, Charlotte, NC).

CMC Determination of Brij 97 in the Presence of O/W Emulsions

Although 20% v/v O/W emulsions containing less than 6.2% w/v Brij 97 were relatively unstable, such systems (1–6.0% w/v Brij 97 and 20% v/v oil phase) were investigated to determine the emulsion CMC value. Micellar phase concentration in emulsions was determined from the difference between the total concentration of Brij 97 present and the emulsion CMC value.

A membrane equilibrium technique and surface tension measurements were used to determine the emulsion CMC value. Water jacketed diffusion cells (glass chambers 40 ml cell volume, 33 mm diameter) mounted with dialysis membranes prerinsed for 48h were used. Freshly prepared emulsions were diluted 1:1 with surfactant/buffer solutions (0–10% w/v Brij 97) and 40 ml samples were placed in the donor cells. Equal volumes of buffer solution were placed in the receiver cells and the systems equilibrated at 37 ± 0.1°C for 72 h. This allowed calculation of surfactant CMC for 10% v/v O/W emulsions.

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 at concentrations of 0–2% w/v. After equilibration for 48h, the model drug suspensions were filtered and analyzed 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 absence of Brij 97 solution) and at 398 nm, 294 nm, and 273 nm, respectively (in the presence of Brij 97 solution). Benzoic acid was analyzed 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 (μBondapak-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.

Oil/Buffer Partition Coefficient Determination

Two ml of oil containing model drug were kept in contact with 2 ml of pH 7.0 phosphate buffer solution at 37 ± 0.1°C for 48 h. After equilibrium, the phases were separated, collected, and analyzed 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 (MW cutoffs 1KD and 50KD) 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 minutes prior to 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 were withdrawn from the receiver cells (2 ml) at intervals and analyzed. 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 above experiments were repeated three times. Mean values and standard deviations were calculated.

RESULTS AND DISCUSSION

Emulsion Stability

Emulsions were prepared at the same initial concentration (6.2% w/v) to avoid variation in mean droplet size and size distribution. Emulsion stability was evaluated as a function of storage time, temperature and dilution using mean droplet diameters, size distributions and polydispersity values (Nicomp analysis) (Fig. 1). Dilution was investigated since all emulsions were diluted prior to use in transport and CMC studies. Emulsions stored at 5, 25, and 37°C were stable over the three week study period. The coefficient of variation of mean droplet size and the polydispersity values (ratio of volume weighted mean droplet diameter to number weighted mean droplet diameter) were always less than 0.07 and 1.4, respectively, indicating stability. Emulsions stored at 60°C deteriorated within 9 to 15 days, as was evident from an increase and then decrease in mean droplet diameter and increases in the coefficient of variation and polydispersity values. These data are considered to be a result of droplet coalescence and Ostwald ripening giving rise to an

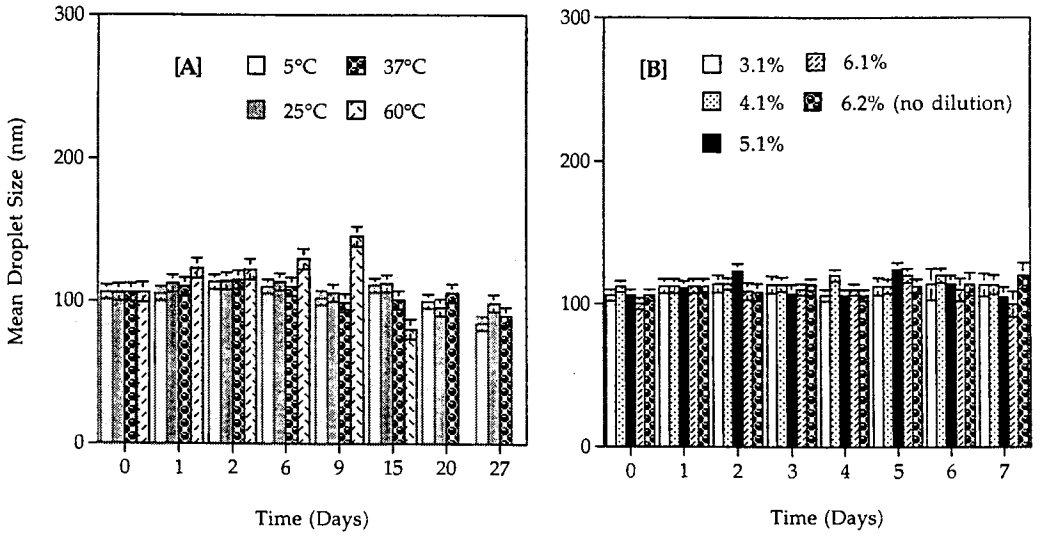

Fig. 1. Mean droplet size of 20% v/v O/W emulsions containing 6.2% w/v Brij 97 (pH 7.0, I = 0.2, 37°C, mean values of three determinations): [A] Effect of storage time and temperature; [B] Effect of storage time and dilution (diluted 1:1 with different Brij 97 solutions).

increase in the number of droplets outside the Nicomp size range (0.01–1 μm) and consequently the measured size decreases. The presence of large droplets resulting from emulsion deterioration was confirmed by Accusizer analysis. These results agree with the work of Burgess and Yoon on perfluorocarbon emulsion stability (12).

Dilution of emulsion samples with surfactant/buffer solution (1:1 dilution) did not affect mean droplet diameter and polydispersity over the one week study period indicaing stability (Fig. 1). Consequently there is not concern with respect to variation in interfacial area would affect micellar concentration and therefore the transport kinetics.

CMC Determination

The emulsion CMC value could not be measured directly since the oil phase would interfere with the various methods available for CMC analysis such as surface tension, conductivity, and osmotic pressure determinations. A method was developed which involved a membrane equilibrium technique in combination with surface tension measurement. Emulsion droplets cannot pass across the membrane, however the bulk surfactant molecules can. Emulsions containing less than 3.1% w/v Brij 97 were relatively unstable and mean droplet sizes and size distributions changed during equilibration. Consequently, surface tension values recorded for these systems may be slightly lower than those at the time of preparation. However, the CMC value is unaffected as at the CMC (3.1% w/v Brij 97), surfactant equilibration takes place without change in droplet size (Fig. 2). Due to the large interfacial area of submicron emulsions, the Brij 97 CMC value increased from 0.0016% w/v in phosphate buffer to 3.1% w/v in the emulsion (10% v/v O/W).

Effect of Micellar Phase on Model Drug Solubilization, Partitioning, and Transport

Diffusion cells mounted with membranes were used to determine model drug transport in emulsions, since it is difficult to separate the aqueous and oil phases without altering droplet size and size distribution. However, this method has the limitation that the rate of model drug appearance in the receiver cell is controlled by both partitioning and membrane transport. It was therefore necessary to determine model drug membrane transport in buffer in the presence and absence of micellar phase.

Micellar Solubilization and Partition Coefficient Studies of Model Drugs

Model drug micellar solubilization and partition coefficient studies were investigated to determine oil and micellar phase distribution. Model drug lipophilicities are in the order of PAA, benzocaine, benzoic acid and phenol (Table I). The solubilities of PAA and benzocaine in buffer (pH 7.0) and benzoic acid (pH 3.0) increased with increasing Brij 97 concen-

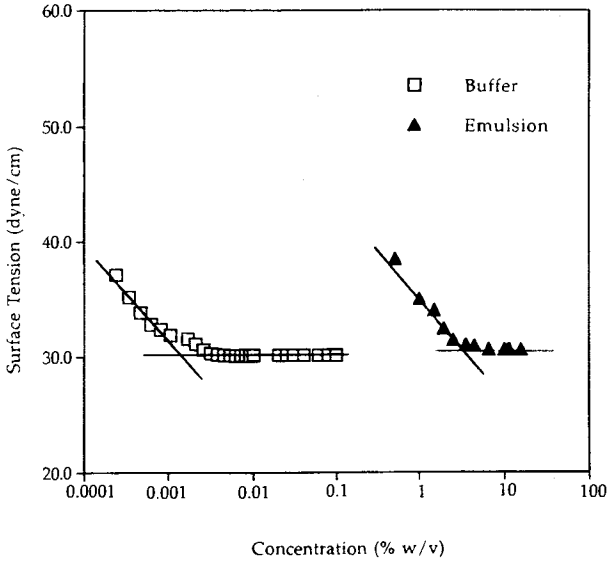

Fig. 2. Determination of the critical micelle concentration of Brij 97 in buffer and in 10% v/v O/W emulsions (pH 7.0, I = 0.2, 37°C, mean values of three determinations). The error bars are within the symbols.

Table I. The Solubilities and O/W Partition Coefficients of Model Drugs in 0.05M Phosphate Buffer (I = 0.2) at 37°C

Model drugs	Solubility (μg/ml)*	Partition coefficient*
Phenol (pH 7.0)	114000 ± 500	0.11 ± 0.005
Benzoic acid (pH 7.0)	6280 ± 200	0.23 ± 0.009
Benzoic acid (pH 3.0)	4950 ± 200	0.25 ± 0.009
Benzocaine (pH 7.0)	1200 ± 40	1.19 ± 0.03
PAA (pH 7.0)	28 ± 1	120 ± 5

*n = 3 (mean ± standard deviation).

tration due to micellar solubilization (Fig. 3). There is an apparent change in the slope of the PAA solubility versus Brij 97 concentration plot at 0.0015% w/v Brij 97. This correlates with the CMC value of Brij 97 as determined by surface tension (0.0016% w/v) (Fig. 2). The solubilities of benzoic acid and phenol in pH 7.0 buffer did not change in the presence of surfactant (Fig. 3). These molecules are relatively hydrophilic and therefore their solubilities are unlikely to be affected by micellar phase.

Amidon et al. (13) described the micelle solubilized drug-free drug equilibrium distribution coefficient, K_m, as follows:

$$C_w + SAA \overset{K_m}{\leftrightarrow} C_m \quad (2)$$

$$K_m = \frac{[C_m]}{[C_w][SAA]} \quad (3)$$

$$[C_T] = [C_w] + [C_m] = [C_w](1 + K_m[SAA]) \quad (4)$$

where $[C_w]$ is drug concentration in aqueous phase, $[C_m]$ is drug concentration in micellar phase, [SAA] is micellar phase concentration, (i.e., [SAA] = total Brij 97 concentration − CMC of Brij 97), and $[C_T]$ is total drug solubility. K_m value can be determined using Equation 4 (Fig. 3). The K_m values for PAA, benzocaine and benzoic acid are 58, 0.25 and 0.18 respectively, indicating that PAA is more lipophilic. These results are in agreement with the partition coefficient studies. K_m values could not be concluded for phenol and benzoic acid (pH 7.0) as their solubilities did not change with surfactant concentration. The partition coefficient values of PAA, benzocaine and benzoic acid between oil and surfactant/buffer solution (K_S) were calculated using the following equation:

$$K_s = \frac{K_o}{1 + K_m[SAA]} \quad (5)$$

where K_o is the O/W partition coefficient. The calculated K_S values were dependent on Brij 97 concentration, decreasing sharply with increase in Brij 97 concentration up to 1% w/v and then decreasing slightly with further increase in concentration (Fig. 4). The change in the partition coefficient values with surfactant concentration are considered to be a result of change in micellar shape and solubilizing capacity.

Determination of Permeability Coefficient of Model Drugs in Surfactant/Buffer Solutions

The effective permeability coefficients (P_{eff}) of drugs under quasi steady state conditions were calculated from the slope of a plot of ln Q_d versus time using Fick's Law equation as follows (9):

$$\ln Q_d = \ln Q_o - A_m P_{eff} t \quad (6)$$

where Q_d is the amount of model drug in the donor cell, Q_o is the initial amount of model drug in the donor cell, A_m is the membrane area available for diffusion, and t is the diffusion time. The decreased P_{eff} values of benzocaine and PAA (pH 7.0) with increase in Brij 97 are considered to be due to reduced free drug concentration in the aqueous phase resulting from

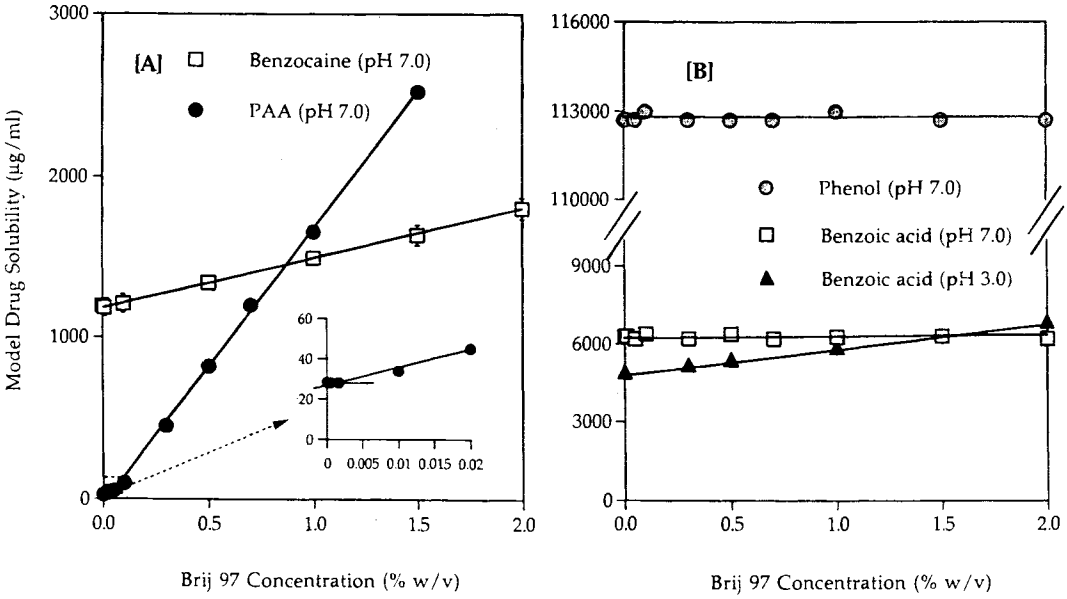

Fig. 3. Effect of Brij 97 concentration on model drug solubilities in 0.05M phosphate buffer (I = 0.2, 37°C, mean values of three determinations): [A] PAA and benzocaine; [B] benzoic acid and phenol. The error bars are within the symbols.

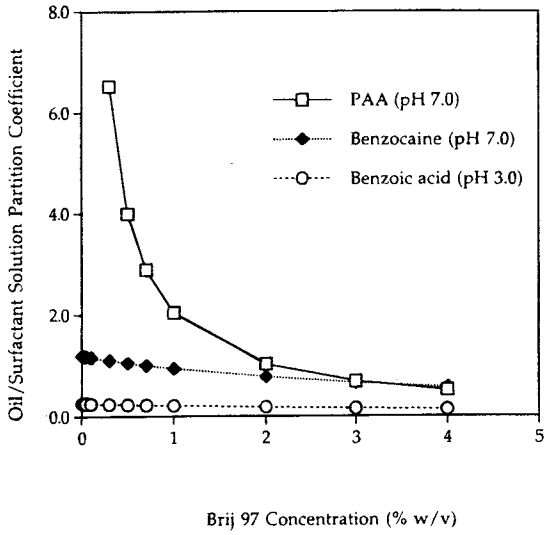

Fig. 4. Effect of Brij 97 concentration on the oil/surfactant buffer solution partition coefficients of model drugs (0.05M phosphate buffer, I = 0.2, 37°C, mean values of three determinations). The error bars are within the symbols.

micellar solubilization (Table II). The P_{eff} values of the relatively hydrophilic compounds, benzoic acid and phenol, in pH 7.0 buffer systems decreased slightly with increase in Brij 97 concentration (Table II). These molecules are not expected to be solubilized in the micellar phase.

The P_{eff} values of the model drugs were dependent on the membrane types (Table II). The P_{eff} value of PAA was highest through the PDMS membrane and lowest through the MW cutoff 1KD membrane as expected. The P_{eff} values of PAA, benzocaine, and phenol through the MW cuttoff 50KD membrane were higher than those through the MW cutoff 1KD membrane as a consequence of pore size. However, the transport rate of benzoic acid at pH 7.0 did not change with dialysis membrane MW cutoff. The cellulose dialysis membrane has hydroxyl groups and consequently dipole interaction may alter benzoic acid (pH 7.0) transport rate. This effect apparently dominates the membrane pore size hindered diffusion effect. Transport studies of benzoic acid and phenol (pH 7.0) through PDMS were not conducted, since it is a hydrophobic membrane.

Transport Studies of Model Drugs in Emulsions

The transport rates of PAA and benzocaine in emulsions (pH 7.0) were higher in the presence of micellar phase at all surfactant concentrations studied (Fig. 5). The addition of micelles is expected to increase the oil to continuous phase partitioning rate and decrease the driving force for membrane transport according to micellar solubilization, partition and membrane transport studies for micellar solubilized drugs. The P_{eff} values of PAA and benzocaine increased with increase in micellar concentration up to 1% w/v and then decreased with further increase in micellar concentration. These effects are probably due to increased partitioning and micellar solubilization, respectively (Table II). Micellar shape changes from spherical to ellipsoidal at high surfactant concentrations (14). These elongated micelles have different solubilizing capacities compared to spherical micelles and cause an increase in continuous phase viscosity. In addition, adsorbed micelles and mesophase are speculated to increase the interfacial barrier. All of these factors are likely to decrease drug transport rates. The transport rates of PAA and benzocaine in emulsions were also dependent on membrane characteristics, following the trend observed in buffer (Table II).

Table II. The Effective Permeability Coefficients of Model Drugs Through Dialysis (MW Cutoffs 1KD and 50KD) and PDMS Membranes in 0.05M Phosphate Buffer and O/W Emulsion Systems Containing Brij 97 Micellar Phase (0–2% w/v), at 37°C (n = 3, mean ± standard deviation)

Model Drugs	Brij 97 micellar conc. (% w/v)	Effective permeability coefficients ($\times 10^2$, cm/h)					
		Buffer			Emulsion		
		1KD	50KD	PDMS	1KD	50KD	PDMS
PAA	0	67.5 ± 1.3	125 ± 4	219 ± 9	0.029 ± 0.002	0.033 ± 0.002	0.089 ± 0.005
(pH 7.0)	0.5	*	*	*	0.060 ± 0.002	0.088 ± 0.001	0.285 ± 0.017
	1.0	0.3 ± 0.01	0.3 ± 0.01	1.3 ± 0.07	0.076 ± 0.005	0.101 ± 0.006	0.306 ± 0.006
	1.5	*	*	*	0.067 ± 0.005	0.095 ± 0.006	0.257 ± 0.008
	2.0	0.1 ± 0.01	0.2 ± 0.01	0.7 ± 0.03	0.050 ± 0.001	0.090 ± 0.003	*
Benzocaine	0	56.1 ± 3.2	76.1 ± 6.4	20.5 ± 1.2	1.70 ± 0.04	2.04 ± 0.10	0.49 ± 0.03
(pH 7.0)	1.0	6.1 ± 0.3	9.0 ± 0.3	2.0 ± 0.1	1.90 ± 0.11	2.37 ± 0.13	0.47 ± 0.03
	2.0	4.4 ± 0.3	4.8 ± 0.2	1.4 ± 0.04	1.46 ± 0.08	1.92 ± 0.10	0.37 ± 0.03
Benzoic acid	0	14.8 ± 0.7	17.8 ± 0.7	*	3.8 ± 0.1	4.4 ± 0.1	*
(pH 3.0)	1.0	*	*	*	3.3 ± 0.1	3.8 ± 0.2	*
	2.0	*	*	*	2.6 ± 0.1	3.0 ± 0.1	*
Benzoic acid	0	14.0 ± 0.7	14.0 ± 0.8	*	7.19 ± 0.10	7.39 ± 0.20	*
(pH 7.0)	1.0	11.8 ± 0.4	13.1 ± 0.7	*	7.08 ± 0.10	7.30 ± 0.30	*
	2.0	12.0 ± 0.4	12.9 ± 0.7	*	7.19 ± 0.10	7.34 ± 0.30	*
Phenol	0	29.7 ± 1.1	38.2 ± 1.0	*	5.03 ± 0.21	5.05 ± 0.19	*
(pH 7.0)	1.0	23.0 ± 0.5	29.0 ± 0.7	*	5.01 ± 0.23	5.05 ± 0.20	*
	2.0	23.0 ± 0.5	29.0 ± 0.7	*	4.99 ± 0.21	5.04 ± 0.20	*

*Not determined.

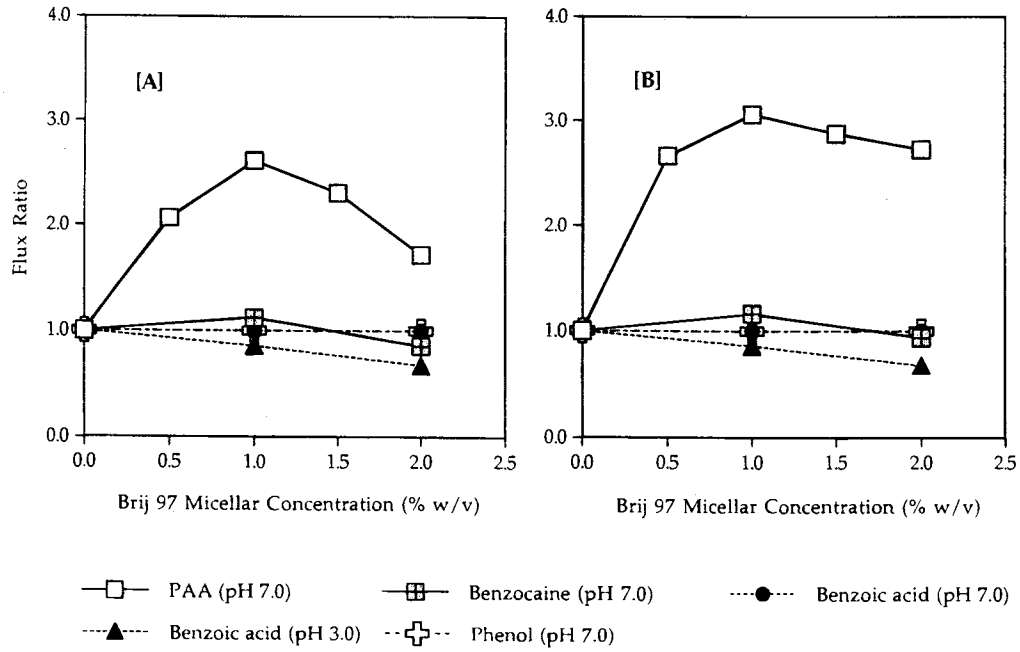

Fig. 5. Effect of Brij 97 micellar concentration on model drug flux ratio (the ratio of the effective permeability coefficient in the presence of micellar phase to that in the absence of micellar phase) in 10% v/v O/W Brij 97 emulsions (I = 0.2, 37°C, mean values of three determinations): [A] MW cutoff IKD; [B] MW cutoff 50KD. The error bars are within the symbols.

The P_{eff} values of benzoic acid and phenol in pH 7.0 emulsions were not significantly influenced by micellar phase concentration (Table II). This is attributed to their hydrophilic nature and consequent lack of micellar solubilization. The P_{eff} value of benzoic acid in pH 3.0 emulsions decreased with increase in Brij 97 concentration (Fig. 5). This is probably due to micellar solubilization. The effect of surfactant on benzoic acid (pH 3.0) partitioning is much less than for PAA and benzocaine (Fig. 4). This may explain why the transport rate of benzoic acid (pH 3.0) does not show an initial increase with increase in surfactant concentration (Fig. 5).

CONCLUSIONS

Excess surfactant present in emulsions in the form of monomers and micelles affected model drug transport rates depending on model drug lipophilicity. Transport rates measured using side-by-side diffusion cells appeared to be governed by oil to continuous phase partitioning rates and membrane type. Partitioning rates were dependent on model drug lipophilicity and surfactant concentration. Membrane transport was dependent on pore size and model drug lipophilicity. This information will be useful in the development of transport models for emulsions and in formulation development. Knowledge of the effect of excess surfactant on drug transport in emulsions may allow the formulation of emulsions with specific drug release profiles for different uses, such as controlled drug delivery. It should be possible to optimize emulsion stability, retention and release kinetics to obtain specific product performance. A novel method to determine surfactant CMC in the presence of emulsions has been developed without disturbing the O/W interfacial area. This method utilizes a combination of a membrane equilibrium technique and surface tension measurement.

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