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Effect of Cationic Surfactant on Transport of Model Drugs in Emulsion Systems

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Abstract

Excess surfactant present in emulsions can influence the rates of transport of incorporated drugs by micellar solubilization, alteration of the partitioning process and by drug–surfactant complexation. Cetyltrimethylammonium bromide (CTAB), a cationic surfactant was selected to investigate these phenomena as it forms relatively stable mineral oil–water (O–W) emulsions and has the potential for ionic interaction. Phenylazoaniline, benzocaine, benzoic acid and phenol were chosen as model drugs for this study.

The emulsion critical micelle concentration (CMC) for CTAB determined using a combination of a membrane equilibrium technique and surface-tension measurement was 1·0% w/v in 10% v/v% O–W emulsion systems. Ionic interaction between model drugs and surfactants and drug hydrophobicity affected their transport rates in the emulsion systems. The transport rates of the lipophilic drugs (benzocaine and phenylazoaniline) and the ionized hydrophillic drug (benzoic acid, pH 7·0) in the emulsion systems increased with increasing CTAB concentration up to 0·5% w/v micellar concentration and then decreased at higher concentrations. The rate of transport of phenol was not affected by the presence of micellar phase.

Ionic interaction between surfactant and model drugs affected transport rates of model drugs in emulsion systems. The micellar phase was considered to affect the overall transport rates of model drugs.

Stable emulsions usually contain surfactant at concentrations in excess of those necessary to form a monolayer coverage of droplets of the dispersed phase (Garrett 1965). Excess surfactant might be present as monomers, micelles or adsorbed at the emulsion droplet interface, or all of these (Friberg & Solans 1986; Courthaudon & Dickinson 1991; McClements et al 1992). Adsorbed micellar or liquid crystalline phases can change interfacial film characteristics (McClements et al 1992) and consequently affect emulsion stability (Friberg & Solans 1986). A recent study from our laboratory has shown that in addition to improving emulsion stability excess non-ionic surfactant influences the rates of transport of model drugs in emulsions by micellar solubilization and alteration of the partitioning process (Yoon & Burgess 1996). Surfactant might also influence transport rates as a result of drug–surfactant complexation at the interface of mineral oil-in-water emulsions and in the continuous phase. In this study the cationic surfactant cetyltrimethylammonium bromide (CTAB) was used to investigate this effect in model oil-in-water emulsions. CTAB has an HLB value of ten which is optimum for formulation of relatively stable emulsions of mineral oil in water (Sherman 1968). Phenylazoaniline, benzocaine, benzoic acid and phenol were selected as model drugs because they have similar structures—each contains a benzene ring—and different lipophilicities (phenylazoaniline > benzocaine > benzoic acid > phenol). The azo group of phenylazoaniline has the potential to complex with CTAB as does the ionized form of benzoic acid (pK_a 4·2). Drug–surfactant complexation can, therefore, occur at the oil–water interface and in the continuous phase. Interfacial complexation of drug with surfactant might affect interfacial film characteristics, and consequently change the rate of partitioning of the drug from the oil to the continuous phases and thus the stability of the emulsion. As a result of the potential drug complexation effect, alteration in micellar size and shape might affect model drug transport rates by changing micellar diffusivity and solubilization capacity. The shapes of CTAB micelles have been reported to change from spherical to elongated in the presence of anionic salt owing to complexation between the surfactant and salt (Candau et al 1990).

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Materials and Methods

Materials

Mineral oil, phenol, sodium chloride, monobasic sodium phosphate and hydrophillic Spectrapor 7 dialysis membranes (molecular weight cut-off 1 kDa and 50 kDa) were purchased from Fisher Scientific (Springfield, NJ). Hydrophobic polydimethylsiloxane membranes (PDMS; 0·005 inch) were purchased from Cardiovascular Instrument (Wakefield, MA). Phenylazoaniline was purchased from Aldrich (Milwaukee, WI). Benzocaine and benzoic acid were purchased from Sigma (St Louis, MO). Cetyltrimethylammonium bromide was purchased from Eastman Kodak (Rochester, NY). All chemicals were used as received without further purification. Deionized water from a Nanopure ultrapure water system (D4700, Barnstead, Dubuque, IA) was used in all experiments.

Emulsion preparation

An initial CTAB concentration of 2% w/v was used for emulsions prepared for the 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 (phenylazoaniline, 65·7 mg;

benzocaine, 40·0 mg; benzoic acid, 61·7 mg; phenol, 51·5 mg, so that the final drug content of the emulsion was 20% v/v) was dissolved in mineral oil (20 mL). 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 0·51 MPa. The resultant emulsions were diluted 1:1 with a solution of buffer or of surfactant and buffer to yield a 10% v/v oil phase and a surfactant concentration varying from 1 to 4% w/v. Emulsion preparation for CMC determination was as above except the initial CTAB concentration varied between 0·2 and 2% w/v.

Determination of emulsion stability

Immediately after emulsion preparation 0·5-mL samples were sealed in 1-mL ampoules and placed in temperature-controlled (±0·05°C) water baths at 5, 25, 37, and 60°C. Mean droplet diameters and size distributions of the emulsions were determined by use of an Accusizer Optical Particle Sizer (size range 1–500 μm, Model 770, Particle Sizing Systems, Santa Barbara, CA) and a Nicomp Submicron Particle Sizer (size range 0·01–1 μm, Model 370, Particle Sizing Systems). The instruments were used in series to cover the entire size range.

Determination of critical micelle concentration (CMC)

Determination of CMC of CTAB in buffer. Surface tension determinations of CTAB buffer solutions were conducted at 37 ± 0·1°C by use of a microbalance surface tensiometer (K12, Krüss USA, Charlotte, NC) equipped with a Dosimat.

Determination of CMC of CTAB in the presence of oil-in-water emulsions. The CMC value of CTAB in the presence of emulsions was determined using a combination of a membrane equilibrium technique and surface tension measurement. Although emulsions containing less than 2% w/v CTAB were relatively unstable, such systems (0·2–1·9% w/v CTAB) were investigated to determine the CMC value in the presence of the emulsion.

Water-jacketed diffusion cells (glass chambers, cell volume 40 mL, diameter 33 mm) mounted with dialysis membranes pre-rinsed for 48 h were used. Freshly prepared emulsions were diluted 1:1 with solutions of surfactant and buffer (0–10% w/v CTAB) and 40-mL samples were placed in the donor cells. Equal volumes of buffer solution were placed in the receiver cells and the systems were equilibrated at 37 ± 0·1°C for 72 h. The CTAB concentration range investigated was 0·1 to 6% w/v in 10% oil-in-water emulsions. This enabled calculation of surfactant CMC for a 10% v/v emulsion, the same emulsion concentration as that used in the transport studies. The CMC value of CTAB in emulsions was determined from a graph of surface tension against surfactant concentration.

Model drug solubility

The solubilities of model drugs were determined in the presence of a solution of CTAB in buffer (0·05 M phosphate buffer, ionic strength 0·2, pH 7·0, 37°C) at CTAB concentrations of 0–2% w/v. These model drug suspensions were equilibrated for 48 h, filtered and analysed spectrophotometrically (Milton Roy Spectronic 3000 Array, Rochester, NY). The peak absorbance values of phenylazoaniline, benzocaine, and phenol occurred at 377 nm, 286 nm, and 271 nm, respectively in phosphate buffer and at 398 nm, 296 nm, and 273 nm, respectively in phosphate buffer in the presence of CTAB solution. Benzoic acid was analysed spectrophotometrically between 210 and 300 nm using a deconvolution programme (Perkin–Elmer 7300), because the benzoic acid absorbance peak occurred on the shoulder of the CTAB peak.

Determination of oil–buffer partition coefficient

Oil (2 mL) containing model drug was kept in contact with phosphate buffer solution (pH 7·0; 2 mL) at 37 ± 0·1°C for 48 h. The phases were separated, collected, and analysed by UV and FTIR (Nicolet 66) for model drug content.

Model drug transport

Studies of model drug transport in emulsions at 37 ± 0·1°C were performed in water-jacketed side-by-side diffusion cells (glass chambers, cell volume 4 mL and 11 mm diameter available for diffusion) equipped with either dialysis or PDMS membranes. The dialysis membranes were hydrated in receiver solution for 30 min before use. Drug-loaded emulsions diluted 1:1 with different solutions of surfactant in buffer were placed into the donor cells. The receiver cells contained drug-free solution of surfactant in buffer at the same concentration as the emulsion micellar phase. Each chamber was stirred by use of a magnetic stirrer. Samples (2 mL) were withdrawn from the receiver cells at intervals and analysed. Sink conditions were maintained by replacing cell samples with solutions of surfactant in buffer. Control studies to determine model drug transport rates in buffer and in solutions of surfactant in buffer were conducted as above. All experiments were repeated three times. Mean values and standard deviations were calculated.

Results and Discussion

Emulsion stability studies

The effects of temperature and dilution on mean diameter of the emulsion droplet were investigated over a period of one month (Table 1). Dilution was studied because the emulsions were diluted before the transport studies. CTAB emulsions stored at 5, 25, and 37°C were stable over the one-month study period. There was no significant change in the mean diameter of the droplets in these emulsions. 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 0·06 and 1·4, respectively, indicating stability. Emulsions stored at 60°C deteriorated within 13 to 15 days, as was evident from changes in the mean droplet diameter, the coefficient of variation of the mean droplet size and the polydispersity values. The mean droplet diameter of samples stored at 60°C increased initially and then decreased. This is considered to be a consequence of droplet coalescence and Ostwald ripening resulting in growth in the size of emulsion droplets to the point where some of the droplet diameters exceed the measurable size range of the Nicomp (0·01–1 μm). Consequently, the measured droplet diameters decreased. This trend of increasing and then decreasing droplet size with time, when using the Nicomp, is in agreement with previous studies (Burgess & Yoon 1995; Yoon & Burgess 1996). The presence of large droplets was confirmed by using the Accusizer which detects droplets larger

Table 1. Effect of storage time, temperature, and dilution (1:1 with different CTAB solutions) on mean droplet size of 20% v/v oil-in-water emulsions containing 2% w/v CTAB (pH 7·0, I = 0·2, 37°C; mean values from three determinations).

	Mean droplet size (μm ± s.d.) of 20% v/v oil-in-water emulsions containing 2%w/v CTAB at different temperatures			
Time (days)	5°C	25°C	37°C	60°C
0	175 ± 5	173 ± 5	173 ± 5	173 ± 5
1	172 ± 5	174 ± 5	175 ± 5	178 ± 8
3	176 ± 8	175 ± 7	175 ± 7	169 ± 8
5	174 ± 8	181 ± 5	172 ± 5	169 ± 8
7	170 ± 5	170 ± 5	179 ± 7	186 ± 7
13	175 ± 7	175 ± 8	184 ± 9	197 ± 9
15	177 ± 7	172 ± 9	175 ± 4	133 ± 12
20	173 ± 5	185 ± 7	175 ± 8	102 ± 16
28	174 ± 7	173 ± 8	177 ± 5	Phase separation

	Mean droplet size (μm ± s.d.) of 10% v/v oil-in-water emulsions containing different CTAB concentrations at 37°C				
Time (days)	1% w/v	1.5% w/v	2% w/v	4% w/v	2% w/v*
0	174 ± 7	176 ± 5	177 ± 7	173 ± 6	176 ± 5
1	180 ± 8	175 ± 7	179 ± 7	171 ± 7	175 ± 8
2	175 ± 8	180 ± 8	175 ± 7	175 ± 7	175 ± 7
3	180 ± 5	175 ± 8	170 ± 9	180 ± 8	180 ± 7
4	175 ± 8	170 ± 8	175 ± 6	169 ± 7	176 ± 5
5	191 ± 8	173 ± 6	170 ± 8	173 ± 7	179 ± 6
6	186 ± 7	186 ± 7	165 ± 8	181 ± 7	170 ± 9
7	201 ± 11	165 ± 9	154 ± 9	165 ± 6	180 ± 7

*In 20% oil-in-water emulsion

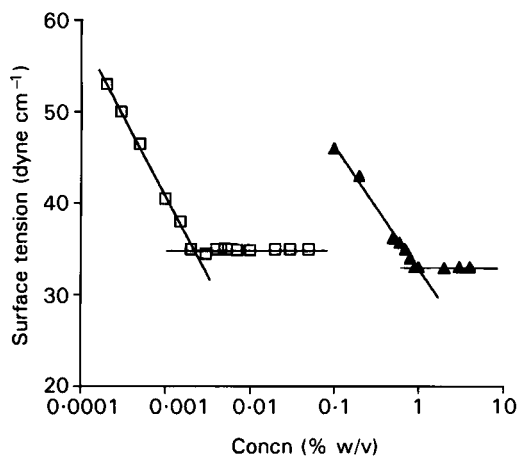

FIG. 1. Determination of the critical micelle concentration of CTAB in buffer and in 10% v/v oil-in-water emulsions (pH 7·0, I = 0·2, 37°C; mean values from three determinations). The error bars are within the symbols. □ Buffer, ▲ emulsion.

than 1 μm. The coefficient of variation of the mean droplet size and the polydispersity values of the diluted emulsions were less than 0·08 and 1·4, respectively, implying that these emulsions were relatively stable over the one-week study period (Table 1). These stability data indicate that there is no significant change in the interfacial area of the emulsion droplets under the conditions used in the transport studies. Charge in area could have affected drug transport rates complicating data interpretation.

CMC determination

The CMC values of CTAB in phosphate buffer and in the presence of emulsions (10% v/v oil-in-water emulsion) were determined from the surface tension data (Fig. 1). The CMC value of CTAB increased from 0·0021% w/v in phosphate buffer to 1·0% w/v in the emulsion systems. This increase is considered to be a consequence of the large interfacial area of the submicron emulsions. At CTAB concentrations above 1·0% w/v, therefore, the surfactant is present in excess of the concentration required for monolayer coverage of the emulsion droplets. The CMC value of CTAB in the emulsions was used to calculate CTAB molecular packing at the emulsion interface. The total interfacial area of 10% v/v emulsions was calculated from the mean droplet size and the dispersed phase volume to be 1 234 000 cm^2. A value of 0·21 nm^2 was obtained for CTAB molecular packing; this is comparable with a value of 0·12 nm^2 for CTAB molecular packing at the air-buffer interface calculated using the Gibbs adsorption equation:

$$\Gamma = -(C/RT)d\gamma/dC \quad (1)$$

where Γ is the amount of surfactant per unit area of surface, C is the concentration of surfactant in the bulk, R is the gas constant, T is the absolute temperature and $d\gamma/dC$ is the change in surface tension of the solution with change of bulk surfactant concentration. The difference between the molecular packing might be attributed to a number of factors: the dielectric constants of the two interfaces are different; the cohesive forces acting on CTAB at the oil–water interface are smaller than those at the air–water interface and the curvature effect at the submicron emulsion droplet interface might interfere with surfactant packing (Ingram & Ottewill 1990). Ingram and Ottewill (1990) reported that adsorbed monolayers of CTAB were more expanded at the oil–water interface than at the air–water interface. The value of 0·12 nm^2 obtained for CTAB molecular packing at the air–buffer interface was different from the literature value of 0·45 nm^2 for CTAB molecular packing at the air–water interface (Ingram & Ottewill 1990). This is probably because of differences in ionic strength. Rosen (1989) reported that the extent of surface adsorption of CTAB decreased from 0·47 nm^2 to 0·35 nm^2 as

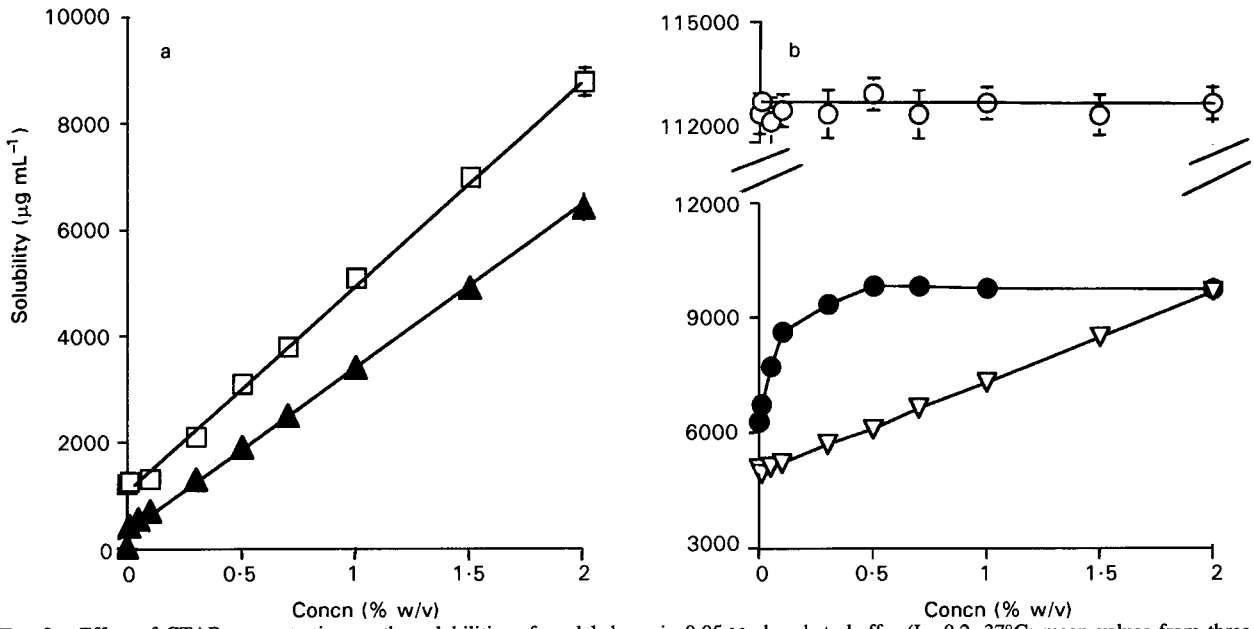

FIG. 2. Effect of CTAB concentration on the solubilities of model drugs in 0·05 M phosphate buffer (I = 0.2, 37°C; mean values from three determinations): a, phenylazoaniline and benzocaine; b, benzoic acid and phenol. The error bars are within the symbols. □ Benzocaine, ▲ phenylazoaniline, ▽ benzoic acid (pH 3·0), ●benzoic acid (pH 7·0), ○ phenol.

the ionic strength increased from 0·001 to 0·002 M potassium bromide. This was attributed to reduced repulsion between the head groups of the adsorbed surfactants. The ionic strength of the pH 7·0 phosphate buffer used here is 0·2 M which might explain the surface adsorption value of 0·21 nm^2.

Effect of micellar phase on model drug solubilization, partitioning and transport

Micellar solubilization and partition coefficient studies of model drugs. The lipophilicities of the model drugs decreased in the order phenylazoaniline, benzocaine, benzoic acid, phenol (Yoon & Burgess 1996). The solubilities of hydrophobic model drugs (phenylazoaniline and benzocaine) at pH 7·0 increased with increasing CTAB concentration (Fig. 2). The UV absorbance peaks of phenylazoaniline and benzocaine shifted from 377 nm and 286 nm, respectively, in buffer solution to 398 nm and 298 nm in solutions of CTAB in buffer. These bathochromic shifts and the increases in the model drug solubilities are probably a result of micellar solubilization.

The solubility of benzoic acid at pH 3·0 increased with increasing CTAB concentration (Fig. 2). This is considered to be because of micellar solubilization of the un-ionized benzoic acid. It has been shown previously that benzoic acid solubility at pH 3·0 increased in the presence of Brij 97 as a result of micellar solubilization (Yoon & Burgess 1996). At pH 7·0 benzoic acid solubility increased as CTAB concentrations increased to 0·5% w/v and reached a plateau at higher concentrations (Fig. 2). By contrast benzoic acid solubility at pH 7·0 was not affected by the presence of Brij 97 (Yoon & Burgess 1996). The increase in benzoic acid solubility at pH 7·0 in the presence of CTAB is attributed to complexation as a result of ionic interaction. Benzoic acid solubility at pH 7·0 is higher than at pH 3·0, both in the presence and absence of CTAB. This is because of ionization of benzoic acid at pH 7·0 and consequent change in polarity. The solubility of phenol was not influenced by the presence of CTAB at pH 7·0 (Fig. 2) owing to its hydrophilicity.

The equilibrium distribution coefficients of drugs between micellar and aqueous phases (K_m) were calculated using the equation (Amidon et al 1982):

$$K_m = [C_m]/([C_w][SAA]) \quad (2)$$

where $[C_w]$ is the concentration of drug in the aqueous phase, $[C_m]$ is concentration of drug in the micellar phase, [SAA] is concentration of micellar phase (i.e., [SAA] = total CTAB concentration − CMC of CTAB). The K_m values for phenylazoaniline and benzocaine at pH 7·0 and benzoic acid at pH 3·0 are 110, 2·56 and 0·50, respectively. The K_m values for phenylazoaniline, benzocaine and benzoic acid were higher than those obtained in the presence of Brij 97 (Yoon & Burgess 1996) at concentrations both above and below the CMC. This is probably a consequence of the formation of soluble complexes between these model drugs and CTAB, resulting in higher solubilities.

The partition coefficients, K_s, between oil and solutions of CTAB in buffer were calculated for phenylazoaniline and benzocaine at pH 7·0 and for benzoic acid at pH 3·0 by use of the equation (Yoon & Burgess 1996):

$$K_s = K_o/(1 + K_m[SAA]) \quad (3)$$

where K_o is the oil–water partition coefficient. The calculated model drug-partition coefficients, K_s, between oil and solutions of CTAB in buffer were dependent on surfactant concentration (Fig. 3). The K_s value of phenylazoaniline decreased sharply with increasing surfactant concentration up to 0·5% w/v CTAB and decreased slowly with further increase in surfactant concentration. The K_s value of benzocaine also decreased with

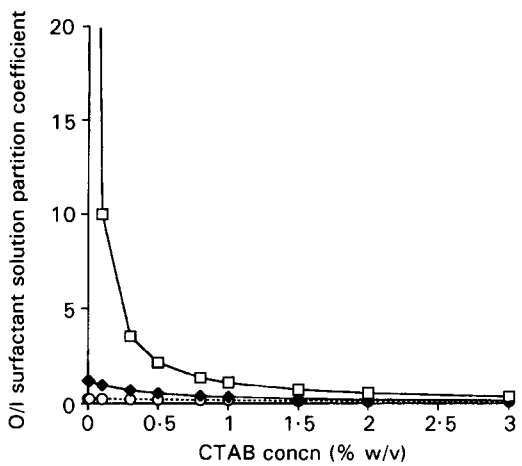

FIG. 3. Effect of CTAB concentration on the partition coefficients of model drugs between oil and solution of surfactant in buffer (0·05 M phosphate buffer, I = 0·2, 37°C; mean values from three determinations). The error bars are within the symbols. □ Phenylazoaniline (pH 7·0), ◆ benzocaine (pH 7·0), ○ benzoic acid (pH 3·0).

increasing surfactant concentration, although the magnitude of the change was much smaller than for phenylazoaniline. The change in the slope of the partition coefficient value of phenylazoaniline with surfactant concentration (Fig. 3) is considered to be a result of change in micellar shape and solubilizing capacity at higher surfactant concentrations. When the concentration of CTAB in the buffer was high a change in the shape and size of the micelle was evident from changes in the consistencies of emulsions of the model drugs (phenylazoaniline, benzocaine, and benzoic acid) to gel-like structures. These gel-like structures were not observed in the Brij 97 studies (Yoon & Burgess 1996). The micellar shape of CTAB in the presence of model drugs changes from spherical to worm-like as a result of complexation (Chidambaram and Burgess, unpublished results). The solubilizing capacity of the worm-like micelles is expected to be different from that of the spherical micelles.

Transport studies of model drugs in solutions of surfactant in buffer and in emulsion systems

Fick's first law equation was used to calculate the effective permeability coefficients of model drugs through dialysis or PDMS membranes under quasi steady-state conditions in solutions of surfactant in buffer and in emulsions from the slope of a plot of ln Q_d against time (Lostritto et al 1987

$$\ln Q_d = \ln Q_o - A_m P_{eff} t \quad (4)$$

where Q_d is the amount of model drug in the donor cell, Q_0 is the initial amount of model drug in the donor cell, A_m is the area of membrane available for diffusion, P_{eff} is the effective permeability coefficient of the drug, and t is the diffusion time. The P_{eff} values of the model drugs in buffer systems decreased as CTAB concentrations increased (Table 2). The decrease in the P_{eff} of the hydrophobic model drug, phenylazoaniline, at pH 7.0 might be a result of reduced free phenylazoaniline in the aqueous phase as a result of micellar solubilization and phenylazoaniline–CTAB complexation. The effect is similar for the less hydrophobic model drug benzocaine, although the decrease in P_{eff} was not as large as occurred with phenylazoaniline. The P_{eff} of benzoic acid at both pH 3·0 and pH 7·0 decreased with increasing CTAB concentration. These decreases are a consequence of reduced free benzoic acid in the aqueous phase owing to micellar solubilization (pH 3·0) and ionic interaction between benzoic acid and CTAB (pH

Table 2. The effective permeability coefficients of model drugs through dialysis (MW cut-offs 1 kD and 50 kD) and PDMS membranes in 0.05 M phosphate buffer and oil-in-water emulsions containing CTAB micellar phase (0–2% w/v) at 37°C (n = 3, mean ± standard deviation).

Model drug	CTAB micellar conc.	Effective permeability coefficients ($\times 10^2$; cm h^{-1})					
		Buffer dialysis			Emulsion dialysis		
	(% w/v)	1 kD	50 kD	PDMS	1 kD	50 kD	PDMS
Phenylazoaniline (pH 7·0)	0	67·5 ± 1·3	125 ± 4	219 ± 9	0·030 ± 0·002	0·028 ± 0·002	0·054 ± 0·002
	0·1	-*	–	–	0·035 ± 0·002	0·046 ± 0·001	0·267 ± 0·010
	0·3	–	–	–	0·041 ± 0·001	0·060 ± 0·002	0·281 ± 0·010
	0·5	0·1 ± 0·01	0·2 ± 0·01	0·7 ± 0·01	0·048 ± 0·002	0·067 ± 0·004	0·376 ± 0·015
	0·8	–	–	–	0·040 ± 0·002	0·047 ± 0·002	0·330 ± 0·006
	1·0	–	–	–	0·030 ± 0·001	0·040 ± 0·001	0·310 ± 0·008
	3·0	0·1 ± 0·01	0·1 ± 0·01	0·5 ± 0·01	0·050 ± 0·001	0·041 ± 0·002	–
Benzocaine (pH 7·0)	0	56·1 ± 3·2	76·1 ± 6·4	20·5 ± 1·2	1·00 ± 0·07	1·66 ± 0·09	0·31 ± 0·01
	0·5	3·3 ± 0·1	4·5 ± 0·3	1·9 ± 0·1	1·20 ± 0·08	2·00 ± 0·13	0·38 ± 0·01
	1·0	3·1 ± 0·2	4·2 ± 0·2	1·3 ± 0·06	0·91 ± 0·07	1·85 ± 0·10	0·31 ± 0·02
Benzoic acid (pH 3·0)	0	14·8 ± 0·7	17·8 ± 0·7	–	2·0 ± 0·1	2·5 ± 0·1	–
	0·5	–	–	–	1·7 ± 0·1	2·1 ± 0·1	–
	1·0	–	–	–	1·6 ± 0·1	2·0 ± 0·1	–
Benzoic acid (pH 7·0)	0	14·0 ± 0·7	14·0 ± 0·8	–	1·19 ± 0·05	2·35 ± 0·10	–
	0·5	3·9 ± 0·2	4·0 ± 0·2	–	1·93 ± 0·10	4·78 ± 0·25	–
	1·0	3·6 ± 0·2	3·5 ± 0·3	–	1·50 ± 0·10	2·86 ± 0·20	–
Phenol (pH 7·0)	0	29·7 ± 1·1	38·2 ± 1·0	–	5·00 ± 0·21	5·05 ± 0·19	–
	1·0	19·0 ± 0·5	22·0 ± 0·7	–	5·01 ± 0·23	5·05 ± 0·20	–
	2·0	19·0 ± 0·5	22·0 ± 0·7	–	4·90 ± 0·20	5·04 ± 0·20	–

*Not determined.

7·0). The P_{eff} values of model drugs in solutions of CTAB in buffer are lower than in solutions of Brij 97 in buffer (Yoon & Burgess 1996). The solubilization capacity of the CTAB micellar phase is higher than that of Brij 97 as a result of the ionic nature of CTAB. The concentration of free model drug in the aqueous phase available for membrane diffusion is, therefore, lower in CTAB solution than that in Brij 97 solution. This is in agreement with the micellar solubilization studies. The P_{eff} of phenol in buffer systems was only slightly affected by an increase in surfactant concentration. Phenol is relatively hydrophillic compared with the other model drugs and therefore not solubilized by the micellar phase.

The flux ratio (the ratio of the effective permeability coefficient in the presence of micelles to that in the absence of micelles) for phenylazoaniline and benzocaine in the emulsions at pH 7·0 and for benzoic acid at both pH 7·0 and 3·0 was altered by the CTAB micellar concentrations (Fig. 4). The optimum flux ratio of phenylazoaniline, benzocaine and benzoic acid in CTAB emulsions at pH 7·0 occurred at a CTAB micellar concentration of 0·5% w/v. The initial increase in the flux ratio of phenylazoaniline (up to 0·5% w/v micellar phase) indicates that the oil droplet to continuous phase partitioning rate of phenylazoaniline was enhanced in the presence of CTAB (Fig. 4). The probable cause of the decrease in the flux ratio at high CTAB micellar concentrations (above 0·5% w/v) is micellar solubilization resulting in a reduction in the amount of free phenylazoaniline available in the aqueous phase. This is in agreement with the oil–surfactant buffer system partition coefficient data for phenylazoaniline. The flux ratios through dialysis membranes of phenylazoaniline in CTAB emulsions, in the presence of 0·5 and 1·0% w/v micellar phase, are 20 and 50% lower, respectively, than those in the Brij 97 emulsions. This difference might be a result of the higher micellar solubilization capacity and larger emulsion droplet size of the CTAB emulsions compared with the Brij 97 emulsions, and with changes in micellar size and shape in the CTAB emulsions resulting from complexation (dipole interaction between phenylazoaniline and CTAB). Interfacial interaction occurs between phenylazoaniline and CTAB forming strong elastic films (Yoon 1995); this probably alters the partition coefficient of phenylazoaniline between membrane and continuous phase. The flux ratio of benzocaine followed a similar trend to that of phenylazoaniline (Fig. 4), although the value for benzocaine was lower, probably because of the less hydrophobic nature of benzocaine.

There was no significant change in the flux ratio of benzoic acid (pH 7·0) in the presence of Brij 97 micellar phase (Yoon & Burgess 1996). The flux ratio of benzoic acid in CTAB emulsion systems at pH 7·0, however, increased with increasing CTAB micellar concentration up to 0·5% w/v and decreased at higher concentrations (Fig. 4).

The flux ratio of benzoic acid in CTAB emulsions at pH 3·0 decreased with increasing CTAB micellar concentration (Fig. 4), a result similar to that obtained for the Brij 97 emulsions (Yoon & Burgess 1996). The change in the flux ratios is probably a result of micellar solubilization at pH 3·0 and to complexation at pH 7·0 (ionic interaction between benzoic acid and CTAB). The P_{eff} of phenol in the emulsions was not significantly influenced by CTAB concentration (Table 2). This is attributed to the lack of micellar solubilization and complexation of this relatively hydrophillic compound.

Candau et al (1990) and Ekwall et al (1971) reported evidence of considerable micellar growth or aggregation at high CTAB concentrations (above 9% w/v) and also at low CTAB concentrations (0·91% w/v) in the presence of anions. Micellar growth and aggregation might result in reduced P_{eff} values for benzoic acid and phenylazoaniline both for dialysis and for PDMS membranes at CTAB micellar concentrations above 0·5% w/v.

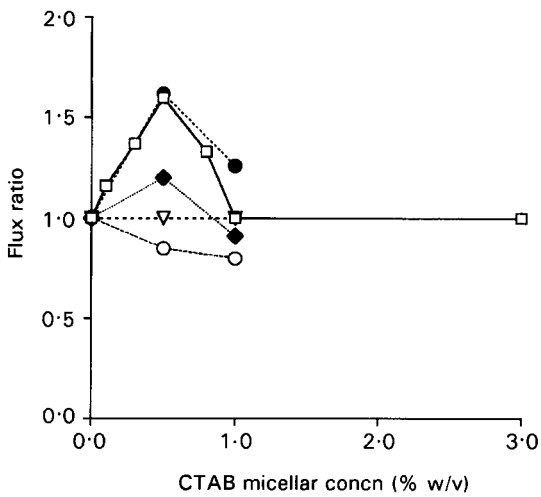

FIG. 4. Effect of CTAB micellar concentration on model drug flux ratio (the ratio of the effective permeability coefficient in the presence of micellar phase to that in the absence of micellar phase) in 10% v/v oil-in-water CTAB emulsions (I = 0·2, 37°C; mean values of three determinations) using a molecular weight cut-off of 1 kD. The error bars are within the symbols. □ Phenylazoaniline (pH 7·0), ● benzoic acid (pH 7·0), ▽ phenol (pH 7.0), ◆ benzocaine (pH 7·0), ○ benzoic acid (pH 3·0).

Conclusions

The transport rates of the model drugs in CTAB emulsion systems determined using side-by-side diffusion cells seemed to be governed by the rate of partitioning of the model drug from the oil to the continuous phase and by the type of membrane. Increasing the micellar concentration resulted in enhanced rates of partitioning of lipophilic model drugs in emulsions. Micellar solubilization of lipophilic model drugs resulted in a reduction in membrane transport. Model drug–CTAB complexation at the oil-water interface and in the continuous phase reduced rates of transport of phenylazoaniline and benzoic acid. This is attributed to a reduction in free drug available for transport, the formation of strong elastic interfacial films and elongated micelles with consequent hindered drug diffusion. These data on the effect of cationic surfactant on emulsion transport will be useful in the development of transport models for emulsion system and in the development of emulsion formulations.

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