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Transport of Micelle-Solubilized Steroids across Microporous Membranes

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Abstract □ The effect of solubilization by micelles on the transport of steroids across microporous membranes has been studied theoretically and experimentally. Our theoretical model requires the following parameters: micelle and drug diffusion coefficients in free solution, the distribution coefficient of the drug between the bulk and micellar phases, and micelle and membrane pore radii. The steroids used were hydrocortisone, testosterone, and progesterone. Since the model accounts for the flux of free drug as well as micelle-solubilized drug, the distribution coefficient of the drug between micelles and the aqueous phase had to be determined by solubilization experiments for each of the steroids. Membrane pore diameters, as determined by scanning electron microscopy (SEM) and transmission electron microscopy (TEM), ranged from ~500 to 4000 Å. Steroid diffusion coefficients were calculated from membrane diffusion experiments. Quasi-elastic light scattering was used to find the free-solution diffusion coefficients and hydrodynamic radii of the micelles. With these experimentally determined parameters, the model is shown to be capable of predicting the rate of transport of micelle-solubilized drugs through microporous membranes. The application of our model to the design of controlled-release devices is also discussed.

Surfactants are used in many pharmaceutical applications: to solubilize drugs, for example; to alter biological membrane permeability; to form emulsions; and to reduce decomposition of drugs in solution.[1–5] Whenever surfactants are used, it is important to assess the effect of surfactant–drug interactions on the bioavailability of the drug. When the availability of drugs in surfactant solutions is reduced by the presence of a porous membrane, the effects of surfactant–membrane interactions, as well as surfactant–drug interactions, must be accounted for. This paper reports our theoretical and experimental results for the diffusion of surfactant-solubilized steroids through microporous membranes.

There are many reports concerning the effects of surfactant concentration on drug solubility.[6–8] Below the critical micelle concentration (CMC), the surfactant tends to have no effect on drug solubility; above the CMC, surfactant micelles may enhance drug solubilization dramatically. However, since micelles may contain between 50 to 100 surfactant monomers,[9] the micelle diameter may be an order of magnitude larger than that of the drug. Hence, drug bound to a micelle will experience a diffusion coefficient decrease, as demonstrated by Amidon et al. in their study of the diffusion of micelle-solubilized progesterone across the boundary layer of synthetic membranes.[10] While their nonporous membranes allowed the transport of drug molecules only, the microporous membranes used in the present study had nominal pore diameters ranging from 500 to 4000 Å and were therefore permeable to surfactant monomers, micelles, and the drug.

Inside a small pore, micelles experience greater hydrodynamic drag than in an unbounded solution. In general, as the ratio of the particle to pore radii increases, the diffusion coefficient of a particle in a pore decreases. Theoretical studies of this phenomenon, known as hindered diffusion, have yielded analytical expressions for the ratio of the intrapore to free solution diffusion coefficients.[11–13] Hindered diffusion experiments have also been performed using polystyrene latex spheres, asphaltenes, and globular polymers as particles.[14–16]

The diffusion of micelles through small pores has been the subject of several recent reports.[17–20] Krovvidi and Stroeve, for example, optimized the flux of micelle-solubilized *n*-heptane through microporous membranes.[20] They found that the solubility of the hydrocarbon was proportional to micelle size, and although the degree of hydrocarbon solubilization increased with micelle size, the membrane permeability of micelles decreased with micelle size. Hence, there was an optimum micelle size that maximized the *n*-heptane flux through a membrane. In contrast to their work with a short-chain hydrocarbon, the present work with steroids shows that a simple relationship between micelle size and solubilization does not exist for all surfactant–solute pairs.

The work reported here concentrates on solubilizate partitioning between micelles and the aqueous phase, and on the effect of this partitioning on solubilizate transport through a microporous membrane. The three steroids selected (hydrocortisone, testosterone, and progesterone) have widely differing aqueous solubilities. The solubilization of these steroids was studied in Brij 35, Triton X 100, and sodium dodecyl sulfate (SDS). The two nonionic surfactants, Brij 35 and Triton X 100, were used in membrane diffusion studies. Our model is described in the next section, followed by a discussion of our experiments (see Glossary for list of symbols). We found that the experimental data agree with model predictions to within ~10%.

Theoretical Section

The microporous membrane in Figure 1 separates two compartments which initially contain solutions having known micelle and drug concentrations. The drug is solubilized in the micellar and aqueous phases of side 1. Initially,

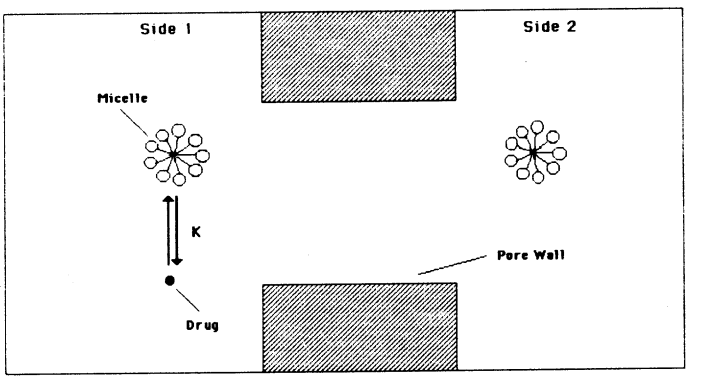

Figure 1—*Two sides of a diffusion cell separated by a microporous membrane. Initially, side 1 contains micelles plus drug while side 2 contains only micelles at a lower concentration than side 1.*

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side 2 contains only micelles at a lower concentration than the micelle concentration in side 1. Since the membrane is permeable to micelles and to the drug, there are fluxes of both micelles and drug across the membrane. The two compartments are well-stirred so that boundary layer resistances to mass transfer are insignificant compared with the membrane resistance. Entrance effects are neglected.

It is assumed that the concentrations of drug in the micellar phase (C_{DM}) and in the aqueous phase (C_D) may be expressed by an equilibrium constant K:

$$K = C_{DM}/(C_D C_M) \tag{1}$$

where C_M is the total surfactant concentration minus the critical micelle concentration (CMC). Since micelles diffuse more slowly than free drug, micelle-bound drug molecules do not pass through the membrane as rapidly as free drug, and hence, bound drug must be released from micelles in order to satisfy eq 1. Because the drug transport process consists of simultaneous diffusion and reaction (free drug $\rightleftharpoons$ bound drug), we write the continuity equations for each species (i) as

$$\partial C_i/\partial t = D_i \partial^2 C_i/\partial x^2 \pm \mathbf{R}_i \tag{2}$$

where i is either drug (D), micelle (M), or micelle-solubilized drug (DM), the x coordinate is parallel to the pore axis, and where $\mathbf{R}_i$ is the rate of exchange of drug between the micellar and aqueous phases, whose sign depends on whether i is generated or consumed. The intramembrane diffusion coefficient of i is D_i, and we take D_{DM} and D_M to be equal; that is, the diffusivity of micelles is unaffected by solubilization of drug (an experimental result discussed in a later section). Both bulk compartments are above the CMC, so we take the unmicellized monomer concentration on both sides of the membrane to be the same. Thus, the contribution of unmicellized monomer to transport processes is neglected.

For a micelle-solubilized solute, others have shown that the rate of exchange between free solution and micelles is generally quite fast.[21,22] Therefore, we assume a diffusion-controlled process, and we neglect $\mathbf{R}_i$ in eq 2. Furthermore, the membrane is thin compared with the dimensions of the diffusion cell, so we assume pseudo steady state; that is, we set $\partial C_i/\partial t$ in eq 2 to zero. With these assumptions, we rewrite eq 2 as

$$D_i d^2 C_i/dx^2 = 0 \tag{3}$$

By integrating eq 3, one eventually obtains the following (see Appendix) for the micelle concentrations in sides 1 and 2:

$$C_{M1} = 0.5\{C_{M10} + C_{M20} - (C_{M20} - C_{M10}) \exp(-\beta D_M t)\} \tag{4}$$

$$C_{M2} = 0.5\{C_{M10} + C_{M20} + (C_{M20} - C_{M10}) \exp(-\beta D_M t)\} \tag{5}$$

where $\beta = A(1/V_1 + 1/V_2)/L$, and where A is the total pore area, L is the membrane thickness, and V_1 and V_2 are the volumes of sides 1 and 2, respectively ($V_1 = V_2$ in our diffusion cell). Defining the total drug concentration in both free and micelle-bound forms as $C_{DT} = C_D + C_{DM}$, we obtain for the rate of change of C_{DT} in side 2 (see Appendix)

$$dC_{DT2}/dt = A[\Phi D_M(C_{M1} - C_{M2}) + D_D(C_{D1} - C_{D2})]/(LV_2) \tag{6}$$

where Φ is the ratio of micelle-solubilized drug to micelles in the donor phase (C_{DM1}/C_{M1}). Using eq 1 we obtain

$$C_D = C_{DT}/(1 + KC_M) \tag{7}$$

$$C_{DM} = C_{DT}KC_M/(1 + KC_M) \tag{8}$$

which when substituted into eq 6 gives

$$\frac{dC_{DT2}}{dt} = \frac{A}{LV_2}\left[\frac{KD_M}{1 + KC_{M1}}(C_{M1} - C_{M2})C_{DT1} + D_D\left(\frac{C_{DT1}}{1 + KC_{M1}} - \frac{C_{DT2}}{1 + KC_{M2}}\right)\right] \tag{9}$$

we eliminate C_{DT1} by a material balance on the cell:

$$C_{DT1} = C_{DT10} - (C_{DT2} - C_{DT20}) = C_{DT10} - C_{DT2} \tag{10}$$

where initially the total drug concentration in side 2 (C_{DT20}) is zero. Substituting eq 10 into eq 9 and rearranging, we obtain

$$\frac{dC_{DT2}}{dt} = \frac{A[D_D + KD_M(C_{M1} - C_{M2})]C_{DT10}}{LV_2(1 + KC_{M1})} - \frac{A}{LV_2}\left[\frac{KD_M}{1 + KC_{M1}}(C_{M1} - C_{M2}) + D_D\left(\frac{1}{1 + KC_{M1}} + \frac{1}{1 + KC_{M2}}\right)\right]C_{DT2} \tag{11}$$

Equation 11 has the form $dC_{DT2}/dt = f_1(t) - f_2(t)C_{DT2}$, and can be solved numerically for $C_{DT2}(t)$ using Euler's method. The constants required for the numerical solution of eq 11 are: A/L, V_1, V_2, C_{M10}, C_{M20}, C_{DT10}, D_M, D_D, and K. The methods for experimentally determining these parameters are described in the next section. Our model for release of a micelle-solubilized drug through a microporous membrane was derived with the following assumptions: pseudo steady-state diffusion; fast exchange of drug solubilized in micelles with drug in free solution; partitioning of the drug between the micellar and aqueous phases was independent of drug concentration; only hard-sphere interactions between pore walls and micelles; and boundary layer and entrance effects were negligible when compared with the membrane resistance. The assumption of hard-sphere interactions between micelles and pore walls results from the need to find the intrapore diffusion coefficient, D_M, from the experimentally determined bulk solution diffusion coefficient, $D_{M\infty}$, and micellar and pore radii, as discussed in the following sections. The validity of assuming negligible boundary layer resistance to mass transfer is discussed in the next section.

Experimental Section

This section describes the materials, instruments, and methods used in experiments. The characterization of the surfactants, drugs, and membranes used is also discussed.

Materials—Triton X 100 (polyoxyethylene alkyl-phenol), hydrocortisone, testosterone, and progesterone were purchased from Sigma Chemicals (St. Louis, MO), and Brij 35 (polyoxyethylene 23 lauryl ether) was donated by ICI Americas, Inc. (Wilmington, DL). Sodium chloride (ACS grade) and isopropyl alcohol (99 mol percent) were purchased from Fisher Scientific, and sodium dodecyl sulfate (SDS; 99% pure) was purchased from BDH Chemicals (Poole, England). All reagents were used as received. The Nuclepore membranes (Pleasanton, CA) used had nominal pore diameters of 500, 2000, and 4000 Å.

Diffusion Measurements—In the diagram of the diffusion cell in Figure 2, the membrane is held between the two glass half-cells by Neoprene gaskets (1.9 cm i.d.). The volume of each half-cell was 19.5 mL. A Teflon-coated magnetic stir bar extended into each half-cell from a Teflon stopper. When the half-cells were clamped together, the stirrers were rotated by an external magnet. The stirrer speed was kept at 300 ± 10 rpm; the differences between the results of experiments run at 250 or 300 rpm were negligible. The temperature during all diffusion experiments was 25 ± 1 °C. All solutions of drugs and surfactants were prepared in 0.15 M NaCl to simulate biological conditions and to minimize possible electrostatic (double layer) interactions with the charged pore walls. To remove dust which could clog pores, all solutions were filtered through membranes (Gelman Sciences) with 0.2-μm pore diameters.

At the start of each experiment, the receptor phase was placed in one half-cell, the donor phase was then placed in the other half-cell, and the stirrers were started. At various times, samples (0.4 mL) were withdrawn from the recepter half-cell and immediately replaced with the same amount of fresh receptor phase. This dilution of the receptor phase was taken into account in all calculations by adding the mass of drug removed at each withdrawal (i.e., 0.4 mL times C_{DT2}) to all subsequent data points. The UV absorbance (at 240 nm) of samples from the receptor phase was determined in a high-pressure liquid chromatograph (HPLC). When steroids were the only diffusing species, sample absorbances (at 240 nm) were measured with a UV-visible spectrophotometer.

Membrane Characterization—Membrane pore diameters and pore densities were checked using electron microscopy. Carbon–platinum replicas of membranes with nominal pore diameters of 500 Å were examined with transmission electron microscopy (TEM), and membranes with 2000- and 4000-Å nominal pore diameters were examined by scanning electron microscopy (SEM) after being sputter-coated with gold. The results of these examinations of membranes are shown in Table I. During examination of the carbon–platinum replicas with TEM, it was apparent that many pores were covered over but not penetrated by the coating, leaving vague depressions rather than definite outlines in the replica, and thus complicating the pore density determination. However, pore diameters from these replicas were determined only from pores that clearly went through the replica. Thus, we believe that pore diameters and densities for the larger pores in Table I are reasonable, and we believe that the pore diameter reported for the membranes with nominal pore diameters of 500 Å is reliable; but because of the difficulties encountered in making carbon–platinum replicas, we believe the pore density for the 500-Å pores is unreliable.

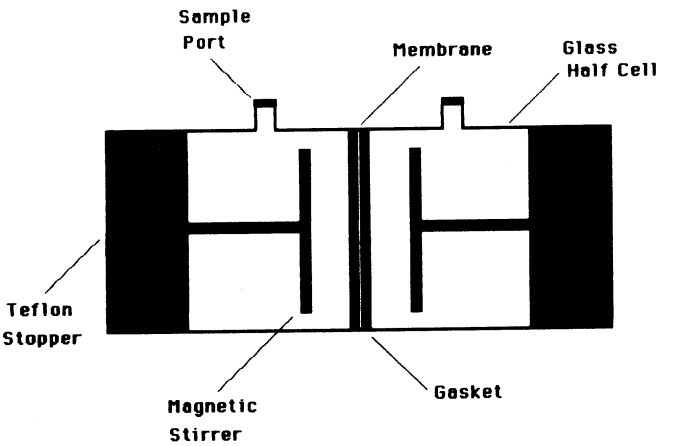

Figure 2—*Glass and Teflon diffusion cell used in experiments. Stirrers were rotated by an external magnet.*

Table I—Membrane Pore Diameters and Pore Densities from Electron Microscopy

Nominal Membrane Pore Diameter, Å	Pore Diameter from Electron Microscopy, Å	Number of Pores/ $cm^2 \times 10^{-8}$ from Electron Microscopy
500[a]	528 ± 54	3.6 ± 1.2
2000[b]	1730 ± 190	3.2 ± 0.2
4000[b]	3820 ± 306	1.1 ± 0.08

[a] Examined by TEM. [b] Examined by SEM.

The ratio of pore area to pore length (membrane thickness), A/L, for a membrane was found from the flux of hydrocortisone ($D_D = 4.24 \times 10^{-6}$ cm^2/s)[23] through the membrane (see eq A10). Before these measurements, membranes were soaked in 0.15 M NaCl for 1 h. The results of the determination A/L values from hydrocortisone diffusion experiments are shown in Table II. Using the average pore diameters and densities found with electron microscopy, but taking the pore length to be that stated by the manufacturer, we also calculated A/L values from electron microscopy (see Table II). With the exception of the 500-Å pores, we found that values of A/L from electron microscopy agree reasonably well with those from the diffusion experiments. The poor agreement between A/L values from electron microscopy and from hydrocortisone diffusion for the 500-Å membranes could be a result of poor replication by the carbon–platinum coating process, as discussed above.

Krovvidi et al. found that pore areas of microporous membranes were reduced by the adsorption of surfactant monomer on the pore walls.[19] Thus, before starting experiments involving surfactants, a membrane was soaked for 24 h in an aqueous solution of 0.15 M NaCl and surfactant above its CMC. The membrane was removed from the surfactant solution, rinsed with distilled, deionized water, and placed in the cell. Using hydrocortisone diffusion, values of A/L were determined for membranes after exposure to Triton X 100 and Brij 35 (see Table III). After exposure to surfactant, A/L was reduced (compare Tables II and III), a result encountered by Krovvidi et al., and the reduction of pore area by either surfactant was approximately the same. Because we could not examine the surfactant adsorbed to the pore wall with electron microscopy, the A/L values from hydrocortisone diffusion (Table III) were used in theoretical calculations. The pore radii used in calculations were based on those (found using electron microscopy) in Table I, values which we believe are reasonably accurate; however, since Table III indicates a reduction of pore diameters after exposure to surfactants, the pore radii in Table I were reduced by 35 Å, the length of a Triton X 100 monomer,[24] before being used in calculations.

Boundary Layer Resistance—The assumption of negligible boundary layer contribution to mass transfer resistance was tested as follows. The overall resistance to mass transfer of the diffusion cell, R_t, may be determined from the following relationship:[25,26]

$$\ln(\Delta C_0/\Delta C(t)) = 2A_m t/(VR_t) \quad (12)$$

where ΔC_0 and $\Delta C(t)$ are the concentration differences of the diffusing solute across the membrane initially and at time t, respectively, and A_m is the membrane area exposed between the Neoprene gaskets (Figure 2). The membrane resistance to mass transfer, R_m, is given by:[25,26]

$$R_m = L/(n\pi r^2 D) \quad (13)$$

Table II—Comparison of the Ratios of Membrane Pore Area-to-Thickness (A/L) for Membranes from Hydrocortisone Diffusion and Electron Microscopy

Nominal Membrane Pore Diameter, Å	A/L from Hydrocortisone Diffusion, cm	A/L from Electron Microscopy, cm	Agreement, %
500[a]	84.2 ± 4.7	44.7	47.3
2000[b]	242 ± 10	213	11.8
4000[b]	390 ± 16	357	8.3

[a] Nominal pore length of 5 μm. [b] Nominal pore length of 10 μm.

Table III—Ratio of Membrane Pore Area-to-Thickness (A/L) after Exposure to Triton X 100 and Brij 35

Nominal Membrane Pore Diameter, Å	A/L After Exposure to Triton X 100, cm	A/L After Exposure to Brij 35, cm
500	66.6 ± 3.6	62.0 ± 3.9
2000	226 ± 12	231 ± 10
4000	378 ± 16	368 ± 16

where n is the pore density, r is the pore radius, and D is the diffusion coefficient of the solute.

For membranes with nominal pore diameters of 2000 and 4000 Å, R_t was determined by hydrocortisone diffusion experiments in which concentration differences across the cell with time were measured by UV absorbance. Scanning electron microscopy was used to measure r and n for these membranes; L was determined by measuring the membrane weight, W, and correcting for porosity ($n\pi r^2$) and pores that are not aligned normal to the surface (0 to 29° from the normal)[27] as follows:[25,26]

$$L = 1.068W/([1 - n\pi a^2]\rho A_d) \quad (14)$$

where A_d is the area of the membrane disk (3.7 cm diameter), ρ is the density of polycarbonate (1.19 g/cm^3),[26] and the factor 1.068 accounts for pore alignments deviating from the normal. The values of r, n, L, R_m, and R_t are given in Table IV. The value of R_m was not calculated for the 500-Å membrane because of the difficulties we had in obtaining the value of n from transmission electron micrographs of carbon–platinum replicas; in addition, boundary layer resistance should have been even less important for the membranes with pore diameters of 500 Å. In Table IV, R_m accounts for 92.7 and 89.3% of R_t for the 2000- and 4000-Å membranes, respectively. Hence, the error in assuming negligible boundary layer resistance (an important assumption in the theoretical treatment) was small. It should be kept in mind that boundary layer resistance in vivo may be significant if there is inadequate stirring. Furthermore, it deserves note that values of A/L used in calculations were found from solute diffusion experiments (Table III) and, therefore, already contained small contributions from boundary layer resistances. As already noted, we were forced to use A/L values from solute diffusion experiments since the surfactant coating the pore wall would not be detected by electron microscopy. Hence, while we neglected boundary layer resistances in theoretical derivations, and while the boundary layer contributions were small as shown here, the values of A/L actually used unavoidably contained contributions from boundary layer resistances.

Steroid Diffusion Coefficients—Diffusion coefficients for testosterone and progesterone were ascertained from diffusion experiments. Using a membrane with a nominal pore diameter of 500 Å, D_D for testosterone was 4.95 ± 0.21 cm^2/s, and D_D for progesterone was 5.86 ± 0.23 × 10^{-6} cm^2/s. After adjusting the results of Amidon et al.,[10] determined at 37 °C, to 25 °C using the Stokes–Einstein equation, their value of D_D agrees well with our value of D_D for progesterone.

Steroid Solubilization by Micelles—The total amount of drug, C_{DT}, that could be solubilized by a micellar solution was determined by adding a slight excess of drug crystals to an aqueous solution of known micelle concentration, C_M (using the Wilhelmy plate method,[28] the CMC values for Brij 35, Triton X 100, and SDS were found to be 0.098, 0.22, and 1.14 mM, respectively). After mixing at 25 °C for 96 h, the suspension was filtered through a membrane with 0.2-μm diameter pores to remove undissolved crystals. The filtrate was diluted with isopropyl alcohol and analyzed by HPLC at 240 nm to determine total drug concentration. For each drug–surfactant pair, plots of C_{DT} versus C_M were linear in the range of surfactant concentrations studied, as shown in Figure 3. The drug distribution coefficient, K, was obtained by linear regression on such data, where the slope of Figure 3 is KC_D and the intercept is C_D (see eq A13). For micelle-solubilized drug diffusion experiments, the initial concentration of drug in the donor phase (C_{DT10}) was only 85 to 95% of saturation in order to completely avoid the possibility of precipitation of drug crystals. However, C_{DT10} was always greater than the aqueous solubility limit of the drug, and since the overall solubility of drug (C_{DT}) is increased by the presence of micelles, more drug was loaded into solutions containing micelles than would be possible in the absence of micelles. This increase in overall solubility is one of the appealing features of micelle-controlled drug release through microporous membranes.

Micelle Characterization—The free solution diffusion coefficients, $D_{M\infty}$, and hydrodynamic radii, a, of micelles were determined by quasi-elastic light scattering (QELS).[29–31] A 3W Spectra Physics argon-ion laser (514.5-nm line) was used in conjunction with a Brookhaven Instruments model BI-2030 64-channel digital correlator. Sample temperatures were kept at 25 ± 0.1 °C. Data were analyzed using software from the manufacturer. Prior to light-scattering experiments, all surfactant solutions were passed through a filter (0.2-μm pore diameter) to remove dust. For spherical micelles, $D_{M\infty}$ is related to the hydrodynamic radius by the Stokes–Einstein equation:

$$D_{M\infty} = kT/(6\pi\mu a) \quad (15)$$

where k is Boltzman's constant, T is temperature, and μ is the viscosity of the continuous phase. Using QELS, the diffusion coefficients for Brij 35 and Triton X 100 micelles were 5.44 ± 0.16 and 5.17 ± 0.12 × 10^{-7} cm^2/s, respectively. Using eq 15, the hydrodynamic radii for Brij 35 and Triton X 100 micelles were 45.0 and 47.5 Å, respectively. In the range of surfactant concentrations used (2 to 20 times CMC), the dependence of the micelle diffusion coefficient on micelle concentration was found to be negligible. In addition, QELS showed that micelle size did not change when steroids were added, as expected, since the drug molecules were small compared with the size of the micelles. It deserves note that these micelle diffusion coefficients are much lower than the diffusion coefficients of the drugs (given above), and as already noted, the overall solubility of the drug increases when micelles are present. The decrease in mobility of micelle-solubilized drug, along with the increase in drug solubility, are the key features of micelle-solubilized drug release through microporous membranes.

Results and Discussion

This section presents the results of steroid solubilization and intrapore micelle diffusion experiments, both of which

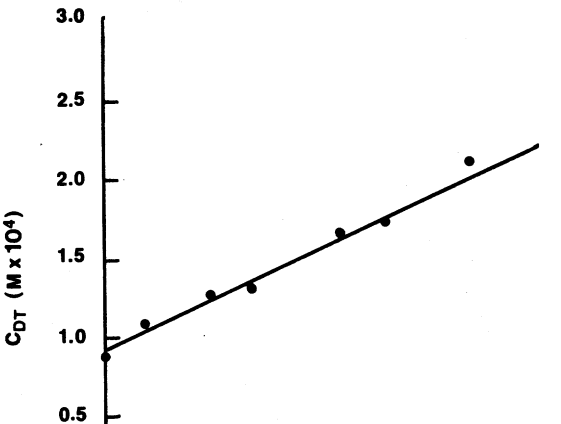

Figure 3—*Total concentration of testosterone (C_{DT}) versus Triton X 100 micelle concentration (C_M). The slope (KC_D) and intercept (C_D) of the line were obtained by fitting the data to eq A13.*

Table IV—Membrane Parameters and Mass Transfer Resistances

Nominal Membrane Pore Diameter, Å	r, Å[a]	n, pores/cm^2[b]	L, μm[c]	R_m, s/cm[d]	R_t, s/cm[e]
2000	895 ± 54	3.4 ± 0.2 × 10^8	9.80	2690	2900 ± 92.8
4000	1810 ± 101	1.2 ± 0.1 × 10^8	10.1	1920	2150 ± 81.7

[a] Micelle radius. [b] Pore density. [c] Membrane thickness. [d] Membrane mass transfer resistance. [e] Total mass transfer resistance.

are needed to predict micelle-solubilized steroid diffusion rates. We then present the results of micelle-solubilized steroid diffusion experiments.

Steroid Solubilization by Micelles—The distribution coefficients (K in eq 1) of hydrocortisone, testosterone, and progesterone in Brij 35, Triton X 100, and SDS with 0.15 M NaCl present are presented in Table V. The aqueous solubilities for the three steroids used also are in Table V. The surfactant concentrations used to obtain K were from 1 to 20 times the CMC of the surfactant. It is important to note that all of the plots of drug solubilization versus micelle concentration (e.g., Figure 3) were linear in the range of surfactant concentrations studied, allowing us to calculate K (eq A10) for the entire range of micelle concentrations studied. In plots such as that shown in Figure 3, several researchers[7-8] have reported nonlinearities at high surfactant concentrations; nonlinearities which they attribute to a change in micelle structure (known as the second CMC). However, since we used relatively low surfactant concentrations, we encountered no such nonlinearities, allowing us to determine K unambiguously.

In Table V, the K values for Triton X 100 solutions were lower than those for Brij 35 (perhaps due to the higher amount of polyethylene oxide per mole of Brij 35). As expected, the most water-soluble steroid, hydrocortisone, had the lowest K in all three surfactants. The K values for the steroids in SDS solutions were much larger than those in the nonionic surfactants. Mazer et al.[32] showed that the hydrodynamic radius of SDS micelles in 0.15 M NaCl is ~25 Å, smaller than the radii of Triton X 100 or Brij 35 micelles. Hence, a comparison of K values for SDS with those for the nonionic surfactants shows that it is not always possible to expect a simple relationship between micelle size and solubilization. The extent of solubilization depends on the interaction between the drug and various sites within the micelle. For example, solubilization can occur at the micelle–water interface, between the polar head groups, in the palisade layer (a region between the polar head groups and the first few carbon atoms), or deep within the micelle core.[33] Thus, the structures of both the surfactant and the solubilizate would have to be considered in order to predict solubilization phenomena.[34]

If ionic surfactant micelles were used in membrane diffusion experiments, electrostatic interactions between pore walls and micelles would have to be considered. In our drug diffusion experiments, we used only nonionic surfactants, so we considered only hard-sphere interactions between pores and micelles.

Intrapore Micelle Diffusion—Intrapore micelle diffusion coefficients for Triton X 100 were measured by membrane diffusion experiments, where the receptor phase surfactant concentration was slightly above the CMC and the donor phase surfactant concentration was ~10 times the CMC. As shown in Table VI for Triton X 100 micelles in Nuclepore membranes, micelle intrapore diffusion coefficients decreased as the pore size decreased. The ratio of the diffusion coefficient of a micelle in a pore, D_{Mp} (based on the concentration of micelles in the pore), to the diffusion coefficient of the micelle in free solution, $D_{M\infty}$, may be estimated by[12]

$$D_{Mp}/D_{M\infty} = 1 - 2.1044(a/r) + 2.089(a/r)^3 - 0.948(a/r)^5 \quad (16)$$

where a is the micelle radius and r is the pore radius. Equation 16 was derived for hard-sphere particles in pores and is valid for particle-to-pore ratios <0.4. The diffusion coefficient of the micelle in the pore based on the bulk concentration of micelles, D_M, is obtained by multiplying eq 16 by the partition coefficient of micelles into the pore, K_M.[20]

$$K_M = (1 - a/r)^2 \quad (17)$$

Using eqs 16 and 17, we estimated the diffusion coefficients of micelles in membranes (D_M), given values of $D_{M\infty}$ and a from QELS, and values of r from electron microscopy (Table IA) with a 35-Å correction for surfactant monomer adsorption on the pore wall (see *Experimental Section*). The results of calculations for D_M are shown in Table VI and Figure 4. The agreement between theory and experiment is viewed as good, and is comparable to the agreement obtained by Krovvidi et al.[19] for a single micelle–membrane combination. The agreement in Figure 4 is interesting because, although eq 16 and 17 were derived for hard spheres, Triton X 100 micelles are not perfect spheres.[35] Furthermore, micelles are quite dynamic: monomers exchange rapidly with the surrounding aqueous phase, and micellar aggregates undergo complete breakdown and reformation.[36] The lifetime of Triton X 100 micelles is of the order of 10 ms,[37] ~3 orders of magnitude lower than the residence time of our micelles in pores. Moreover, as discussed earlier, the reduction in A/L in Table III (compared with A/L values in Table II) implies that the pore wall is at least partially coated with surfactant monomer, and this coating complicates micelle interactions with the wall. Given these complications, the agreement between theory and experiments for $D_M/D_{M\infty}$ in Table VI and Figure 4 is surprisingly good. Because this agreement for Triton X 100

Table V—Steroid Distribution Coefficients (K) in Triton X 100, Brij 35, and Sodium Dodecyl Sulfate (SDS)

Steroid	K, mM^{-1}			Solubility, $M \times 10^4$ [a]
	In Triton X 100	In Brij 35	In SDS	
Hydrocortisone	0.095 ± 0.003	0.12 ± 0.004	0.25 ± 0.012	8.3 ± 0.1
Testosterone	0.35 ± 0.009	0.46 ± 0.013	1.65 ± 0.066	0.79 ± 0.02
Progesterone	1.86 ± 0.025	2.35 ± 0.094	6.87 ± 0.25	0.21 ± 0.01

[a] Solubility in 0.15 M NaCl.

Table VI—Experimental and Theoretical Diffusion Coefficients (D_M) for Triton X 100 Micelle Diffusion through Microporous Membranes

Nominal Membrane Pore Diameter, Å	Experimental D_M, $cm^2/s \times 10^7$	a/r, Å [a]	Theoretical D_M, $cm^2/s \times 10^7$	Agreement, %
500	1.47 ± 5.2%	0.21	1.86	20.1
2000	4.37 ± 3.1%	0.057	4.04	8.2
4000	5.03 ± 3.0%	0.025	4.65	8.2

[a] Ratio of micelle radius (a) to membrane pore radius (r); corrected for surfactant monomer adsorption on pore wall.

may be fortuitous, further studies like those in Table VI and Figure 4 are needed.

For Brij 35, we used QELS to obtain a from $D_{M\infty}$ (eq 15). Given the membrane pore sizes as determined above, we then used eqs 16 and 17 to obtain D_M from $D_{M\infty}$. Since Brij 35 does not absorb in the UV-visible region, we were unable to check this theoretical result for D_M. Because we were forced to use this procedure to obtain D_M for Brij 35, we also used this procedure for Triton X 100 (i.e., the theoretical values for D_M in Table VI were used for numerical solutions of eq 11).

Effect of Steroid Solubilization on Transport—The solubilization of drugs by micelles can dramatically affect the diffusion of drugs through microporous membranes, as expected intuitively and as shown by eq 11. Figures 5–7 show the results of experiments and model calculations for hydrocortisone, testosterone, and progesterone in Brij 35 solutions; the nominal membrane pore diameter in Figures 5–7 was 2000 Å. The circles in each figure are the data and the four curves are the results of model calculations: curve A is the numerical solution to eq 11 assuming that the drug in solution does not associate at all with the micelle ($K = 0$); curve B assumes that the drug is completely solubilized in the micellar phase ($K = \infty$); curve C is the result if the donor phase were an aqueous solution saturated with the drug (no

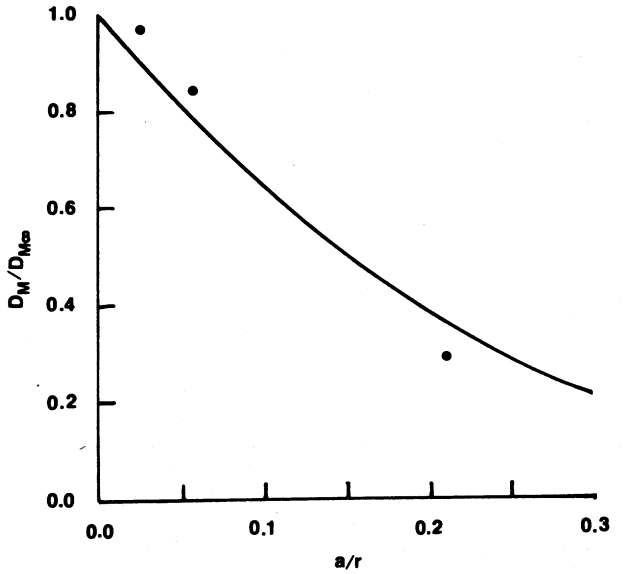

Figure 4—*The ratio of the intrapore micelle diffusion coefficient to the micelle diffusion coefficient in free solution ($D_M/D_{M\infty}$) for Triton X 100 micelles versus the ratio of micelle to pore radii (a/r). The curve is the product of eqs 16 and 17.*

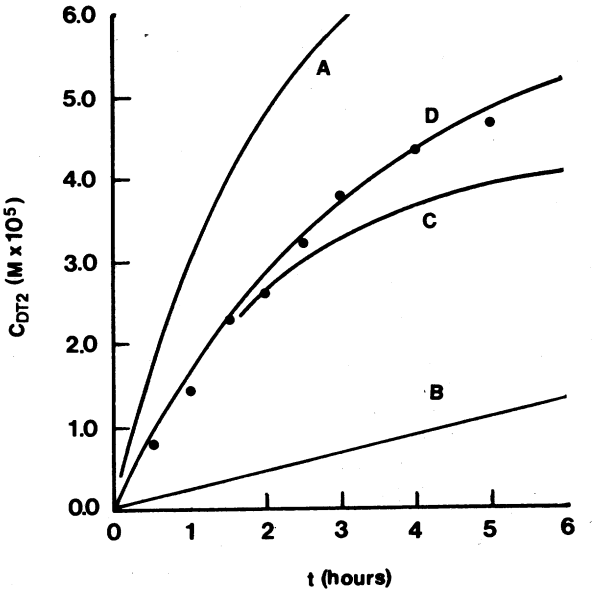

Figure 6—*Total concentration of testosterone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is Brij 35, the nominal membrane pore diameter is 2000 Å, C_{M10} = 1.87 mM, C_{M20} = 0.14 mM, and $C_{DT10} = 1.57 \times 10^{-4}$ M. Curves: (**A**) $K = 0$; (**B**) $K = \infty$; (**C**) C_{DT10} from aqueous solubility in Table V; and (**D**) model calculations from eq 11.*

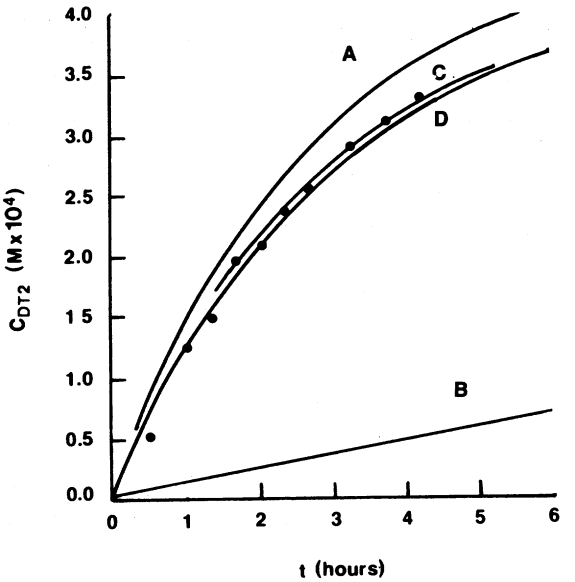

Figure 5—*Total concentration of hydrocortisone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is Brij 35, the nominal membrane pore diameter is 2000 Å, C_{M10} = 1.88 mM, C_{M20} = 0.13 mM, and $C_{DT10} = 9.12 \times 10^{-4}$ M. Curves: (**A**) $K = 0$; (**B**) $K = \infty$; (**C**) C_{DT10} from aqueous solubility in Table V; and (**D**) model calculations from eq 11.*

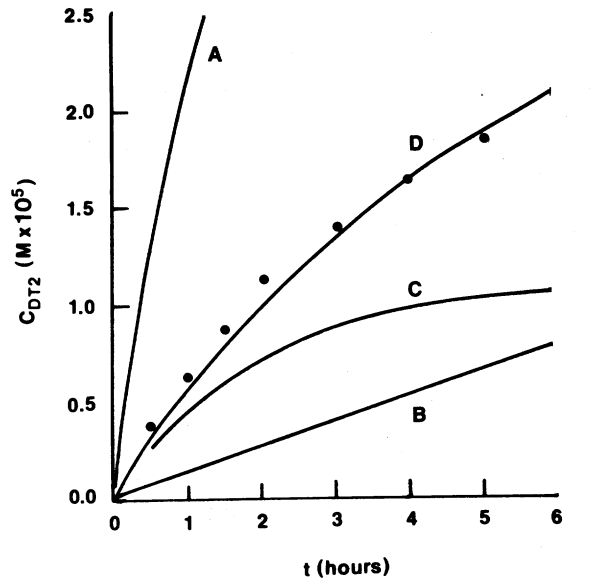

Figure 7—*Total concentration of progesterone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is Brij 35, the nominal membrane pore diameter is 2000 Å, C_{M10} = 1.80 mM, C_{M20} = 0.14 mM, and $C_{DT10} = 1.02 \times 10^{-4}$ M. Curves: (**A**) $K = 0$; (**B**) $K = \infty$; (**C**) C_{DT10} from aqueous solubility in Table V; and (**D**) model calculations from eq 11.*

micelles present); and curve D accounts for the actual partitioning of the drug between the free solution and micelles using the experimentally determined values of K from Table V. Curves A–D are plotted to illustrate that K can have a significant influence on the actual release of steroids into the receptor phase. The average deviations of data from model calculations (curve D) in Figures 5, 6, and 7 are 5.1, 4.3, and 9.4%, respectively.

The significantly lower pore diffusion coefficients of micelles, when compared with the diffusion coefficients of the drugs in free solution, is the basis of the controlled-release technique. Since hydrocortisone in Figure 5 does not partition strongly into micelles (K for hydrocortisone is low in Table V), the rate of release of hydrocortisone into the receptor phase closely follows the release rate that would be expected if hydrocortisone did not partition into micelles (i.e., if K were zero as in curve A of Figure 5). Thus, hydrocortisone transport is dominated by free drug diffusion, and both the data (circles) and the theoretical predictions (curve D) are relatively close to curve A. On the other hand, for testosterone and progesterone, where more of the drug partitions into micelles (K is larger), the data and the theoretical predictions (curve D) in Figures 6 and 7 move away from the curve A towards curve B. When micelles significantly influence drug solubilization, the total amount of drug delivered to the receptor phase ($0.5C_{DT10}$) increases, and the rate of delivery (compare the slopes of curves C and D in Figures 5–7) can be increased over those achieved in the absence of micelles. Thus, the affinity of the drug for the micellar phase—as indicated by K, which for hydrocortisone (Figure 5) is ~20 times less than that for progesterone (Figure 7)—can dramatically increase the rate and amount of drug transported through the membrane, especially if K is large, as in Figure 7. It also deserves note that for the 6-h experiment in Figure 7, the actual rate of drug released (curve D) is not only higher but more nearly constant than if no micelles were present (curve C). This more nearly constant rate over a prolonged period is an appealing feature of the micelle-controlled delivery technique.

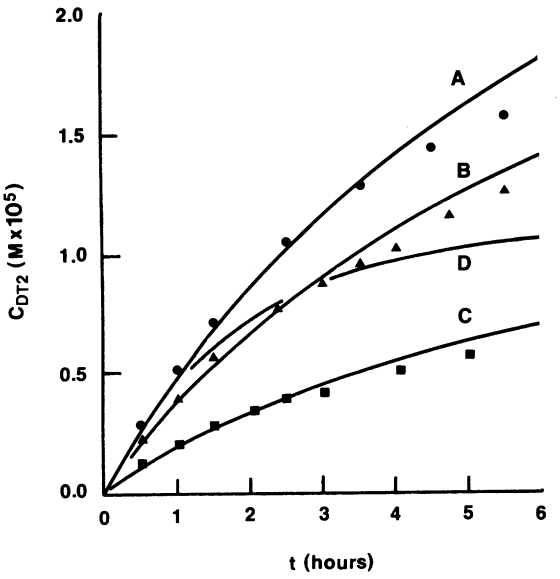

Figure 8—*Total concentration of progesterone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is Triton X 100, the nominal membrane pore diameter is 2000 Å, C_{M10} = 2.69 mM, and C_{M20} = 0.24 mM. Curves:* (**A**) (●) *80% saturation (C_{DT10} = 1.01 × 10^{-4} M);* (**B**) (▲) *62% saturation (C_{DT10} = 7.80 × 10^{-5} M);* (**C**) (■) *31% saturation (C_{DT10} = 3.98 × 10^{-5} M); and* (**D**) *the delivery that would be obtained from a saturated aqueous solution (C_{DT10} from Table V).*

Partition Coefficient (K) Values Below Saturation—The K values in Table V were determined for micellar solutions saturated with drug, and the donor phases in Figures 5–7 initially had drug concentrations between 85 and 95% of saturation, still above the aqueous solubility limit (see Table V and Figure 3) of the drug in aqueous solution. However, it is important to determine whether the K values calculated by solubilization experiments are still valid at lower drug concentrations. Figure 8 shows the results of experiments using progesterone in Triton X 100 solutions and membranes with pore diameters of 2000 Å. In each experiment, the initial surfactant concentrations in the donor and receptor compartments were the same while the degree of drug saturation was changed. Curves A, B, and C are for 80, 62, and 31% saturation, respectively, and for each experiment, the data had approximately the same agreement with solutions to eq 11; the average deviations of data from model calculations (curves A–C) in Figure 8 for 80, 62, and 31% saturation are 5.2, 5.5, and 7.4%, respectively. Since no parameters other than the degree of saturation were changed, we conclude that K remained constant for all three experiments in Figure 8.

Curve D in Figure 8 is the result that would be obtained if the donor phase were an aqueous solution saturated with progesterone. Comparing curve A with curve D, it is clear that more drug can be released at a more constant rate (as indicated by the slopes of the curves) when micelles are present (curve A) than when they are not (curve D). Furthermore, the same amount of drug can be delivered at a more constant rate over a longer period of time. Both of these results are favorable for controlled drug delivery.

It is worth noting that the agreement of data with curves A–C is not particularly surprising, since even if our Triton X 100 solutions had been saturated with progesterone, the mole fraction of drug appearing in the micellar phase would have been 0.03, and the mole fraction of progesterone appearing in the aqueous phase also would have been low (3.8×10^{-7}). Thus, both micellar and aqueous phases had dilute concentrations of the drug, and we would not expect K to change since we were close to infinite dilution. We would also not expect K to change for the other drug–surfactant combinations, since the maximum mole fraction in the nonionic micellar phase of any of the drugs used was 0.092 (for

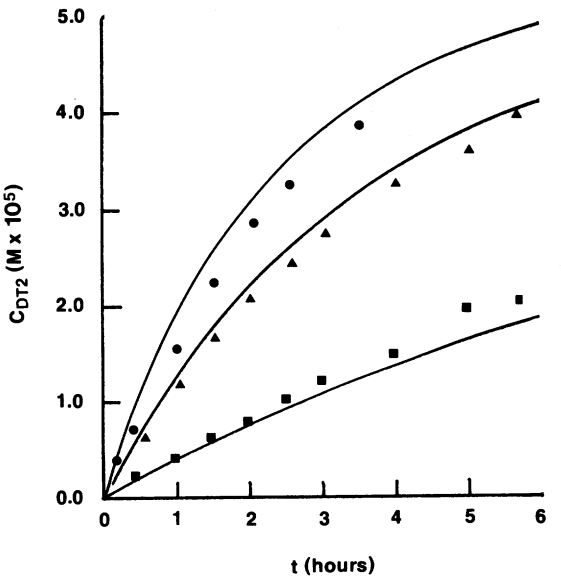

Figure 9—*Total concentration of testosterone in receptor phase (C_{DT2}) versus time (t), where the surfactant is Triton X 100, C_{M10} = 2.7 mM, C_{M20} = 0.27 mM, and C_{DT10} = 1.31 × 10^{-4} M; and the nominal membrane pore diameters are:* (●) *4000 Å;* (▲) *2000 Å; and* (■) *500 Å.*

hydrocortisone in Brij 35).

Effect of Pore Size on Steroid Release—Equations 16 and 17 predict that $D_M/D_{M\infty}$ decreases as a/r increases. Figure 9 shows the results of diffusion experiments using testosterone in Triton X 100 and membranes with nominal pore diameters of 500, 2000, and 4000 Å. The reduction in the rate of testosterone delivery to the receptor compartment with decreasing pore size reflects (1) a reduction in membrane pore area (A/L in Table III), as well as (2) decreased values of D_M due to hindered diffusion (Table VI). In Figure 9, the average deviations of data from model calculations for membranes with nominal pore diameters of 500, 2000, and 4000 Å are 10.3, 4.1, and 8.4%, respectively. Although the two effects [(1) and (2)] cannot be separated here, the agreement of the data in Figure 9 with the solutions to eq 11 implies that our theoretical model is valid for a variety of membrane pore sizes, even for pores in which micelle size is significant compared with the pore radius.

Conclusions

Using eq 11 and the experimentally determined constants, we found that the average deviations of experiments from numerical calculations were small (see Figures 5–9). To summarize our experimental results, the model was found to be valid for (1) steroids with high (progesterone) and low (hydrocortisone) distribution coefficients (K); (2) two nonionic surfactants; and (3) pore sizes ranging from large to only a few times larger than the micelle size.

Our experiments show that it is possible to regulate the release of a drug through a microporous membrane by binding the drug to micelles. If a drug has a significant preference for the micellar phase as compared with the aqueous phase, the solubility of the drug can be significantly increased by the presence of micelles. The rate of drug release can be maintained at higher and more constant levels than in the absence of micelles. If drugs are added to micellar solutions below the solubility limit, the same amount of drug can be released at a more constant rate than if the drug is added at its aqueous solubility limit in the absence of micelles. These results make the micelle-solubilized drug-release technique very appealing. To summarize, some advantages of the micelle-solubilized drug-release technique are: (1) the release of more drug than would be possible if micelles were absent; (2) the release of the same amount of drug over a longer interval than if micelles were absent; and (3) the release of drug at a more nearly constant rate. All of these aspects of the micelle-solubilized drug-release method are more pronounced if the distribution coefficient for the drug, K, is high.

Even though the SDS micelles were smaller than the nonionic surfactant micelles used, our studies showed that SDS micelles were able to solubilize more steroid than the nonionic surfactants. However, using SDS micelles in membrane diffusion experiments would introduce electrostatic interactions between the micelles and the pore walls.

Appendix

In this Appendix, we explain the equations that describe the individual fluxes for the three components in our system: micelles (M), free drug (D), and micelle-bound drug (DM). We also show the relationships for the total drug concentration (C_{DT}) to the free (C_D) and micelle-bound (C_{DM}) drug concentrations.

Equation 3 can be integrated to obtain

$$j_i = -D_i dC_i/dx \quad \text{(A1)}$$

where j_i is the flux of species i in mol/area–time. The flux of micelles from side 1 can be expressed as

$$j_M = -(V_1/A)dC_{M1}/dt \quad \text{(A2)}$$

where A is the membrane pore area and V_1 is the volume of side 1. Substituting eq A2 into A1, at pseudo steady state we have

$$dC_{M1}/dt = AD_M(C_{M2} - C_{M1})/(LV_1) \quad \text{(A3)}$$

where D_M, the intrapore diffusion coefficient of micelles, is viewed as accounting for both steric exclusion of micelles from pores and viscous drag between the micelles and the pore wall. The values C_{M1} and C_{M2} are the micelle concentrations in sides 1 and 2, respectively, and L is the membrane thickness. We can write a similar equation for the flux of micelles into side 2:

$$dC_{M2}/dt = -AD_M(C_{M2} - C_{M1})/(LV_2) \quad \text{(A4)}$$

Subtracting eq A3 from eq A4 we obtain

$$d(C_{M2} - C_{M1})/dt = -\beta D_M(C_{M2} - C_{M1}) \quad \text{(A5)}$$

where β is a constant equal to $A(1/V_1 + 1/V_2)/L$, and for our diffusion cell, $V_1 = V_2$. Integrating eq A5 with respect to time, we obtain

$$C_{M2} - C_{M1} = (C_{M20} - C_{M10}) \exp(-\beta D_M t) \quad \text{(A6)}$$

where C_{M10} and C_{M20} are the initial concentrations of micelles in sides 1 and 2, respectively.

A material balance on the diffusion cell with respect to the micellar concentrations yields

$$C_{M1} = C_{M10} - (C_{M2} - C_{M20}) \quad \text{(A7)}$$

where the micelles inside the membrane are neglected since the membrane volume is very small compared with the volume of the diffusion cell. With two unknowns in eq A6 and A7, we can calculate C_{M1} and C_{M2} at any time, t, if we know C_{M10}, C_{M20}, D_M, and β:

$$C_{M1} = 0.5[C_{M10} + C_{M20} - (C_{M20} - C_{M10}) \exp(-\beta D_M t)] \quad \text{(A8)}$$
$$C_{M2} = 0.5[C_{M10} + C_{M20} + (C_{M20} - C_{M10}) \exp(-\beta D_M t)] \quad \text{(A9)}$$

In a similar way, the equations for the flux of micelle-solubilized and free drug through the microporous membrane can be derived. By analogy with eq A4, rates of change in concentration of free and micelle-solubilized drug in side 2 are

$$dC_{D2}/dt = AD_D(C_{D1} - C_{D2})/(LV_2) \quad \text{(A10)}$$
$$dC_{DM2}/dt = A\Phi D_M(C_{M1} - C_{M2})/(LV_2) \quad \text{(A11)}$$

where Φ is the ratio of micelle-solubilized drug to micelles in the donor phase (C_{DM1}/C_{M1}). It is important to note that C_D and C_{DM} in both sides of the cell are related to the equilibrium distribution coefficient, K, and C_M by eq 1. When added, these rates of change yield the rate of change of the total drug concentration in side 2:

$$dC_{DT2}/dt = A[\Phi D_M(C_{M1} - C_{M2}) + D_D(C_{D1} - C_{D2})]/(LV_2) \quad \text{(A12)}$$

The relationship between the free, micelle-solubilized, and the total drug concentrations found from eq 1 gives

$$C_{DT} = C_{DM} + C_D = C_D(1 + KC_M) \quad \text{(A13)}$$

Equation A13 can be arranged to give the following for C_D:

$$C_D = C_{DT}/(1 + KC_M) \quad \text{(A14)}$$

The value of C_{DT} may also be expressed as

$$C_{DT} = C_{DM} + C_{DM}/(KC_M) = C_{DM}[1 + 1/(KC_M)] \quad \text{(A15)}$$

After some algebraic manipulation, eq A15 becomes

$$C_{DM} = KC_MC_{DT}/(1 + KC_M) \quad \text{(A16)}$$

These equations (A12, A14, and A16) are then used to obtain eq 11 whose numerical solutions are shown in Figures 5–9.

Glossary

A	membrane pore area, cm^2
A_m	exposed membrane area between the gaskets in diffusion cell, cm^2
A_d	area of membrane disk, cm^2
a	micelle radius, Å
C_i	concentration of species i
D_i	diffusion coefficient of species i, cm^2/s
$D_{M\infty}$	diffusion coefficient of micelle in free solution, cm^2/s
D_{Mp}	diffusion coefficient of micelle in pore based on local concentration of micelles, cm^2/s
j	flux, mol/area–time
k	Boltzmann's constant
K_M	micelle partition coefficient into membrane pore
K	partition constant for drug between micelle and water, mM^{-1}
L	membrane thickness, cm
n	pore density, pores/cm^2
r	membrane pore radius, Å
R_t	total mass transfer resistance, s/cm
R_m	membrane mass transfer resistance, s/cm
R_i	rate of drug exchange between the micellar and aqueous phases
t	time
V_1	volume, side 1 of diffusion cell, cm^3
V_2	volume, side 2 of diffusion cell, cm^3
μ	viscosity
ρ	membrane density, g/cm^3
β	diffusion cell constant, $A/L(1/V_1 + 1/V_2)$

Subscripts

D	free drug
M	micelle
DM	micelle-solubilized drug
DT	total drug, D + DM
i	species D, M, DM, or DT
1	side 1
2	side 2
0	initially, at t = 0

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