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Report

Controlled Release of Steroids Through Microporous Membranes with Sodium Dodecyl Sulfate Micelles

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The effect of solubilization by sodium dodecyl sulfate (SDS) micelles on the transport of steroids across synthetic microporous membranes has been studied experimentally in a diffusion cell and compared with theoretical calculations. The model used for calculations accounted for the fluxes of free and micelle-solubilized drug. Since the pores of the microporous membranes were only 10 times larger than the micelle, hindered diffusion effects for the micelles were taken into account. The compounds of interest (hydrocortisone, testosterone, and progesterone) had a wide range of aqueous solubilities and distribution coefficients between the aqueous and the micellar phases. In general, the theoretical predictions of drug diffusion agreed with the data to within approximately 10%.

KEY WORDS: micelle; drug solubilization; microporous membranes; hindered diffusion; controlled release.

INTRODUCTION

It has been demonstrated by several researchers that the flux of a solute through a microporous membrane can be controlled by the presence of micelles (1,2). Micelles, which can significantly increase the solubility of compounds with low aqueous solubilities (3–5), are usually much larger than the solute. Therefore, the mobility of a compound solubilized in a micelle is reduced compared to its mobility when micelles are absent (6,7). The enhancement of solubility and decrease in mobility are the basis of the micelle-controlled release technique.

If the micelle is not much smaller than the pore through which it diffuses, the intrapore diffusion coefficient of the micelle may be less than the diffusion coefficient of the micelle in free solution due to the proximity of the pore wall (2,8–10). This phenomenon, known as hindered diffusion, has been studied experimentally and theoretically by several researchers (11–14). The diffusion coefficient of a particle in a small pore may be estimated if the particle diffusion coefficient in free solution, the particle size, and the pore size are known. Any reduction in the mobility of the micelle in a small pore, such as hindrance due to the presence of the pore wall, can significantly affect the release of a micelle-solubilized compound through the membrane (1,2).

In a previous study on the diffusion of micelle-solubilized steroids, it was shown that calculations for drug delivery to the receptor side of a diffusion cell were in agreement with data from diffusion-cell experiments (2). The calculations were made using a model which accounted for the flux of free and micelle-solubilized drug. Anionic sodium dodecyl sulfate (SDS) micelles were found to have a higher solubilization capacity for the steroids than the nonionic micelles used in previous diffusion–cell experiments (2). Therefore, the use of SDS micelles in steroid diffusion experiments would provide a better test for the model. However, the use of ionic micelles could complicate calculations of micelle diffusion coefficients in the pore because of potential electrostatic interactions between the pore wall and the micelle. Previous studies of charged micelle diffusion through charged microporous membranes showed that by using sufficient concentrations of a supporting electrolyte, electrostatic interactions between micelles and micropores can be eliminated (15). Therefore, the diffusion coefficients of SDS micelles in microporous membranes can be estimated by the same equations used for nonionic micelles (2) if a sufficient concentration of supporting electrolyte is used.

In the present work, model calculations of the diffusion of micelle-solubilized steroids through microporous membranes are compared with data from diffusion-cell experiments where SDS micelles were used to enhance the solubility of steroids having a wide range of aqueous solubilities (hydrocortisone, testosterone, and progesterone). All experiments were performed in 0.15 *M* NaCl to eliminate electrostatic interactions between the micelle and the membrane pore wall (15) as well as to simulate biological conditions.

THEORY

Micelle-Solubilized Steroid Diffusion

Two sides of a diffusion cell are separated by a microporous membrane. The receptor side of the cell (Side 2)

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contains a surfactant solution above the critical micelle concentration (CMC). The donor side of the cell (Side 1) contains a surfactant solution at a higher concentration than the receptor side plus a solute (or drug) that is distributed between the micellar and the aqueous phases. The concentrations of drug in the aqueous (C_D) and micellar (C_{DM}) phases may be expressed by an equilibrium constant K:

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

where C_M is the total surfactant concentration minus the CMC. This distribution coefficient is large for compounds having a higher affinity for the micellar phase compared to the aqueous phase.

In the diffusion experiment described above, there is a flux of micelles as well as the drug. Both sides of the cell are assumed to be well stirred so that the membrane is the only resistance to mass transfer. The membrane volume is small when compared to the volume of the diffusion cell, so a pseudo-steady-state approximation is made. The result for the rate of change of the total drug concentration ($C_{DM} + C_D$) in Side 2 (dC_{DT}/dt) is (2):

$$\frac{dC_{DT2}}{dt} = \frac{A}{LV_2}\left[\frac{KD_M(C_{M1} - C_{M2})C_{DT1}}{1 + KC_{M1}} + D_D\left(\frac{C_{DT1}}{1 + KC_{M1}} - \frac{C_{DT2}}{1 + KC_{M2}}\right)\right] \quad (2)$$

where A is the membrane pore area, L is the membrane pore length, V_2 is the volume of Side 2, D_M is the intrapore micelle diffusion coefficient, D_D is the drug diffusion coefficient, and the subscripts 1 and 2 refer to Sides 1 and 2 of the diffusion cell, respectively. It is assumed that the drug diffusion coefficient is unaffected by the presence of the pore wall since the drug molecule is much smaller than the pore.

A material balance on the diffusion cell yields the following expression for C_{DT1}:

$$C_{DT1} = C_{DT10} - (C_{DT2} - C_{DT20}) = C_{DT10} - C_{DT2} \quad (3)$$

where the initial concentration of drug in the receptor phase (C_{DT20}) is zero. The following expressions can be used to calculate the micelle concentrations in Sides 1 and 2 at any time t (2):

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

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

where β is the cell constant $[A/L(1/V_1 + 1/V_2)]$ and C_{M10} and C_{M20} are the initial concentrations of micelles in Sides 1 and 2. After Eqs. (3)–(5) are substituted into Eq. (2), it can then be integrated to calculate C_{DT2} at any time if the following parameters are known: A/L, V_1, V_2, C_{M20}, C_{DT10}, D_M, D_D, and K (2).

Hindered Diffusion

The diffusion coefficient of a hard sphere in a cylindrical pore (D_p), relative to the diffusion coefficient of the same particle in free solution (D_∞), is given by the following expression (13):

$$D_p/D_\infty = 1 - 2.1044\xi + 2.089\xi^3 - 0.948\xi^5 \quad (6)$$

where ξ is the ratio of the particle to the pore radii. Equation (6) is valid for all values of ξ less than 0.4 and assumes that the particle diffuses along the axis of the pore. It is important to note that D_p is the intrapore particle diffusion coefficient based on the concentration of particles in the pore. The intrapore particle diffusion coefficient based on the bulk concentration of particles (D) is the product of D_p and the ratio of the concentration of particles in the pore relative to the concentration of particles in the bulk (K_M) (10):

$$K_M = (1 - \xi)^2 \quad (7)$$

Therefore, the diffusion coefficient of the particle in the pore based on the bulk concentration of particles can be found if both sides of Eq. (6) are multipled by Eq. (7):

$$D/D_\infty = (1 - \xi)^2[1 - 2.1044\xi + 2.089\xi^3 - 0.948\xi^5] \quad (8)$$

EXPERIMENTS

Materials

Hydrocortisone (Sigma), testosterone (Sigma), progesterone (Sigma), sodium dodecyl sulfate (BDH), isopropanol (Fisher), and NaCl (Baker) were used as received. The polycarbonate membrane (nominal pore diameter of 300 Å) used in this study was purchased from Nuclepore.

Steroid Solubilization by SDS 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. After mixing at 25°C for 96 hr, a time selected based on previous experiments, the suspension was filtered through a Gelman syringe filter with 0.2-μm-diameter pores to remove undissolved crystals. The Gelman filters were rinsed with 1 ml of the filtrate before a sample was collected. The filtrate was diluted with isopropanol and analyzed by absorbance spectrophotometry at 248 nm (Perkin–Elmer UV/visible spectrophotometer Model 572) to determine the total drug concentration. The K values for the three steroids, obtained from plots of C_{DT} versus C_M, are given in Table I with the aqueous solubilities of the drugs.

Drug Diffusion Measurements

Diffusion experiments were performed at 25°C in a diffusion cell that was described in a previous study (2). The receptor side of the cell (Side 2) was filled with a SDS solution above the CMC (1.14 mM) (2). The donor side of the cell was filled with a SDS solution, with a higher surfactant con-

Table I. K Values in SDS and Aqueous Solubilities of Steroids

Steroid	K (mM^{-1})	Solubility ($M \times 10^4$)[a]
Hydrocortisone	0.25 ± 0.01	8.30 ± 0.10
Testosterone	1.65 ± 0.07	0.79 ± 0.02
Progesterone	6.87 ± 0.25	0.21 ± 0.01

[a] Solubility in 0.15 M NaCl.

centration than the receptor side, plus a steroid (hydrocortisone, testosterone, or progesterone). Both solutions were prepared at least 48 hr before the experiment. Initial drug concentrations in the donor side were approximately 85% below saturation to avoid any problems with precipitation. Over the range of drug concentrations expected in the receptor phase, plots of absorbance versus drug concentration in a SDS solution (C_M = 1 m*M*) were linear. Therefore, at various times during experiments, a 1-ml sample of the receptor phase was withdrawn and immediately analyzed for drug concentration by absorbance spectrophotometry, then replaced.

Membrane Characterization

The Nuclepore membrane used in this study was characterized with a combination of three independent experiments: measuring the pressure drop/flow rate relationship for a fluid through the membrane, measuring the weight of the membrane, and measuring the flux of hydrocortisone [D_D = 4.24 × 10^{-6} cm^2/sec (16)] through the membrane (15,17). With the results of these measurements, the membrane pore radius, pore length, and pore density were calculated to be 272 Å, 6.15 μm, and 8.8 × 10^8 pores/cm^2, respectively. SDS monomers adsorbed on the membrane surface and reduced the pore radius by 15 Å (15). Previous measurements of the boundary layer resistances to mass transfer in the diffusion cell while stirring at 300 rpm (2), showed such contributions to the diffusion process to be negligible.

Steroid and Micelle Diffusion Coefficients

Diffusion coefficients for testosterone (4.95 × 10^{-6} cm^2/sec) and progesterone (5.86 × 10^{-6} cm^2/sec) were ascertained from diffusion experiments (2). The diffusion coefficient of a SDS micelle in 0.15 *M* NaCl was determined by quasi-elastic light scattering (18–20) using equipment described previously (2). The diffusion coefficient of SDS micelles in 0.15 *M* NaCl was found to be 9.41 × 10^{-7} cm^2/sec and the hydrodynamic radius calculated from the Stokes–Einstein equation was 26 Å. SDS micelles showed an ~4% increase in size when saturated with hydrocortisone. This was the largest increase in micelle size with any solute, and therefore it was neglected.

The ratio of the micelle radius to the pore radius, or ξ, was 0.10. Using Eq. (8), the ratio of the micelle diffusion coefficient in the pore (D_M) to the micelle diffusion coefficient in free solution ($D_{M\infty}$, measured by light scattering) was calculated as 0.64. Therefore, the intrapore micelle diffusion coefficient used for drug delivery calculations was 6.02 × 10^{-7} cm^2/sec.

RESULTS

The data in Table I show that *K* is the lowest for hydrocortisone and the highest for progesterone. This is as expected since hydrocortisone has a much higher aqueous solubility than progesterone (2). Testosterone, with a solubility between that of hydrocortisone and that of progesterone, has a *K* value between those of the other two drugs in Table I.

The results of transmembrane steroid diffusion experiments using SDS micelles to enhance steroid solubility are shown in Figs. 1 to 3. In each figure, the circles are the data and the four curves are the results of model calculations: curve A is the numerical solution to Eq. (2) 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 = ∞); curve C is the result if the donor phase were an aqueous solution saturated with the drug (no micelles present); and curve D accounts for the actual partitioning of the drug between the free solution and the micelles using the experimentally determined values of *K*. Curves A–D are plotted in Figs. 1–3 to demonstrate the significant influence of micelles on the release of solutes into the receptor phase.

Of all the solutes, hydrocortisone had the lowest partition coefficient into the micelles (see Table I), so the diffusion process should be dominated by free hydrocortisone in the aqueous phase. This hypothesis is confirmed by the results in Fig. 1, where the data and curve D are closer to curve A than curve B. As *K* increases from a low value for hydrocortisone (Fig. 1) to a high value for progesterone (Fig. 3), the data and curve D move away from curve A and toward curve B. This result is expected since progesterone has the highest partition coefficient into the SDS micelles. As the *K* value increases, the diffusion of the drug becomes dominated by the solute in the micelles. Since the micelle diffusion coefficient in the pore is approximately seven times lower than the diffusion coefficients of the free steroids, the release of solute to the receptor phase is much slower. This is confirmed by comparing the data in Figs. 1 through 3 with calculations using our model that accounts for the flux of both free and micelle-solubilized drug (curve D). The average deviations of calculations, using the experimentally determined *K* values, from data are 2.1, 7.4, and 12.5% for Figs. 1, 2, and 3, respectively. Furthermore, the agreement of the

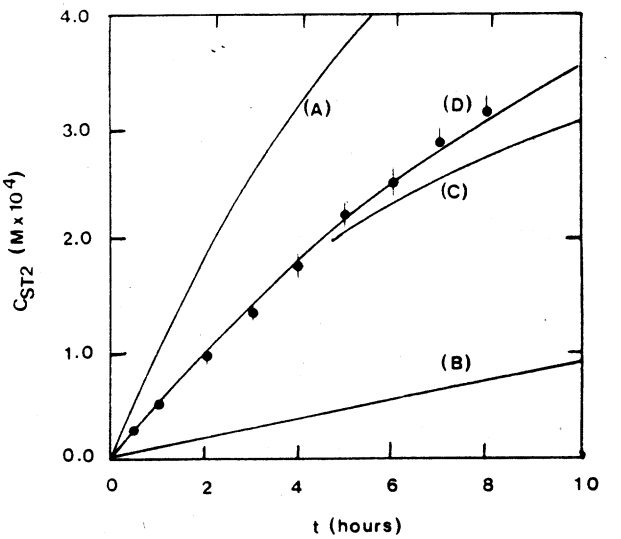

Fig. 1. Total concentration of hydrocortisone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is SDS (0.15 *M* NaCl), the nominal membrane pore diameter is 300 Å, C_{M10} = 4.0 m*M*, C_{M20} = 1.0 m*M*, and C_{DT10} = 1.53 × 10^{-3} *M*. (A) K = 0, (B) K = ∞, and (C) C_{DT10} from aqueous solubility (2); (D) model calculations from Eq. (2).

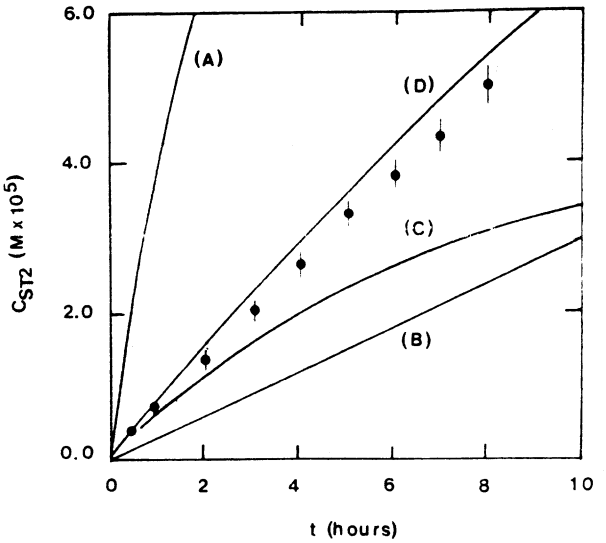

Fig. 2. Total concentration of testosterone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is SDS (0.15 M NaCl), the nominal membrane pore diameter is 300 Å, C_{M10} = 4.0 mM, C_{M20} = 1.0 mM, and C_{DT10} = 5.0 × 10^{-4} M. (A) K = 0, (B) K = ∞, and (C) C_{DT10} from aqueous solubility (2); (D) model calculations from Eq. (2).

data with curve D in Figs. 1, 2, and 3 indicates that the model is able to predict experimental results over a wider range of K values than was tested in a previous study on the diffusion of micelle-solubilized steroids through microporous membranes (2).

The average deviation of the calculations from the data increased as K increased from hydrocortisone to progesterone. Calculations for the diffusion of pyrene solubilized by SDS micelles deviated from the data by approximately 11% (15). The K value of pyrene in SDS is 21.5 or approximately

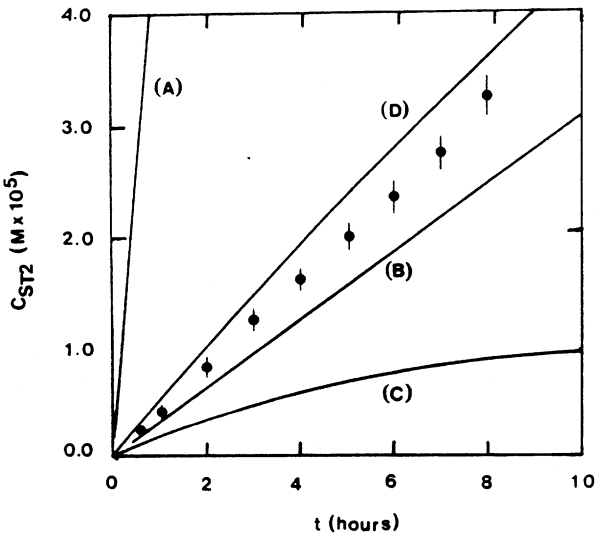

Fig. 3. Total concentration of progesterone in the receptor phase (C_{DT2}) versus time (t), where the surfactant is SDS (0.15 M NaCl), the nominal membrane pore diameter is 300 Å, C_{M10} = 4.0 mM, C_{M20} = 1.0 mM, and C_{DT10} = 5.1 × 10^{-4} M. (A) K = 0, (B) K = ∞, and (C) C_{DT10} from aqueous solubility (2); (D) model calculations from Eq. (2).

three times higher than the K value of progesterone in SDS (15). Therefore, the deviation between data and calculations does not continue to increase as K increases. The K values used in calculations were determined from micellar solutions that were saturated with solute. The donor side of the cell was approximately 10 to 15% below saturation at the beginning of the experiment and the receptor side of the cell contained no solute. It has been shown that distribution coefficients of solutes between micellar and aqueous phases can change as the number of solute molecules per micelle, or micelle loading, changes (21). This could be a source of error since the K values are used in calculations for a solution with a lower degree of micelle loading than the solution in which they were measured (i.e, a saturated solution).

The data and curve D for progesterone and testosterone deviate less from linearity than those for hydrocortisone. Thus, the fluxes for progesterone and testosterone are nearly constant since these solutes are more strongly bound than hydrocortisone to the slower moving SDS micelles. The flux from a micellar solution was higher than the flux from a saturated aqueous solution, as predicated by Eq. (2), since there is a drug flux with the micelles as well as from the aqueous phase. These results illustrate an important aspect of the micelle-controlled release technique. More drug can be released at a constant rate with micelles present if the drug's solubility is significantly enhanced by the presence of micelles.

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NOMENCLATURE

A	Membrane pore area, cm^2
C_i	Concentration of species i
D_i	Diffusion coefficient of species i, cm^2/sec
D_∞	Diffusion coefficient in free solution, cm^2/sec
D_M	Intrapore micelle diffusion coefficient, cm^2/sec
D_p	Diffusion coefficient in pore based on local concentration, cm^2/sec
K_M	Micelle partition coefficient into membrane pore
K	Partition constant for drug between micelle and water, mM^{-1}
L	Membrane thickness
t	Time
V_1	Volume, Side 1 of diffusion cell, cm^3
V_2	Volume, Side 2 of diffusion cell, cm^3
β	Diffusion-cell constant, $A/L(1/V_1 + 1/V_2)$
ξ	Ratio of micelle radius to pore radius

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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