Diffusion of an Ionic Drug in Micellar Aqueous Solutions

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Supramolecular carriers such as micelles can be used to noncovalently bind drug molecules for pharmaceutical applications. However, these carriers can fundamentally affect diffusion-based drug transport due to host−guest coupled diffusion. We report a ternary interdiffusion study on an ionic drug in aqueous micellar solutions. Specifically, high-precision Rayleigh interferometry was used to determine the four multicomponent diffusion coefficients for the potassium naproxenate−tyloxapol−water ternary system at 25 °C and pH 7. In addition, we have measured drug solubility as a function of tyloxapol concentration. These measurements were used to characterize drug−surfactant thermodynamic interactions using the two-phase partitioning model. Furthermore, we propose a novel model on host−guest coupled diffusion that includes counterions. We show that quantitative agreement between model and experimental diffusion results can be achieved if the effect of micelle solvation on transport parameters is included in the model. This work represents an essential addition to our previous diffusion study on a nonionic drug and provides guidance for the development of accurate models of drug diffusion-based controlled release in the presence of nanocarriers.

Introduction

Supramolecular systems such as micelles, liposomes, and other nanoparticles are valuable tools in the chemical and pharmaceutical fields because they can be used to reversibly bind drug compounds, thereby enabling controlled release and targeted delivery. They also reduce toxicity, enhance bioavailability, and improve stability of therapeutic agents.[1−3]

Inter-diffusion (or mutual-diffusion) coefficients of drug compounds are crucial parameters used for modeling, predicting, and designing drug release from delivery devices (gels or other porous materials) and other processes such as transport across membranes.[4−8] However, in the presence of supramolecular systems, drug diffusion becomes coupled to that of the hosting particle.[9−13] The description of drug−host diffusion transport in solution requires the use of Fick's first law extended to ternary systems:[14]

$$-J_1 = D_{11}\nabla C_1 + D_{12}\nabla C_2 \quad (1a)$$

$$-J_2 = D_{21}\nabla C_1 + D_{22}\nabla C_2 \quad (1b)$$

where C_1 and C_2 are the molar concentrations of the two solutes, drug(1) and host system(2), respectively, and J_1 and J_2 are the corresponding molar fluxes. The four D_{ij} (with $i,j = 1,2$) are the ternary diffusion coefficients. Main-diffusion coefficients, D_{11} and D_{22}, describe the flux of a solute due to its own concentration gradient, while cross-diffusion coefficients, D_{12} and D_{21}, are responsible for the flux of a solute due to the concentration gradient of the other solute.

Several inter-diffusion studies have been reported in relation to host−guest systems forming 1:1 complexes. The most relevant cases involve binding of small molecules to cyclodextrines.[10,11] One important aspect of these investigations is the observation of large negative values of the cross-diffusion coefficient responsible for the flux of guest molecules from low to high cyclodextrine concentration.[15−17] However, in many cases, host particles may bind more than one guest molecule.[3] The most common example is represented by micellar systems.[1] Clearly, diffusion studies on these systems represent an essential addition to those performed on 1:1 host−guest complexes.

We note that accurate self-diffusion coefficients for drug and surfactant molecules in solution have been obtained by pulsed-gradient spin−echo NMR (PGSE-NMR). The dependence of self-diffusion coefficients on system composition has been used to determine micellization parameters and drug−micelle binding.[18−21] However, self-diffusion coefficients cannot generally replace inter-diffusion coefficients when describing transport processes in the presence of concentration gradients. This is especially true when considering ionic species and chemical association.[22,23] Furthermore, self-diffusion studies on multi-

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component systems yield no information on cross-diffusion effects.

Several interdiffusion studies have been reported on surfactant multicomponent systems.[9,24−28] These investigations have mainly focused on the formation of mixed micelles in aqueous solutions.[24−26] In relation to micellar solubilization, few studies have been reported on aqueous solutions of *n*-alcohols and sodium dodecylsulfate.[27,28] In relation to drug compounds, we have recently reported a diffusion study on drug molecules in micellar aqueous solutions.[9] Specifically, using Rayleigh interferometry, we have determined the four diffusion coefficients for the hydrocortisone−tyloxapol−water ternary system at 25 °C, where hydrocortisone is a nonionic drug and tyloxapol is a nonionic surfactant.

Tyloxapol, which is a commercially available surfactant at a relatively low cost, is essentially an oligomer of octoxynol 9 (Triton X-100) mostly used in marketed ophthalmic products and as a mucolytic agent for treating pulmonary diseases.[29−32] Tyloxapol has a critical micellar concentration (cmc) of 0.038_5 g/L in water at 25 °C.[29] This cmc value is much lower than that of Triton X-100. Hence, the presence of free surfactant can be neglected with respect to micellar surfactant for concentrations of the order of 1 g/L or higher. We note that tyloxapol micelles are spherical with a diameter of 7 nm, and their size and shape do not change significantly for concentration as high as 10% by weight according to cryo-transmission electron microscopy.[30] We also point out that tyloxapol hydrophilic groups are poly(ethylene glycol) chains, a chemical motif often encountered in supramolecular systems of pharmaceutical relevance.[33] All of these features make tyloxapol micelles a model supramolecular system for host−guest physicochemical studies relevant to pharmaceutical science.

For the previously investigated hydrocortisone−tyloxapol−water system, the determined diffusion coefficients were examined using a drug−micelle coupled-diffusion model based on drug partitioning between the aqueous and micellar pseudophases. Drug partitioning was characterized by measuring the solubility of hydrocortisone as a function of tyloxapol concentration. A quantitative agreement between the experimental behavior of drug diffusion coefficients, D_{11} and D_{12}, and a model based on dependence of drug solubility on surfactant concentration was obtained. One important result of this investigation is that hydrocortisone diffusion is not only modulated by its binding to the slowly diffusing micelles but also because of the presence of gradient of micelle concentration.[9]

In this article, we extend our interdiffusion studies to the case of ionic drugs. Drugs with ionic structure are frequently encountered in pharmaceutical applications.[34] Furthermore, they can be also generated from nonionic drugs in situ by a pH change under physiological conditions. This feature is very important in targeting and controlled-release applications because drug binding strength to the host particle can be tuned by physicochemical changes of their surrounding environment.[35,36] Hence, investigating diffusion of an ionic drug in the presence of micelles represents an essential addition to our previous diffusion study on a nonionic drug.

We report measurements of the four diffusion coefficients for the naproxen−tyloxapol−water ternary system at 25 °C and pH 7.3 by Rayleigh interferometry. Naproxen (*S*(+)-2−(6-methoxy-2-naphthyl) propionic acid, $pK_a = 4.2$) is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties.[36−39] At the experimental pH, naproxen exists predominantly in its anionic form. In our investigation, the drug is a potassium salt. We include solubility measurements for potassium naproxenate as a function of tyloxapol concentration. We then introduce a novel model on host−guest coupled diffusion that includes counterion effects. We show that quantitative agreement can be obtained between model and behavior of the four experimental diffusion coefficients if the effect of micelle hydration is taken into account.

Materials and Methods

Materials. Naproxen was purchased from TCI America (Portland, OR). Potassium hydroxide and tyloxapol (SigmaUltra grade) were purchased from Sigma Chemical Co. (St. Louis, MO). Glacial acetic acid and acetonitrile were purchased from EMScience and EMD Chemicals Inc. (Gibbstown, NJ), respectively. Materials were used as received from the manufacturers. The molecular weights for naproxen and tyloxapol were taken to be 230.26 and 4500 g mol^{-1}, respectively. Deionized water was passed through a four-stage Millipore filter system to provide high-purity water for all of the experiments. Stock solutions of tyloxapol−water and naproxen−water were made by weight to 0.1 mg. To prepare potassium naproxenate, the pH of the naproxen stock solution was increased to pH $\approx$ 7 using KOH. Precise masses of stock solutions were added to flasks and diluted with pure water to reach the final target concentrations of the solutions used for the diffusion experiments. All final solutions used for diffusion and solubility measurements displayed pH values within the range 7.3 $\pm$ 0.3. At these pH values, the neutral form of naproxen has a concentration of 0.1% or lower based on $pK_a = 4.2$.[39]

Density Measurements. Molar concentrations of the solutions were obtained from density. All density measurements were made at 25.00 °C with a computer-interfaced Mettler-Paar DMA40 density meter, thermostatted with water from a large, well-regulated (±1 mK) water bath.

Solubility Measurements. Solid naproxen compound was added in excess to tyloxapol−water solutions in glass vials, and pH was adjusted to pH 7.3 using KOH. The obtained heterogeneous samples were continuously agitated for 10 days in a regulated water bath at 25.0 ± 0.1 °C. Aliquots of the suspensions were then passed through 0.2 μm filters (Millipore) and, if necessary, diluted with the HLPC mobile phase (see below) so that the final drug concentration was around 0.1 mg/mL. The drug concentration of the properly diluted samples was then measured using HPLC (Waters Alliance 2695) equipped with a UV detector (Waters model 2487). A Waters Symmetry C18 column (size: 4.6 150 mm) was employed with a mobile phase consisting of a 39.7/59.5/0.008 (v/v/v) mixture of acetonitrile/water/glacial acetic acid with a flow rate of 1.2 mL/min. Chromatograms were obtained at 254 nm.

Rayleigh Interferometry. Diffusion measurements on naproxen (1)−tyloxapol(2)−water(0) ternary systems and corresponding binary aqueous systems were made with the high-precision Gosting

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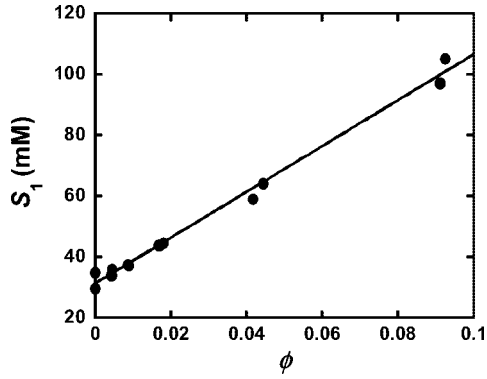

Figure 1. Solubility of naproxen in tyloxapol−water mixtures as a function of tyloxapol volume fraction at 25 °C and pH 7. The solid curve is a linear fit through the data using eq 3.

diffusiometer operated in its Rayleigh interferometric mode.[14,40−43] A comprehensive description of the Gosting diffusiometer can be found in ref 43 and references therein.

Diffusion experiments were accomplished by setting up a sharp horizontal interface (free boundary) between a bottom and a top solution with different composition in a vertical diffusion channel. A necessary condition for eliminating convection is that the fluid density must decrease from bottom to top along the diffusion channel at any point during the experiment.[44] For each ternary solution composition, at least four diffusion experiments were performed at virtually the same average concentration of naproxen, $\bar{C}_1$, and tyloxapol, $\bar{C}_2$. To obtain the four diffusion coefficients, experiments must be performed with different values of the ratio $\Delta C_1/(\Delta C_1 + \Delta C_2)$, where ΔC_i is the difference in concentration of solute i between the bottom and top sides of the initial diffusion boundary. Details on the method and individual diffusion experiments are given as Supporting Information. We note that experiments with $\Delta C_1/(\Delta C_1 + \Delta C_2) \approx 1$ displayed double-diffusive convection due to dynamic gravitational instability,[44−46] which arises at the interface (see Supporting Information). Hence, the experiments used for the determination of ternary diffusion coefficients were performed away from this condition.

Results

Drug Solubility. Figure 1 shows solubility of potassium naproxenate(1), S_1, as a function of volume fraction, ϕ, of tyloxapol(2) at 25 °C and pH 7.3. Surfactant volume fractions were calculated using $\phi = C_2\bar{V}_2$, where $\bar{V}_2 = 3.98$ dm^3 mol^{-1} is the tyloxapol partial molar volume.[9] Drug solubility, S_1, linearly increases with ϕ within the experimental error up to surfactant volume fractions as high as 0.10. This result demonstrates that naproxenate anions bind to tyloxapol micelles. Binding can be quantitatively characterized by employing a two-phase partitioning model.[35,47] Within this model, drug molecules are assumed to partition between the micelle-free aqueous pseudophase (free drug) and the micellar pseudophase (bound drug). This partitioning equilibrium is described by the following ideal-dilute condition:[9,19,28,47]

$$K = \frac{C_D^{(M)}}{C_D^{(W)}} = \frac{C_1 - C_D}{C_D}\frac{1-\phi}{\phi} \quad (2)$$

where K is the partitioning constant, $C_D^{(M)}$ and $C_D^{(W)}$ are the drug molar concentrations in the micellar and water pseudophases, respectively, and C_D is the free drug molar concentration in the total volume. We note that $C_D^{(W)}$ is also the drug solubility, S_1^0, in pure water. Drug solubility, S_1, is the sum of two contributions: $C_D = S_1^0(1 - \phi)$ (free drug) and $C_D^{(M)}\phi = K S_1^0\phi$ (bound drug). We therefore obtain the following linear relation:[9]

$$S_1 = S_1^0[1 + (K - 1)\phi] \quad (3)$$

We note that eq 3 applies to both neutral and ionic drugs and electroneutrality is not assumed to hold for the pseudophases. We fit our solubility data to eq 3 and obtain: $S_1^0 = (31 \pm 1)$ mM and $K = 25 \pm 1$ at 25 °C and pH 7.3. The obtained value of K will be used to compare the experimental diffusion results with the proposed diffusion model.

Ternary Diffusion Coefficients. The interdiffusion coefficients in eqs 1a,b can be described relative to different reference frames.[48] Diffusion measurements yield, to an excellent approximation, diffusion coefficients relative to the volume-fixed frame. Here, the fluxes of the components of a ternary system satisfy $(J_0)_V\bar{V}_0 + (J_1)_V\bar{V}_1 + (J_2)_V\bar{V}_2 = 0$, where the subscripts "1", "2", and "0" denotes the drug, surfactant, and solvent components, respectively, and the subscript "V" appended outside the parentheses identifies the volume-fixed frame. Hence, the measured diffusion coefficients will be denoted as $(D_{ij})_V$ (with $i,j = 1,2$).[48]

The four interdiffusion coefficients for the naproxen−tyloxapol−water ternary system were determined as a function of tyloxapol concentration at 25 °C and pH 7.3. The naproxen concentration was kept constant at $C_1 = 6$ mM. Our results are shown in Figure 2. The value $(D_{11})_V = 0.899 \times 10^{-9}$ m^2 s^{-1} at $C_2 = 0$ in Figure 2a is the diffusion coefficient, $(D_1)_V$, for the drug−water binary system. At infinite dilution, $(D_1)_V = D_\pm$, where $D_\pm$ is the mean-ionic tracer diffusion coefficient. This coefficient is related to the tracer diffusion coefficients of the naproxenate anion, D_D, and the potassium cation, D_K, through the Nernst−Hartley equation: $D_\pm = 2D_DD_K/(D_D + D_K)$.[14] Because our experimental drug concentration is low, the obtained diffusion value can be assumed to be equal to $D_\pm$. Because $D_K = 1.96 \times 10^{-9}$ m^2 s^{-1},[49] we obtain $D_D = 0.58 \times 10^{-9}$ m^2 s^{-1} through the Nernst−Hartley equation. Comparison between D_D and $(D_1)_V$ shows that diffusion of ionic drugs can be significantly faster than that predicted from its tracer diffusion value. In other words, counterion diffusion generates an electrostatic dragging effect on the slower drug ions.

The drug main-diffusion coefficient $(D_{11})_V$ in Figure 2a decreases as the surfactant concentration increases. This behavior, which can be related to the formation of drug−micelle complexes,[9] is qualitatively consistent with our solubility results. The relation between $(D_{11})_V$ and K for the case of ionic drugs will be given in the following section.

In Figure 2b, we show the surfactant main-diffusion coefficient, $(D_{22})_V$. For comparison, we include the corresponding surfactant binary values, $(D_2)_V$ (dashed curve).[9] We can see that $(D_2)_V$ slightly increases with increasing surfactant concentration. This behavior can be attributed to steric repulsive interactions between micelles.[9] The ternary values have been found to be 5−8% higher than the

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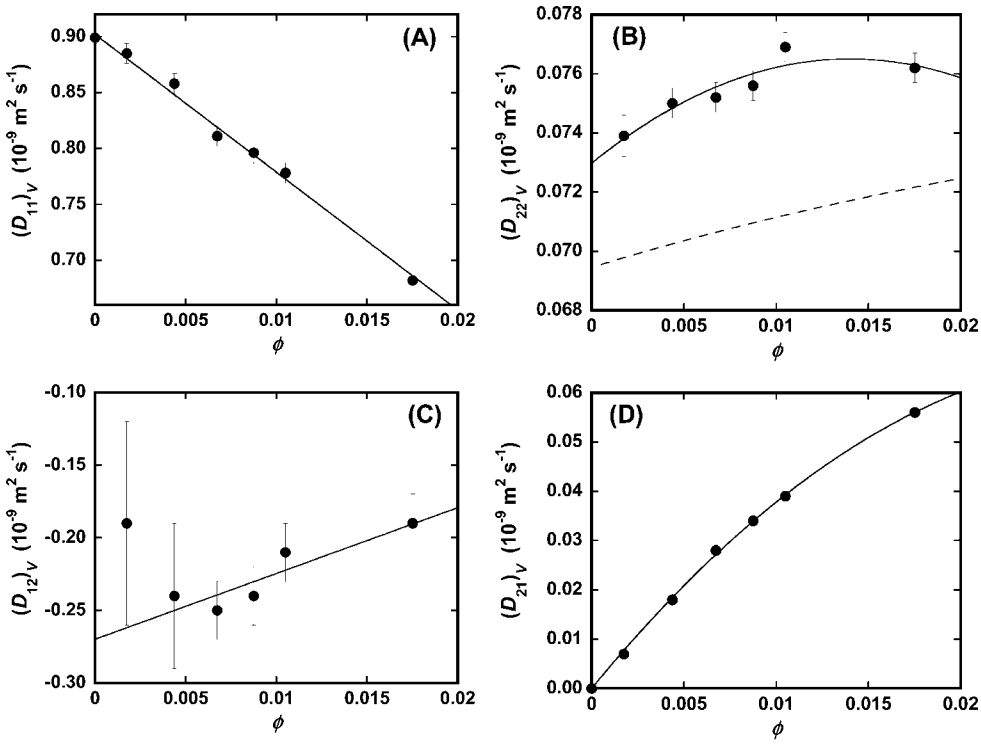

Figure 2. Ternary interdiffusion coefficients for the naproxen(1)−tyloxapol(2)−water system as a function of tyloxapol volume fraction at 25 °C and pH 7.3. (A) Naproxen main-diffusion coefficient $(D_{11})_V$. (B) Tyloxapol main-diffusion coefficient $(D_{22})_V$; the dashed curve represents the corresponding binary interdiffusion coefficients for the tyloxapol−water system calculated using $(D_2)_V = D_M\,(1 + 17.13\,\phi)\,/\,(1 + 14.34\,\phi)$, where $D_M = 0.06945 \times 10^{-9}$ m^2 s^{-1} is the tracer diffusion coefficient of tyloxapol micelles in water. Binary diffusion data are reported in ref 9. (C) Naproxen cross-diffusion coefficient $(D_{12})_V$. (D) Tyloxapol cross-diffusion coefficient $(D_{21})_V$. Solid curves are weighted fits through the data.

corresponding binary ones. This change, which has not been observed in the case of the hydrocortisone−tyloxapol−water system, can be related to a drug-induced charge on the micelles and counterions. We will discuss this electrostatic effect in the following section.

The drug cross-diffusion coefficient $(D_{12})_V$ in Figure 2c is negative. This result has been obtained also in the case of the hydrocortisone−tyloxapol−water system, and it has been generally observed for host−guest systems. A direct comparison between the hydrocortisone and naproxen systems can be performed by considering the ratio $(D_{12})_V/C_1$, because D_{ij} (with $i \neq j$) is directly proportional to C_i.[14] We find that $(D_{12})_V/C_1$ ranges from -3 to -4×10^{-8} m^2 s^{-1} M^{-1} for the naproxen case and from -3 to -7×10^{-8} m^2 s^{-1} M^{-1} for the hydrocortisone case[9] in the same range of tyloxapol concentrations. Thus, the two sets values have similar magnitude. The negative sign of $(D_{12})_V$ can be understood by considering a concentration gradient of micelles in the presence of a uniform concentration of the drug component. In these conditions, the concentration of free drug molecules increases from high to low micelle concentration. The resulting gradient will induce drug diffusion from low to high micelle concentration on a time scale shorter than that required for dissipating the concentration gradient of the slowly diffusing micelles. As in the case of $(D_{11})_V$, we will discuss the relation of $(D_{12})_V$ to the partitioning constant, K, in the following section.

The surfactant cross-diffusion coefficient $(D_{21})_V$ in Figure 2d significantly increases with C_2. The positive value of $(D_{21})_V/C_2$ can be attributed to a drug-induced charge on the micelles and can be understood by considering a concentration gradient of drug component in the presence of a uniform concentration of micelles. In these conditions, both free drug and micelle−drug complexes will be electrostatically dragged by the faster potassium counterions. Hence, a net diffusion of surfactant component occurs from high to low drug concentration. We will discuss this electrostatic effect in the following section.

Diffusion Model

General Diffusion Equations. Multicomponent interdiffusion coefficients, D_{ij}, are combinations of thermodynamic factors and fundamental transport coefficients. Hence, to obtain theoretical expressions for D_{ij}, we need to model both thermodynamic and transport properties of the system. Although diffusion coefficients are obtained in the volume-fixed frame, the relation of diffusion to thermodynamics is simpler in the solvent-fixed frame for which $(J_0)_0 = 0$.[50−52] Here, the subscript "0" appended outside the parentheses identifies the solvent-fixed frame. The corresponding diffusion coefficients will be denoted as $(D_{ij})_0$ (with $i,j = 1,2$). The theoretical $(D_{ij})_V$ values can be calculated from the corresponding $(D_{ij})_0$, provided that the $\bar{V}_i$ are known.

According to nonequilibrium thermodynamics, diffusion for a ternary system can be described using the following linear laws:[14]

$$-(J_1)_0 = (L_{11})_0 \nabla \mu_1 + (L_{12})_0 \nabla \mu_2 \quad (4a)$$

$$-(J_2)_0 = (L_{21})_0 \nabla \mu_1 + (L_{22})_0 \nabla \mu_2 \quad (4b)$$

where μ_i is the chemical potential of the ith component, and $(L_{ij})_0$ are the solvent-frame Onsager transport coefficients. These coefficients satisfy the Onsager reciprocal relation (ORR): $(L_{12})_0$

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$= (L_{21})_0$.[53,54] We can use eqs 1a,b and 4a,b to relate the solvent-fixed diffusion coefficients and Onsager transport coefficients according to

$$(D_{11})_0 = (L_{11})_0\mu_{11} + (L_{12})_0\mu_{21} \quad (5a)$$

$$(D_{12})_0 = (L_{11})_0\mu_{12} + (L_{12})_0\mu_{22} \quad (5b)$$

$$(D_{21})_0 = (L_{21})_0\mu_{11} + (L_{22})_0\mu_{21} \quad (5c)$$

$$(D_{22})_0 = (L_{21})_0\mu_{12} + (L_{22})_0\mu_{22} \quad (5d)$$

where $\mu_{ij} \equiv (\partial\mu_i/\partial C_j)_{T,p,C_k,k\neq j}$, T is the temperature, and p is the pressure.[50−54] We will now derive expressions for the thermodynamic factors, μ_{ij}, and the Onsager coefficients $(L_{ij})_0$.

Thermodynamic Factors. We consider a drug(1)−surfactant (2)−water(0) ternary system at constant temperature. The drug component is ionic, and the surfactant component is neutral. The composition of this system is characterized by the drug and surfactant molar concentrations, C_1 and C_2, respectively. We neglect the concentration of the free surfactant because the tyloxapol cmc is significantly lower than our experimental C_2 values. Micelles are assumed to be monodisperse with aggregation number, m, and molar concentration, C_2/m.

Solubilization of ionic drug molecules into micelles is related to the formation of a wide range of micelle−drug complexes and generally includes counterion binding. We will denote the generic micelle complex by MD_iK_j, where M, D, and K identify micelle, drug, and counterion, respectively. For anionic drugs, micellar complexes display a net charge equal to $j - i$. Concentrations of individual species are related to the component concentrations through the following mass balances:

$$C_1 = C_D + \sum_{i=0}\sum_{j=0} iC_{MD_iK_j} = C_K + \sum_{i=0}\sum_{j=0} jC_{MD_iK_j} \quad (6a)$$

$$C_2/m = \sum_{i=0}\sum_{j=0} C_{MD_iK_j} \quad (6b)$$

where C_D, C_K, and $C_{MD_iK_j}$ are the molar concentrations of free drug, free counterion, and drug−micelle complexes, respectively. These concentrations can be determined if the equilibrium constants for the formation the drug−micelle complexes are known. This complicated chemical-equilibrium problem can be simplified using the two-phase partitioning model[19,47] based on eq 2. To take into account binding of counterions to micelles, we also introduce the following partitioning equilibrium condition:

$$\tau = \frac{C_K^{(M)}/C_K^{(W)}}{C_D^{(M)}/C_D^{(W)}} = \frac{C_1 - C_K}{C_1 - C_D}\frac{C_D}{C_K} \quad (7)$$

where τ is the drug-counterion partitioning constant, and $C_K^{(M)}$ and $C_K^{(W)}$ are the counterion molar concentrations in the micellar and water pseudophases, respectively. The value of $\tau = 0$ corresponds to the case of no counterion binding to micelles. On the other hand, the value of $\tau = 1$ corresponds to the case of counterion and drug binding strengths to micelles being identical. In this latter case, the net micelle charge is zero. It can be easily shown that the product $K\tau$ represents the partitioning constant for the counterions between the aqueous and micellar pseudophases.

We note that counterion binding is likely to occur within the hydrophilic domain of the micelles. Because the volume of the micellar hydrophilic domain is directly proportional to the total micellar volume, the use of $C_K^{(M)}$ to characterize counterion partitioning remains valid. Because K and τ are related to C_D and C_K (see eqs 2 and 7), the values of these binding constants can be used to calculate the average number of drug species, $\langle i\rangle$, and counterions, $\langle j\rangle$, bound to each micelle by:

$$\langle i\rangle = \frac{\sum_{i=0}\sum_{j=0} iC_{MD_iK_j}}{(C_2/m)} = \frac{C_1 - C_D}{(C_2/m)} = \frac{C_1}{(C_2/m)}\frac{K\phi}{1 + (K-1)\phi} \quad (8a)$$

$$\langle j\rangle = \frac{\sum_{i=0}\sum_{j=0} jC_{MD_iK_j}}{(C_2/m)} = \frac{C_1 - C_K}{(C_2/m)} = \frac{C_1}{(C_2/m)}\frac{K\tau\phi}{1 + (K\tau-1)\phi} \quad (8b)$$

To obtain expressions for the four thermodynamic factors in eqs 5a−d, the following chemical-potential expressions are hypothesized:

$$\mu_1 = \mu_1^0 + RT\ln C_D^{(W)} + RT\ln C_K^{(W)} \quad (9a)$$

$$m\mu_2 = m\mu_2^0 + RT\ln C_M + RT\ln y(\phi) \quad (9b)$$

where μ_1^0 and μ_2^0 are the standard chemical potentials, C_M is the molar concentration of the free micelles (MD_iK_j with $i = j = 0$), and R is the ideal-gas constant. Equation 9a is consistent with the two-phase partitioning model. On the other hand, eq 9b is an addition to the two-phase model and characterizes the translational entropy of the micelles, which is the driving force for their diffusion. The micelle activity coefficient, $y(\phi)$, describing the deviation from ideal-dilute solution, is assumed to be not affected by the drug component.

The free micelle concentration in eq 9b cannot be directly determined from the two-phase partitioning model. Its determination requires knowledge of the distribution function, $f(i,j)$, of the MD_iK_j species so that $C_{MD_iK_j} = f(i,j)\,(C_2/m)$. However, if drug−micelle binding is assumed to be independent of $i + j$, we can assume that $f(i,j)$ is given by the bivariate Poisson distribution function $f(i,j) = (e^{-\langle i+j\rangle}/(i+j)!)\langle i+j\rangle^{(i+j)}$.[55] For this special case, C_M can be determined provided that $\langle i\rangle$ and $\langle j\rangle$ are known:

$$C_M = f(0,0)(C_2/m) = e^{-\langle i\rangle}e^{-\langle j\rangle}(C_2/m) \quad (10)$$

The concentrations $C_D^{(W)}$ and $C_K^{(W)}$ in eq 9a can be related to C_1 using eqs 2 and 7, while the concentration C_M in eq 9b can be related to C_2 using eqs 8a,b and 10. We can therefore rewrite the expressions of the solute chemical potentials in the following way:

$$(\mu_1 - \mu_1^0)/RT = 2\ln C_1 - \ln[1 + (K-1)\phi] - \ln[1 + (K\tau-1)\phi] \quad (11a)$$

$$(\mu_2 - \mu_2^0)/RT = \frac{1}{m}\ln\frac{y(\phi)C_2}{m} - \frac{C_1}{C_2}\left[\frac{K\phi}{1-\phi+K\phi} + \frac{K\tau\phi}{1-\phi+K\tau\phi}\right] \quad (11b)$$

Expressions for the thermodynamic factors are then extracted from differentiation of eqs 11a,b:

$$C_1(\mu_{11}/RT) = 2 \quad (12a)$$

$$C_2(\mu_{12}/RT) = -\phi\left(\frac{K-1}{1-\phi+K\phi} + \frac{K\tau-1}{1-\phi+K\tau\phi}\right) \quad (12b)$$

$$C_2(\mu_{21}/RT) = -\phi\left(\frac{K}{1-\phi+K\phi} + \frac{K\tau}{1-\phi+K\tau\phi}\right) \quad (12c)$$

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(54) Miller, D. G. *J. Phys. Chem.* **1959**, *63*, 570–578.
(55) Brownlee, K. A. *Statistical Theory and Methodology in Science and Engineering*, 2nd ed.; John Wiley & Sons: New York, 1965.

$$C_2(\mu_{22}/RT) = \frac{\beta}{m} + \left[\frac{K(K-1)\phi^2}{(1-\phi+K\phi)^2} + \frac{K\tau(K\tau-1)\phi^2}{(1-\phi+K\tau\phi)^2}\right]\frac{C_1}{C_2} \quad (12d)$$

where $\beta \equiv 1 + (\mathrm{d}\ln y/\mathrm{d}\ln C_2)$ is the thermodynamic factor of the binary surfactant−water system, and $\beta = 1$ in the limit of low surfactant concentrations. We observe that the expression of μ_{21} based on the Poisson distribution is equal to $(1-\phi)\,\mu_{12} - \phi\,(C_1/C_2)\,\mu_{11}$. This result could be also derived from the thermodynamic relation between the four μ_{ij} provided that $\bar{V}_1 = 0$.[9,54] This is consistent with the two-phase partitioning model, which assumes that drug molecules do not affect the volume of both pseudophases. This approximation is reasonable at low drug concentration.

Onsager Transport Coefficients. The determination of the solvent-frame Onsager transport coefficients, $(L_{ij})_0$, requires the identification of the actual diffusing species in solution. Typically coupled diffusion between these species is assumed to be negligible, and models are then constructed to obtain expressions for the $(L_{ij})_0$.

Recently, it has been experimentally observed that the solvent-frame cross-term $(L_{12})_0$ is negative for poly(ethylene glycol), a hydrophilic macromolecule, in aqueous salt solutions.[56] This result can be explained by considering the role of solute solvation. Indeed, the actual diffusing solute species are solvated, and their diffusion behavior should be described with respect to the free-solvent reference frame, where $(J_{\hat{0}})_{\hat{0}} = 0$ with the subscript "$\hat{0}$" denoting the free solvent.[57] Because surfactants with polyethylene oxide head groups are significantly hydrated, we will include the effect of micelle solvation in our model.

The actual thermodynamic driving forces for diffusion described in the free-solvent reference frame are the chemical potentials for hydrated solutes, $\hat{\mu}_1$ and $\hat{\mu}_2$.[57] Because of solvent binding, the chemical potential of the hydrated surfactant is $\hat{\mu}_2 = \mu_2 + (\nu/m)\ \mu_0$, where ν is the number of solvent molecules bound to the micelle and μ_0 is the water chemical potential. We shall neglect the contribution of drug and counterion hydration because (1) it is expected to be significantly smaller than that of the micelles and (2) it considerably increases the number of variables because the hydration state of these species will change upon binding to the micelles. We will therefore set $\hat{\mu}_1 = \mu_1$.

Linear laws in the free-solvent reference frame are:[57]

$$-(J_1)_{\hat{0}} = (L_{11})_{\hat{0}}\nabla\hat{\mu}_1 + (L_{12})_{\hat{0}}\nabla\hat{\mu}_2 \quad (13a)$$

$$-(J_2)_{\hat{0}} = (L_{21})_{\hat{0}}\nabla\hat{\mu}_1 + (L_{22})_{\hat{0}}\nabla\hat{\mu}_2 \quad (13b)$$

where $(L_{ij})_{\hat{0}}$ are the corresponding Onsager transport coefficients that satisfy the ORR: $(L_{12})_{\hat{0}} = (L_{21})_{\hat{0}}$. The relation of $(L_{ij})_0$ to $(L_{ij})_{\hat{0}}$ can be obtained by considering the following relations for the fluxes:[57]

$$(J_1)_0 = (J_1)_{\hat{0}} - C_1[(\nu/m)\bar{V}_0/(1-\phi)](J_2)_{\hat{0}} \quad (14a)$$

$$(J_2)_0 = [1 - C_2(\nu/m)\bar{V}_0/(1-\phi)](J_2)_{\hat{0}} \quad (14b)$$

where we have used $(J_i)_0 = (J_i)_{\hat{0}} - (C_i/C_0)(J_0)_{\hat{0}}$, and the following relations for the chemical-potential gradients:

$$\nabla\hat{\mu}_1 = \nabla\mu_1 \quad (15a)$$

$$\nabla\hat{\mu}_2 = [1 - C_2(\nu/m)\bar{V}_0/(1-\phi)]\nabla\mu_2 - C_1[(\nu/m)\bar{V}_0/(1-\phi)]\nabla\mu_1 \quad (15b)$$

where we have applied the Gibbs−Duhem equation to eliminate $\nabla\mu_0$. By inserting eqs 15a,b into eqs 13a,b and then inserting the resulting expressions into eqs 14a,b, we obtain two equations that can be directly compared to eqs 4a,b. This comparison allows us to obtain the following expressions for the $(L_{ij})_0$:

$$(L_{11})_0 = (L_{11})_{\hat{0}} - 2C_1[(\nu/m)\bar{V}_0/(1-\phi)](L_{12})_{\hat{0}} + C_1^2[(\nu/m)\bar{V}_0/(1-\phi)]^2(L_{22})_{\hat{0}} \quad (16a)$$

$$(L_{12})_0 = [1 - C_2[(\nu/m)\bar{V}_0/(1-\phi)]\{(L_{12})_{\hat{0}} - C_1[(\nu/m)\bar{V}_0/(1-\phi)](L_{22})_{\hat{0}}\} \quad (16b)$$

$$(L_{22})_0 = [1 - C_2(\nu/m)\bar{V}_0/(1-\phi)]^2(L_{22})_{\hat{0}} \quad (16c)$$

We will now derive expressions for the $(L_{ij})_{\hat{0}}$ by assuming that (1) the free-solvent fluxes of individual solvated species in solution are uncoupled, (2) the diffusion coefficient of each species is constant and equal to the corresponding tracer diffusion coefficient in water, and (3) the diffusion coefficient of the micelle−drug complexes is equal to that of the free micelles. We can therefore write:[14]

$$-J_D = C_D D_D \nabla\tilde{\mu}_D/RT \quad (17a)$$

$$-J_K = C_K D_K \nabla\tilde{\mu}_K/RT \quad (17b)$$

$$-J_{MD_iK_j} = C_{MD_iK_j} D_M \nabla\tilde{\mu}_{MD_iK_j}/RT \text{ with } i,j = 0, 1, 2, ... \quad (17c)$$

where D_D, D_K, and D_M are the tracer diffusion coefficients of free drug anion, free counterion, and micelle complexes, respectively. In eqs 17a−c, J_D, J_K, and $J_{MD_iK_j}$ are the free-solvent frame fluxes of the individual species (where we have omitted frame notation for simplicity), and $\tilde{\mu}_D$, $\tilde{\mu}_K$, and $\tilde{\mu}_{MD_iK_j}$ are the electrochemical potentials of the solvated species.

To determine the relations between the $(L_{ij})_{\hat{0}}$ and the tracer diffusion coefficients, we need to link the fluxes and the electrochemical-potential gradients of the species to the fluxes and the chemical-potential gradients of the components. Fluxes of individual species are linked to those of the components through the following mass balances based on eqs 6a,b:

$$(J_1)_{\hat{0}} = J_D + \sum_{i=0}\sum_{j=0} iJ_{MD_iK_j} = J_K + \sum_{i=0}\sum_{j=0} jJ_{MD_iK_j} \quad (18a)$$

$$(J_2)_{\hat{0}}/m = \sum_{i=0}\sum_{j=0} J_{MD_iK_j} \quad (18b)$$

Electroneutrality and chemical-equilibrium conditions allow us to write: $\tilde{\mu}_D + \tilde{\mu}_K = \hat{\mu}_1$ and $\tilde{\mu}_{MD_iK_j} = i\,\tilde{\mu}_D + j\,\tilde{\mu}_K + m\,\hat{\mu}_2$. These results can be extended to the corresponding gradients:

$$\nabla\tilde{\mu}_D + \nabla\tilde{\mu}_K = \nabla\hat{\mu}_1 \quad (19a)$$

$$\nabla\tilde{\mu}_{MD_iK_j} = i\nabla\tilde{\mu}_D + j\nabla\tilde{\mu}_K + m\nabla\hat{\mu}_2 \text{ with } i,j = 0, 1, 2, ... \quad (19b)$$

If we insert eqs 17a−c and eq 19b into eq 18a, we obtain an equation that relates $\nabla\tilde{\mu}_D$ and $\nabla\tilde{\mu}_K$ to $\nabla\hat{\mu}_2$. This equation together with eq 19a allows us to obtain the following expressions for $\nabla\tilde{\mu}_D$ and $\nabla\tilde{\mu}_K$:

$$\nabla\tilde{\mu}_D = \frac{[C_K D_K + (C_2/m)D_M(\langle j^2\rangle - \langle ij\rangle)]\nabla\hat{\mu}_1 - C_2 D_M(\langle i\rangle - \langle j\rangle)\nabla\hat{\mu}_2}{[C_D D_D + C_K D_K + (C_2/m)D_M(\langle i^2\rangle + \langle j^2\rangle - 2\langle ij\rangle)]} \quad (20a)$$

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(57) Annunziata, O. *J. Phys. Chem. B* **2008**, *112*, 11968–11975.

$$\nabla\tilde{\mu}_K = \frac{[C_D D_D + (C_2/m)D_M(\langle i^2\rangle - \langle ij\rangle)]\nabla\hat{\mu}_1 - C_2 D_M(\langle j\rangle - \langle i\rangle)\nabla\hat{\mu}_2}{[C_D D_D + C_K D_K + (C_2/m)D_M(\langle i^2\rangle + \langle j^2\rangle - 2\langle ij\rangle)]} \quad (20b)$$

where we have used the definition $\langle x\rangle \equiv \sum_{i=0}\sum_{j=0} x\ f(i,j)$. The corresponding expression for $\nabla\tilde{\mu}_{MD,K_j}$ can be obtained by inserting eqs 20a,b into eq 19b. We are now in position to obtain expressions for the $(J_i)_{\hat{0}}$ (with $i = 1,2$) as a function of the $\nabla\hat{\mu}_i$. Comparison with eqs 13a,b yield the following expressions for the $(L_{ij})_{\hat{0}}$:

$$(L_{11})_{\hat{0}} = \frac{C_D D_D C_K D_K + (C_2/m)D_M[C_D D_D\langle j^2\rangle + C_K D_K\langle i^2\rangle + (C_2/m)D_M(\langle i^2\rangle\langle j^2\rangle - \langle ij\rangle^2)]}{RT[C_D D_D + C_K D_K + (C_2/m)D_M(\langle i^2\rangle + \langle j^2\rangle - 2\langle ij\rangle)]} \quad (21a)$$

$$(L_{12})_{\hat{0}} = C_2 D_M \frac{C_D D_D\langle j\rangle + C_K D_K\langle i\rangle + (C_2/m)D_M[\langle i\rangle(\langle j^2\rangle - \langle ij\rangle) + \langle j\rangle(\langle i^2\rangle - \langle ij\rangle)]}{RT[C_D D_D + C_K D_K + (C_2/m)D_M(\langle i^2\rangle + \langle j^2\rangle - 2\langle ij\rangle)]} \quad (21b)$$

$$(L_{22})_{\hat{0}} = mC_2 D_M \frac{C_D D_D + C_K D_K + (C_2/m)D_M[\langle i^2\rangle - \langle i\rangle^2 + \langle j^2\rangle - \langle j\rangle^2 - 2(\langle ij\rangle - \langle i\rangle\langle j\rangle)]}{RT[C_D D_D + C_K D_K + (C_2/m)D_M(\langle i^2\rangle + \langle j^2\rangle - 2\langle ij\rangle)]} \quad (21c)$$

The values of $\langle i\rangle$ and $\langle j\rangle$ can be determined from eqs 8a,b provided that K and τ are known. However, the determination of $\langle i^2\rangle$, $\langle j^2\rangle$, and $\langle ij\rangle$ requires a further assumption on $f(i,j)$. Although the values of $\langle i\rangle$ and $\langle j\rangle$ are related to each other, we can assume that $j - \langle j\rangle$ for the counterion does not correlate with $i - \langle i\rangle$ for the drug. Within this assumption, $f(i,j)$ becomes the product of two independent Poisson distribution functions:[55]

$$f(i,j) = \frac{e^{-\langle i+j\rangle}}{(i+j)!}\langle i+j\rangle^{(i+j)} = \left(\frac{e^{-\langle i\rangle}}{i!}\langle i\rangle^i\right)\left(\frac{e^{-\langle j\rangle}}{j!}\langle j\rangle^j\right) \quad (22)$$

Using the mathematical properties of independent Poisson distribution functions, we can determine $\langle i^2\rangle$, $\langle j^2\rangle$, and $\langle ij\rangle$ from $\langle i\rangle$ and $\langle j\rangle$ according to:

$$\langle i^2\rangle = \langle i\rangle + \langle i\rangle^2 \quad (23a)$$

$$\langle j^2\rangle = \langle j\rangle + \langle j\rangle^2 \quad (23b)$$

$$\langle ij\rangle = \langle i\rangle\langle j\rangle \quad (23c)$$

Diffusion Coefficients. The values of $(L_{ij})_0$ and μ_{ij}/RT can be determined provided that K, τ, m, ν, D_D, D_K, and D_M are known. We can then calculate $(D_{ij})_0$ using eqs 5a−d. Finally, the $(D_{ij})_0$ can be converted into $(D_{ij})_V$ using previously reported equations based on the two-phase model:[9]

$$(D_{11})_V = (D_{11})_0 \quad (24a)$$

$$(D_{12})_V = (D_{12})_0 - C_1(\phi/C_2)(D_{22})_0 \quad (24b)$$

$$(D_{21})_V = (1-\phi)(D_{21})_0 \quad (24c)$$

$$(D_{22})_V = (1-\phi)(D_{22})_0 \quad (24d)$$

The explicit expressions for the $(D_{ij})_V$ are cumbersome. Thus, to gain physical insight on the behavior of the diffusion coefficients, we shall consider simplified expressions obtained by considering limit conditions. We further notice that this model describes diffusion of nonionic drugs[9] in the limit of $\tau = 1$ and $D_K = D_D$.

To examine $(D_{11})_V$, we consider the limit of infinite dilution with respect to C_1, where $(D_{11})_V = (D_{11})_0$. We obtain:

$$(D_{11})_V = \frac{2(1-\phi)^2 D_D D_K + 2K\phi[(1-\phi)(\tau D_D + D_K) + K\tau\phi D_M]D_M}{(1-\phi)\{[1+(K\tau-1)\phi]D_D + [1+(K-1)\phi]D_K\} + K\phi[(1+\tau)(1-\phi) + 2K\tau\phi]D_M} \quad (25)$$

In the case of nonionic drugs, eq 25 reduces to $(D_{11})_V = \tilde{D}_D$, where $\tilde{D}_D = [(1-\phi)D_D + K\phi D_M]/(1-\phi+K\phi)$ is the self-diffusion coefficient of the nonionic drug in the presence of micelles. We note that $\tilde{D}_D$ is a weighed average between D_D and D_M. We can also consider eq 25 in the limiting case of $\tau = 0$ (no counterions binding). In this case, we obtain the Nernst−Hartley equation: $(D_{11})_V = 2\tilde{D}_D D_K/(\tilde{D}_D + D_K)$. Here, $1/(D_{11})_V$ is the average between $1/\tilde{D}_D$ and $1/D_K$. Because $D_K > \tilde{D}_D$ for small counterions, we conclude that $(D_{11})_V > \tilde{D}_D$. In other words, counterions exert an electrostatic dragging effect on the slower drug ions to preserve electroneutrality. Finally, we note that m and ν have no effect on $(D_{11})_V$ in this limit.

To examine the other three interdiffusion coefficients, we shall consider the limit of infinite dilution with respect to both C_1 and C_2. In the case of $(D_{12})_V$, we obtain:

$$\frac{(D_{12})_V}{C_1\bar{V}_2} = -D_{\pm}[K(1+\tau) - 2] + D_M\left[\frac{\tau D_D + D_K}{D_D + D_K}K - \frac{\nu\bar{V}_0}{m\bar{V}_2} - 1\right] \quad (26)$$

In eq 26, the second term contributes marginally to the value of $(D_{12})_V/C_1$, because D_M is small as compared to $D_{\pm} = 2D_D D_K/(D_D + D_K)$. Indeed, we can approximately write: $(D_{12})_V/C_1 \approx -D_{\pm}\bar{V}_2 K(1+\tau)$, where we have also assumed that $K \gg 2$. We conclude that also this coefficient is not very sensitive to the values of m and ν. This cross-term is predicted to be negative and directly proportional to K for both ionic and nonionic drugs. In other words, due to drug−micelle binding, a concentration gradient of micelle induces a flux of drug component from low to high micelle concentration. Our experimental results on both potassium naproxenate and hydrocortisone are in agreement with the predicted behavior.

The limiting expression of $(D_{21})_V$ is

$$\frac{(D_{21})_V}{C_2\bar{V}_2} = mD_M\left[K\left(2\frac{\tau D_D + D_K}{D_D + D_K} - 1 - \tau\right) - 2\frac{\nu\bar{V}_0}{m\bar{V}_2}\right] \quad (27)$$

In eq 27, $(D_{21})_V/\phi$ is directly proportional to m and D_M. This coefficient is also proportional to a difference between two terms. The first term, which is associated with drug-induced micelle charge, is equal to $K(D_K - D_D)/(D_D + D_K)$ when $\tau = 0$ and becomes zero when $\tau = 1$ corresponding to neutral micelles. The second term is associated with micelle solvation. The relative contributions of these two terms depend on the values of τ and ν/m. If $\tau = 0$ and $\nu = 0$, eq 27 reduces to $(D_{21})_V/\phi = K(D_K - D_D)/(D_D + D_K)$. We therefore conclude that the sign of $(D_{21})_V$ strongly depends on the sign of $D_K - D_D$. This prediction is in qualitative agreement with our experimental results and explanation given in the previous section.

Finally, we examine $(D_{22})_V$. The effect of ionic drugs can be described by considering the limiting expression: $(D_{22})_V = (D_2)_V(1 + \alpha C_1\bar{V}_2\phi + \ldots)$, where

$$\alpha = m\left[K^2(1-\tau)\times \frac{(1-K^{-1})D_D - (1-K^{-1}\tau^{-1})\tau D_K - (1-\tau)D_M}{D_D + D_K} + \frac{\nu\bar{V}_0}{m\bar{V}_2}(K + K\tau - 2)\right] \quad (28)$$

In eq 28, α is directly proportional to m and a sum of two terms. The first term is associated with drug-induced micelle charge and vanishes when $\tau = 1$. The second term in eq 28 is associated with micelle solvation. Interestingly, micelle solvation has opposite effects on $(D_{22})_V$ and $(D_{21})_V$. If $K\tau \gg 1$ and $D_M \ll D_D$, the first term becomes $K^2(1-\tau)(D_D - \tau D_K)/(D_D + D_K)$. This indicates that the effect of ionic drugs on the surfactant main diffusion coefficient depends on the sign of $D_D - \tau D_K$, provided that $D_D < D_K$. Small values of τ imply that micelle diffusion is enhanced by drug binding. However, as τ increases, D_D becomes smaller than τD_K. This implies that micelle diffusion is hindered in these conditions. This behavior can be physically understood by considering that a micelle concentration gradient at constant C_1 generates a concentration gradient of free drug anions and counterions. These gradients generate a net flux of drug component toward the micelles as discussed above. Drug cross-diffusion can be driven either by drug ions or by counterions, depending on the mobility ratio D_D/D_K and the corresponding ratio in concentration gradient $(\partial C_D/\partial C_K)_{C_1}$. We obtain $(\partial C_D/\partial C_K)_{C_1} = 1/\tau$ from differentiation of eqs 8a,b in the limit of small ϕ. If $\tau = 0$, the concentration of counterions is uniform and drug diffusion toward the micelles is driven by the concentration gradient of drug anions. This diffusion process drives a net negative charge toward the micelles. The corresponding electric field drives the negatively charged micelles in the direction opposite of that of drug diffusion and equal to that of micelle diffusion. The net result is an enhancement of micelle diffusion. However, as τ increases, concentration gradients of both drug anions and counterions are present. Because $D_K > D_D$, drug diffusion toward the micelles becomes driven by the concentration gradient of counterions if τ is large enough. This diffusion process drives a net positive charge toward the micelles. The corresponding electric field drives the negatively charged micelles in the same direction as that of drug diffusion. Hence, the net result corresponds to a reduction of micelle diffusion.

Discussion

In this section, we quantitatively compare our results with the proposed diffusion model. We set $D_K = 1.96 \times 10^{-9}$ m^2 s^{-1},[43] $D_D = 0.58 \times 10^{-9}$ m^2 s^{-1} from our drug−water diffusion data, and $D_M = 0.0694 \times 10^{-9}$ m^2 s^{-1} from our tyloxapol−water diffusion data previously reported.[9] We then set $K = 25$ according to our solubility results. The tyloxapol micelle aggregation number is set to $m = 12$. This value was estimated from the micelle hydrodynamic volume and micelle hydration.[9] It corresponds to ~90 octyl-phenol-ethoxylate monomers inside one micelle and is comparable with the aggregation number of ~100 for the octyl-phenol-ethoxylate surfactant.[58] According to our diffusion model, m is expected to have a significant effect only on the behavior of $(D_{21})_V$ and $(D_{22})_V$. The number of water molecules bound to a micelle can be estimated from the chemical properties of the hydrophilic ethoxy groups of the surfactant. Because it is known that there are about four water molecules associated with an ethoxy group,[59] and each tyloxapol consists of ~70 ethoxy groups, we obtain $\nu/m \approx 280$ and $\nu \approx 3400$. Estimation of τ is difficult. This quantity is expected to depend on the chemical nature of the surfactant hydrophilic groups and charge distribution on the micelle. Thus, we examine our model by varying the value of τ from zero to one.

The surfactant nonideality term, $\beta(\phi)$ in eq 12d, is expected to be close to unity at our experimental low values of ϕ. Nonetheless, we have estimated it from the experimental binary values of $(D_2)_V$[9] using

$$\beta = \frac{(D_2)_V/D_M}{(1-\phi)[1 - C_2(\nu/m)\bar{V}_0/(1-\phi)]^2} \quad (29)$$

Equation 29 was obtained by assuming that $(L_{22})_{\hat{0}} = C_2 D_M$ for the binary tyloxapol−water system, consistent with our diffusion model. We have also used $(D_2)_V = (1-\phi)[(L_{22})_0/C_2]\beta$ (see eqs 4d and 24d) and converted $(L_{22})_{\hat{0}}$ into $(L_{22})_0$ using eq 16c. We note that β can be calculated provided that ν/m is known.

To evaluate whether micelle solvation can be invoked to explain our experimental diffusion results, we initially compute $(D_{ij})_V$ by setting $\nu = 0$ and changing τ. Our experimental results and theoretical predictions are shown in Figure 3.

In Figure 3, we note that our experimental $(D_{ij})_V$ values with $\phi < 0.005$ display some discrepancy from those at a higher ϕ. This small deviation encountered at low surfactant concentrations can be attributed to a relatively large drug load of micelles, which may have a small effect on the micellization process itself. Furthermore, we also note that the precision of diffusion measurements reduces as the solute concentration decreases.[9] Thus, we give more relevance to our results with $\phi > 0.005$.

For $(D_{11})_V$ and $(D_{12})_V$, our model is in good quantitative agreement with the experimental results if we set $\tau = 0.4 \pm 0.2$. Numerical analysis shows that the behavior of these two diffusion coefficients significantly depends on K. This implies that our K value extracted from solubility measurements characterizes the behavior of $(D_{11})_V$ and $(D_{12})_V$ quite well. Similar conclusions were drawn for the hydrocortisone case.[9]

For $(D_{21})_V$, our model is in good quantitative agreement with the experimental results if $\tau = 0.5 \pm 0.1$. However, a good quantitative agreement for $(D_{22})_V$ can be obtained only if $\tau < 0.2$. Although $\tau < 0.2$ may still give acceptable predictions for $(D_{11})_V$ and $(D_{12})_V$, it predicts $(D_{21})_V$ values 100% larger than the experimental data (see Figure 3d). Furthermore, our calculation shows that $(D_{22})_V$ is lower than $(D_2)_V$ if $\tau > 0.2$. On the other hand, we experimentally obtain the opposite behavior. We have examined whether this discrepancy can be related to inaccurate estimations of m. However, eqs 25−28 indicate that (1) m has a small effect on $(D_{11})_V$ and $(D_{12})_V$; (2) $(D_{21})_V$ is directly proportional to m; and (3) a change in m has no effect on the sign of α. Numerical examination on the $(D_{ij})_V$ general expressions confirms our conclusions. Thus, a change in m does not account for the observed discrepancy between $(D_{21})_V$ and $(D_{22})_V$.

We now examine the role of micelle solvation. Equations 27 and 28 show that micelle solvation has an opposite effect on the behavior of $(D_{21})_V$ and $(D_{22})_V$. As ν increases, $(D_{22})_V/(D_2)_V$ increases, while $(D_{21})_V/\phi$ decreases. Thus, ν can be used to improve the agreement between the model and the experimental results. By varying both τ and ν, we find that the best agreement is obtained for all four diffusion coefficients when $\tau = 0.27$ and $\nu = 5000$. The results are shown in Figure 4. Our results with $\tau = 0.27$ and $\nu = 3400$ estimated from the hydration of ethoxy groups are also included in the same figure. We can see that the

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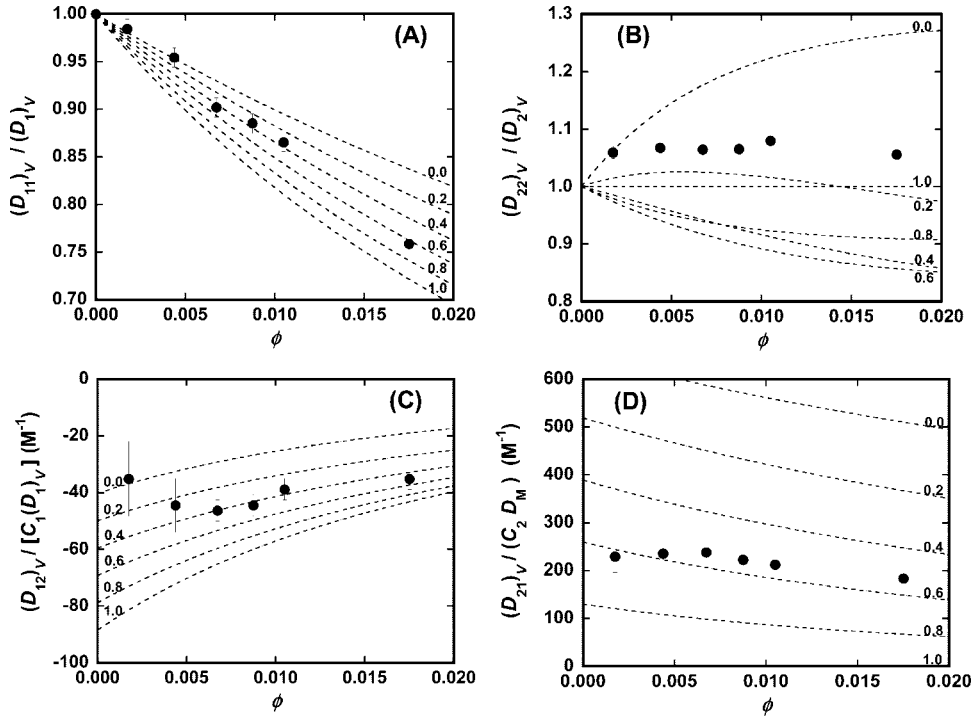

Figure 3. Ternary diffusion ratios for the naproxen(1)−tyloxapol(2)−water system ($(D_{11})_V/(D_1)_V$, A; $(D_{22})_V/(D_2)_V$, B; $(D_{12})_V/[C_1(D_1)_V]$, C; $(D_{21})_V/[C_2D_M]$, D). The dashed curves represent the model predictions for $K = 25$ and $\nu = 0$. The numbers associated with each curve identify the corresponding values of τ.

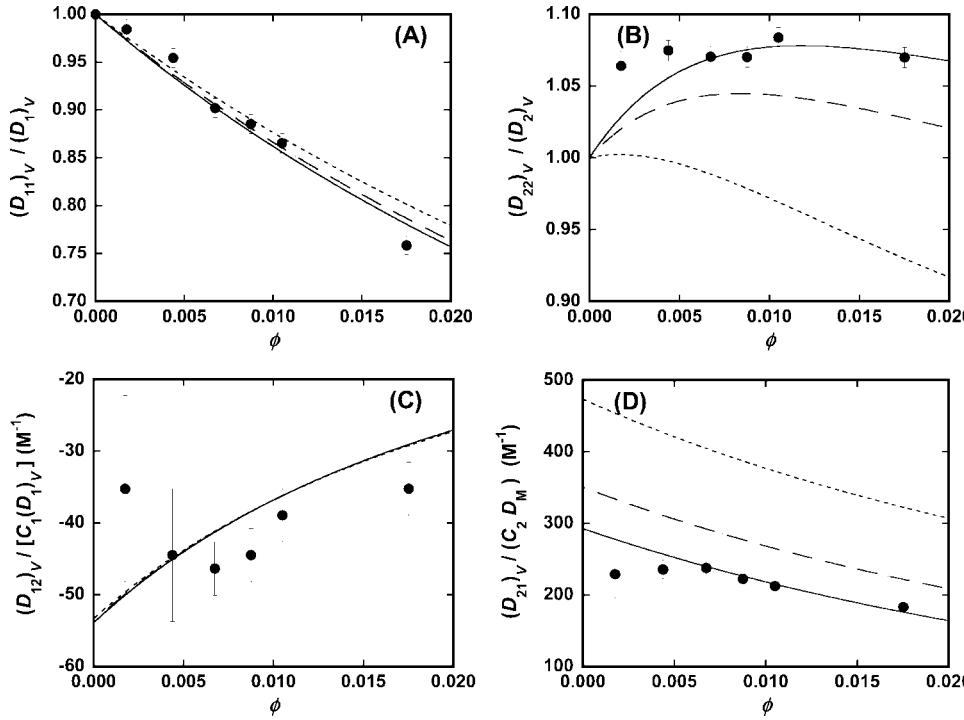

Figure 4. Ternary diffusion ratios for the naproxen(1)−tyloxapol(2)−water system ($(D_{11})_V/(D_1)_V$, A; $(D_{22})_V/(D_2)_V$, B; $(D_{12})_V/[C_1(D_1)_V]$, C; $(D_{21})_V/[C_2D_M]$, D). The curves represent the model predictions for $K = 25$ and $\tau = 0.27$. The solid curves, long dashed curves, and short dashed curves were obtained setting $\nu = 5000$, $\nu = 3400$, and $\nu = 0$, respectively.

experimental behavior of both $(D_{21})_V$ and $(D_{22})_V$ is reproduced fairly well also for $\nu = 3400$. It is expected that neglecting electrostatic nonideality effects in the model may account for the observed discrepancy.

We note that our proposed diffusion model assumes that drug binding has no effect on D_M. However, drug binding may affect D_M by changing the size of micelles. To examine the accuracy of our assumption, we calculate the average number of bound drug, $\langle i \rangle$, within the experimental range of micelle volume fraction using eq 8a. As ϕ increases from 0.0018 to 0.018, $\langle i \rangle$ decreases from 6.9 to 5.0. Using $m = 12$ and component molar masses, we estimate that the drug contribution to the micelle mass (ignoring the contribution of solvation) is 2−3%. For globular particles such as micelles, the estimated increase in mass is

expected to reduce the corresponding value of D_M by less than 1%. We therefore conclude that the assumption of D_M constant is accurate within 1% error.

Finally, we discuss the obtained value of τ. Using eqs 8a,b, we can use $\tau = 0.27$ to calculate the degree of counterion binding, $\langle j \rangle / \langle i \rangle$. Within the experimental range of micelle volume fraction, $\langle j \rangle / \langle i \rangle$ varies from 0.28 to 0.35. For ionic surfactants, it has been experimentally and theoretically found that the degree of counterion binding for the corresponding micelles is significantly higher and ranges from 0.5 to 0.8.[20,60] However, in the case of ionic−nonionic mixed micelles, it has been shown that $\langle j \rangle / \langle i \rangle$ steadily decreases approaching zero as the contribution of neutral surfactant to the micelle increases.[61−63] Our drug-loaded tyloxapol system is better described as a mixed micelle. Furthermore, because there are about 90 neutral head groups in a tyloxapol micelle, the ratio of naproxenate anions to tyloxapol head groups is quite small within our experimental range. Thus, the obtained small value of τ is qualitatively consistent with previous experimental and theoretical studies on mixed micelles.

Conclusions

To quantitatively understand the experimental data of the four interdiffusion coefficients, we have built a diffusion model based on drug−micelle binding, counterion effects, and micelle solvation for a drug−micelle−water ternary system. We remark that diffusion-based transport of ionic drugs is relatively fast due to the presence of counterions. Because $(D_{11})_V$ decreases as the surfactant concentration increases, micellar systems can be used to bind drug molecules, thereby reducing their diffusion in a controllable fashion. Moreover, because $(D_{12})_V$ is negative, a concentration gradient of micelles may be used as a tool to further reduce drug diffusion rate from high to low micelle concentration. This work provides guidance for the development of models for controlled drug release in the presence of nanocarriers based on multicomponent diffusion coefficients.

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Supporting Information Available: Interferometric diffusion data; convective flow induced by drug diffusion. This material is available free of charge via the Internet at http://pubs.acs.org.

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