Amphiphilic Association of Ibuprofen and Two Nonionic Cellulose Derivatives in Aqueous Solution

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Abstract □ The aqueous interaction of the sodium salt of ibuprofen with the cellulose ethers ethyl hydroxyethyl cellulose, EHEC, and hydroxypropyl methyl cellulose, HPMC, has been investigated in the concentration range 0–500 mM ibuprofen and 0.1–1% (w/w) polymer, by cloud point, capillary viscometry, equilibrium dialysis, and fluorescence probe techniques. Ibuprofen forms micelles in pure water, with the critical micelle concentration, cmc, at 180 mM. A combination of time-resolved and static fluorescence quenching shows that micelle-like ibuprofen aggregates are formed in the solution. The average aggregation number of pure ibuprofen micelles in water is about 40. In the presence of EHEC or HPMC the aggregation numbers decrease. The interaction of ibuprofen with cellulose ethers is similar to the normally accepted model for polymer–surfactant interaction, although more complex. Ibuprofen adsorbs to the polymer in the form of mixed polymer–drug micelles, noncooperatively up to cmc and cooperatively when cmc is passed. The interaction starts below 50 mM ibuprofen as monitored by the fluorescent probes pyrene and 1,3-di(1-pyrenyl)-propane, P3P, with a maximum in microviscosity below cmc, corresponding to polymer-dense mixed micelles. The study illustrates the importance of a precise apprehension of the aggregation behavior as a background for transport studies in drug–polymer systems.

Introduction

Amphiphilic molecules are characterized by the presence of both polar and nonpolar regions of the same molecule. This dual nature is responsible for the surface activity of these substances leading to accumulation at hydrophobic interfaces and formation of aggregates. Many types of drug molecules, such as antihistamines, antidepressants, tranquilizers, local anesthetics, and nonsteroidal antiinflammatory drugs (NSAIDs) are known to be amphiphilic in character and to form ordinary micelles or micelle-like associations[1] above a critical concentration value. Although the self-association of surface active drugs usually occurs at concentrations well above average therapeutic levels, the local concentration can reach, under certain circumstances, high values, for instance when the drug is instantaneously released from a tablet or accumulated at a membrane.

Cellulose derivatives play an important role in many technical applications and especially in the pharmaceutical field[2,3] where they have several uses such as to regulate the rheology of a system and to control the release of the drug. These polymers have an amphiphilic structure with mixed hydrophilic/hydrophobic segments, thus leading to an apparent surface activity the magnitude of which depends on type and degree of substitution.[4]

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The interaction between polymers and surfactants in aqueous solution has attracted great interest during the last 20−30 years, and the topic has recently been reviewed.[5] As a prerequisite for a better understanding of polymer−drug interaction there has in this laboratory been a specific focus on the interaction of nonionic cellulose derivatives and the common anionic surfactant sodium dodecyl sulfate, SDS, in dilute aqueous solutions.[6−8] It has been shown that the surfactant forms interaction complexes with the polymer in a cooperative manner, giving rise to formation of a three-dimensional polymer network where mixed micelles of surfactant and polymer act as connecting tie points.

Since a surface active drug can form micelles by itself or bind hydrophobically to membranes, proteins, or other biological macromolecules as well as associate with hydrophobic excipients present in pharmaceutical formulations, all these types of associations may affect the release of the drug and alter the therapeutic effect.

The present paper deals with the general problem of the aqueous association of surface active drugs and polymers. The sodium salt of ibuprofen is an NSAID which is surface active[9] and was chosen as model substance, due to its, contrary to normal surfactants, high critical micelle concentration (180 mM) and hence a wider molar concentration interval of interest for the buildup of the interaction. Previous studies of NSAIDs have reported on dissolution properties,[10−12] solubility behavior,[13] release,[14] and other thermodynamic properties[12,15] of the drugs. In this work we have studied the association behavior in aqueous solutions between ibuprofen and two nonionic cellulose derivatives ethyl hydroxyethyl cellulose, EHEC, and hydroxypropyl methyl cellulose, HPMC. These two cellulose ethers are well-characterized materials[16] and represent polymers of different hydrophobicity. Both macroscopic and microscopic system properties are presented. The results will furthermore be discussed and compared in close relation to previous knowledge about the features of the corresponding polymer/SDS complexes.

Materials

The ethyl hydroxyethyl cellulose (EHEC) fraction CST-103, $DS_{ethyl} = 1.5$, $MS_{ethylene\ oxide} = 0.7$, was obtained from Akzo Nobel AB, Stenungssund, Sweden. The hydroxypropyl methyl cellulose (HPMC) fraction Methocel E4MCR was obtained from Pharmacia and Upjohn, Stockholm, Sweden. The sodium salt of ibuprofen (α-methyl-4-[isobutyl]phenylacetic acid), 9-methylanthracene, 98% (9-MA), and tris(2,2′-bipyridyl)ruthenium(II) chloride ($Ru(bipy)_3^{2+}$) were bought from Sigma-Aldrich Chemie, Steinheim, Germany, and used as supplied. Pyrene (+98%), Janssen Chimica, Geel, Belgium, was recrystallized twice from absolute ethanol prior to use. 1,3-Bis-(1-pyrenyl)propane (P3P) was bought from Molecular Probes, Eugene, OR, and used as supplied. Analytical grade NaCl was obtained from Merck, Darmstadt, Germany. The standard

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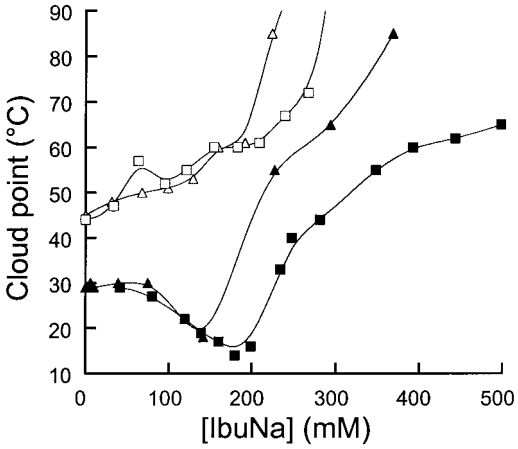

Figure 1—Cloud point, CP, as a function of the concentration of ibuprofen, [IbuNa], for different polymer concentrations; ▲ 0.1% and ■ 0.5%. Filled symbols are EHEC and open symbols are HPMC.

procedure for producing an EHEC or HPMC stock solution is presented elsewhere.[6] After preparation, the stock solutions were rinsed from low molecular weight material and salts using a Spectra/Por tube dialysis membrane, Spectrum Medical Ind., Houston, TX, with molecular weight cut off at 12 000−14 000. Dialysis was performed against Milli Q water (Millipore) during 1 week, and then the stock solutions were centrifugated at 20 000 rpm. The polymer concentrations of these stock solutions were determined gravimetrically by drying samples to constant weight at 105 °C. All polymer/ibuprofen solutions were prepared using Milli Q water as solvent. The pH of all solutions containing ibuprofen was close to 7.0. The pK_a of the corresponding acid of ibuprofen is about 4.6. It is thus taken that the sodium salt of ibuprofen is quantitatively ionized. To achieve appropriate concentrations of the very hydrophobic substances P3P and 9-MA, these substances were dissolved in absolute acetone of which aliquots were dissolved in the solutions to be measured by fluorescence.

Experimental Section

Cloud Point—The cloud point of polymer/ibuprofen solutions was determined visually in glass tubes and taken as the temperature when the last visible sign of clouding in the solution disappeared upon cooling.

Capillary Viscometry—The viscosity measurements were performed in ordinary Ostwald viscometers with a water flow time of approximately 100 s at 20 °C. The samples were thermostated in a Lauda CD 20 water bath for 15 min prior to measurements. Corrections for capillary and end effects were considered unnecessary.

Equilibrium Dialysis—The equilibrium dialysis experiments were performed in order to determine the adsorption isotherm of ibuprofen onto the cellulose ethers. The dialysis cell used consists of two compartments of 2 mL volume each, separated by a dialysis membrane (Spectra/Por with a M_w-cutoff of 12 000−14 000) according to the principle developed by Fischman and Eirich.[17] The polymer solution was placed on one side of the dialysis membrane, and a water solution on the other side, both sides with equal ibuprofen concentrations at the start. The cells were maintained at 20 °C for one week, and the ibuprofen concentrations on both sides of the membrane were determined spectrofotometrically at 273 nm ($\epsilon = 256.5\ M^{-1}\ cm^{-1}$). Kinetic studies showed that 6 days were needed to reach equilibrium. Since the ternary system EHEC (CST-103)/ibuprofen/water shows phase separation at 20 °C in the ibuprofen concentration range ≈120−200 mM, cf., Figure 1, dialysis experiments on this system were also performed at 10 °C in order to confirm the adsorption isotherm to be correct. The equilibrium ibuprofen concentration not bound to the polymer ($[ibu]_{eq}$), the amount of ibuprofen bound to the polymer (y, in mmol/g polymer), and the total ibuprofen concentration ($[ibu]_{tot}$) can then be calculated. Since the system studied is salt-free, a correction for the Donnan effect has been made as described previously.[6] The mass balance equation then becomes

$$[ibu]_{tot} = [ibu]_{eq} + c_p y \quad (1)$$

where c_p is the polymer concentration in grams per liter. This methodology has been utilized in several recent investigations of interactions in aqueous mixtures of the surfactant sodium dodecyl sulfate and nonionic cellulose ethers.[6,7,18−22]

Steady-State Fluorescence Measurements—All steady-state fluorescence measurements were performed at room temperature on a SPEX Fluorolog 2 model FL1T2 spectrometer operated in the "s" mode with 1.88 nm excitation and 0.85 nm emission bandwiths. All fluorescence measurements including time-resolved were run in duplicates, and the error was ±5% or less. The fluorescent probe concentrations were about 10^{-6} M. The concentration of the quencher 9-MA was ≤ 10^{-4} M.

Emission spectra were recorded for pyrene excitation at $\lambda = 334$ nm. The first (I_1, $\lambda = 374$ nm) to third (I_3, $\lambda = 388$ nm) emission intensity peak height ratio (I_1/I_3, the micropolarity index) of the vibrational emission spectrum of pyrene is a qualitative measure of the micropolarity at the probe solubilization site.[23] The micropolarity index is at most 2.0 in pure water and 1.0 in hydrophobic solvents such as toluene. It has been shown[23] that I_1/I_3 suddenly drops when the critical micelle concentration (cmc) is passed since pyrene quantitatively distributes to the more hydrophobic micellar phase if present. Micropolarity measurements with pyrene have been utilized in several papers from this laboratory on ternary surfactant/cellulose ether/water systems.[7,8,22,24]

P3P consists of two pyrene molecules connected by a propane chain, making this fluorescent probe capable of forming intramolecular excimers. Emission spectra were recorded between $\lambda = 350$ nm and $\lambda = 500$ nm for P3P excitation at $\lambda = 348$ nm. The extent of intramolecular excimer formation of P3P is dependent on the local friction of the probe imposed by its surroundings.[25] Hence, the monomer (I_M, $\lambda = 377$ nm) to excimer (I_E, $\lambda = 485$ nm) emission intensity peak ratio, I_M/I_E, is a qualitative index of the microviscosity at the probe solubilization site. P3P have been used in this laboratory to measure the microviscosity in polymer−surfactant systems,[8,24,26] and the method has been validated by NMR relaxation measurements.[27]

Time-Resolved Fluorescence Measurements—Time-resolved fluorescence measurements were recorded on a Photon Technology International model C-72 apparatus, equipped with a pulsed GL 3300 nitrogen laser/GL 320 dye laser as light source. Time-resolved fluorescence quenching, TRFQ, was used here in combination with steady-state fluorescence quenching, SSFQ, to measure the average aggregation number, the average number of ibuprofen monomers per aggregate or micelle, in aqueous solution. $Ru(bipy)_3^{2+}$ was used as probe and 9-MA as quencher. The fluorescence decay or steady-state luminescence of $Ru(bipy)_3^{2+}$ was recorded at $\lambda = 625$ nm for excitation at $\lambda = 450$ nm. In TRFQ experiments the decay was recorded up to 1000 ns. The concentration of 9-MA was determined spectrofotometrically at $\lambda = 388$ nm. Fluorescence decay curves were recorded for each sample both in the presence and absence of quencher. The lifetime of $Ru(bipy)_3^{2+}$ in solutions without quencher, τ_0, was determined by fitting the decay to a single-exponential function. Suggested by Infelta et al.[28] and proved by Tachiya,[29] the time evolution of the quenched fluorescence decay signal $F(t)$ from an ensemble of probe molecules situated in small monodisperse micelles can be expressed by

$$F(t) = A_1 \exp[-A_2 t + A_3\{\exp(-A_4 t) - 1\}] \quad (2)$$

If the probe and quencher can be considered as stationary within the micelle during the time of activation−deactivation, and a Poisson distribution of the quencher among the micelles is assumed, the parameters A_i in eq 2 take the simple forms

$$A_1 = F(0) \quad (2.1)$$

$$A_2 = 1/\tau_0 \quad (2.2)$$

$$A_3 = \langle n \rangle \quad (2.3)$$

$$A_4 = k_q \quad (2.4)$$

where k_q is the quenching rate constant, $F(0)$ the decay intensity signal at time zero, and $\langle n \rangle$ the average number of quencher molecules per micelle. Since the quencher concentration, [Q], is known, the average aggregation number, N, can be calculated by

putting

$$N = \langle n \rangle ([\text{ibu}]_{\text{tot}} - \text{cmc})/[\text{Q}] \quad (3)$$

where $[\text{ibu}]_{\text{tot}} - \text{cmc}$ represents the molar concentration of ibuprofen monomers constituting the aggregates, taken that all ibuprofen exceeding cmc are incorporated in micelles. In SSFQ the micellar concentration in the solution, denoted [micelles], is obtained from the relationship[30]

$$\ln(I^{\circ}/I) = [\text{Q}]/[\text{micelles}] \quad (4)$$

where I° and I are the steady-state luminescence in absence and presence of quencher, respectively. The mean aggregation number is then simply calculated by putting

$$N = ([\text{ibu}]_{\text{tot}} - \text{cmc})/[\text{micelles}] \quad (5)$$

SSFQ works well if there is no migration between probe and quencher and if the quenching is efficient. This is the case if an efficient probe-quencher pair is employed that distributes quantitatively to the micelles, and if the aggregation numbers to be determined are small, ≤ 120.[31] TRFQ showed no sign of migration between probe and quencher for any of the solutions investigated, as the semilogarithmic decay curves with and without added quencher at longer times were parallel, that is, equations 2:1−4 are valid. The quenching rate constant was in all cases larger than 3×10^7 s^{-1}. The use of TRFQ thus monitors the presence of micelle-shaped clusters, or aggregates of finite sizes, which can be considered as zero-dimensional entities as monitored by fluorescence quenching. Since the concentration of micelles in the solutions is high—up to 10 mM—compared to the highest quencher concentration that can be used practically, which is $\leq 5 \times 10^{-4}$ M, the effect of added quencher is quite small. Therefore the aggregation numbers presented here were finally determined by SSFQ since fitting a quenched decay time curve by global analysis only with very low $\langle n \rangle$ available gives a higher error than using steady-state luminescence, which has a very high signal-to-noise ratio.

Results and Discussion

A characteristic feature of nonionic cellulose ether/water systems is the existence of reversible phase separation including a lower critical solubility temperature, LCST, also denoted cloud point, CP, above which the solution becomes "cloudy". At the CP the polymer precipitates out of solution as a consequence of equal chemical potentials between two phases, one richer in polymer, of solute and solvent, respectively.[32] Thus CP provides a simple and powerful tool for qualitative characterization of the polymer thermodynamics in systems with LCST behavior and their interactions with low molecular amphiphiles. A more hydrophobic cellulose ether will have a lower CP than a more hydrophilic one. The EHEC fraction CST-103 in this study is more hydrophobic than the HPMC fraction as can be seen in Figure 1, where CP is plotted as a function of the ibuprofen concentration. The CP values for the binary 0.1% EHEC/water and 0.1% HPMC/water systems are 29 and 45 °C, respectively. When ibuprofen is added, the systems diverge even more. The CP of HPMC increases with increasing ibuprofen concentration, slowly at first, and with an increasing positive derivative in the ibuprofen concentration range 150−200 mM. The EHEC fraction on the other hand has an unaffected CP up to 80 mM ibuprofen and then passes through a minimum at 150 mM whereafter CP increases steeply. Both polymers thus interact with ibuprofen which at higher drug concentrations markedly increases the solubility of the polymers. The reason for this is the formation of a micellar ibuprofen phase into which the polymers solubilize their hydrophobic parts. Similar CP curves have been reported for these cellulose ethers in the presence of sodium dodecyl sulfate, SDS.[20,33] From these CP data a rough estimate of cmc of ibuprofen in the presence of the polymer fractions can be made; its value is found to be about 150−200 mM for both EHEC and HPMC. The minimum in CP observed for the EHEC/ibuprofen system is most likely a salting-out effect due to a combination of a quite hydrophobic polymer and the considerable ionic strength from >100 mM of the sodium salt of ibuprofen, resulting in conformational changes of the polymer. The salting-out effect is further illustrated by the addition of NaCl (not shown in figure) which lowers CP over the whole drug concentration span for both polymers. An interesting effect is the difference in derivatives of the CP curves between the polymer concentrations, at higher drug concentrations. For both polymers, the derivative is higher at 0.1% polymer than at 0.5% polymer. This is a composition-dependent effect as it takes more ibuprofen to increase CP by one degree by solubilization, if more polymer is present in the solution.

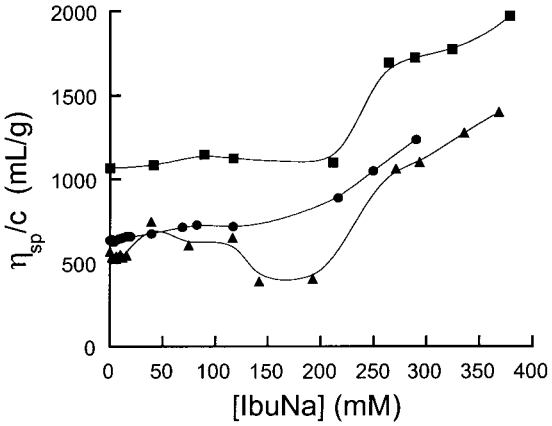

Figure 2—The reduced viscosity, η_{sp}/c, for the EHEC/ibuprofen-system as a function of the ibuprofen concentration, [IbuNa], for ▲ 0.1%, ● 0.2% and ■ 0.5% EHEC at 20 °C.

Capillary viscometry is another experimentally simple but very powerful method to explore semidilute polymer systems since aggregation phenomena most often affect the hydrodynamic flow properties, especially in polymer−amphiphile systems.[5] The EHEC/SDS/water system, for example, shows a maximum in the reduced viscosity close to the onset of polymer−surfactant interaction with respect to the surfactant concentration, for certain compositions, due to network formation.[6] The reduced viscosity for the EHEC/ibuprofen/water system is shown in Figure 2. The system HPMC/ibuprofen/water follows the same trends although the effects with this more hydrophilic polymer are smaller. Not shown in the figure but important to note is that the relative viscosity of the binary ibuprofen/water system is close to 1 for the whole concentration range investigated. The formation of pure ibuprofen micelles, as expected, was thus not measurable by capillary viscometry. No data are shown between approximately 100 and 200 mM ibuprofen because of the phase separation, cf. Figure 1. For the polymer concentrations shown in Figure 2, the reduced viscosity increases at higher drug concentrations above cmc. This evidence for EHEC−ibuprofen interaction is most likely an effect of the extension in space of the polymer chains, i.e., an increase in hydrodynamic volume, as these solubilize into ibuprofen micelles. For the lowest EHEC concentration, 0.1%, there is a decrease in the reduced viscosity prior to the cmc, which is coupled to the salting-out effect as discussed above. The polymer shrinks in this region of composition, with a notable effect on the reduced viscosity since the polymer concentration is here below the critical overlap concentration, c^*. c^* is the onset of polymer coil−coil entanglement with respect to the polymer concentration. A similar effect, also due to in-

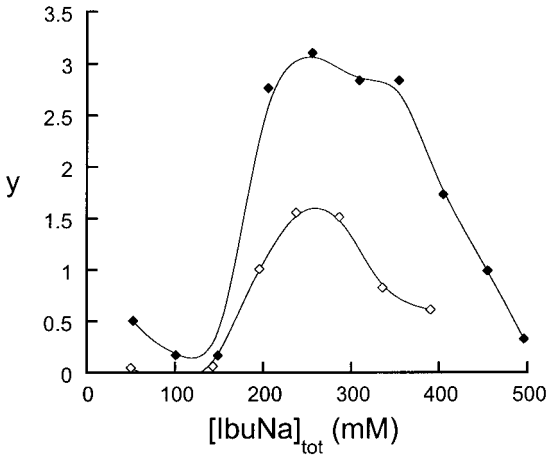

Figure 3—Equilibrium dialysis data for ◆ 1.0% EHEC, and 1.0% ◇ HPMC at 20 °C. y, mmoles of iboprofen bound per gram polymer as a function of the total concentration of ibuprofen, $[IbuNa]_{tot}$.

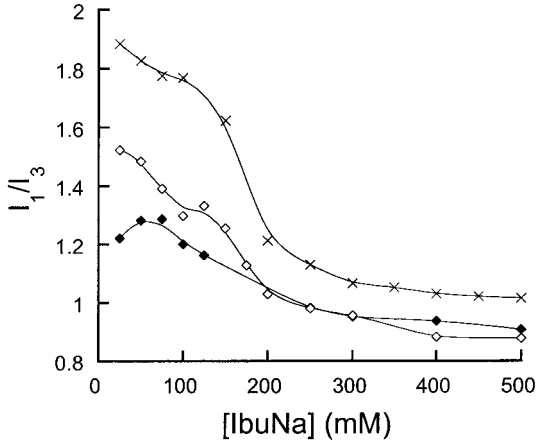

Figure 4—The micropolarity index, I_1/I_3, of pyrene in: × water solutions of ibuprofen, ◆ the ibuprofen/1.0% EHEC/water system, and ◇ the ibuprofen/1.0% HPMC/water system, as functions of the ibuprofen concentration, [IbuNa], at 20 °C.

tramolecular aggregation with respect to EHEC, but most likely not by salting-out, has been reported for the 0.1% EHEC/SDS/water system.[6] The absolute values in reduced viscosity, ≤2000 mL/g for 0.5% EHEC, are low compared to that of the maximum detected for the EHEC/SDS/water system, about 3800 mL/g for 0.3% EHEC,[6] indicating a more flexible network with weaker intermolecular tie points for the present system under study. Only 5 mM of SDS is present at the maximum in reduced viscosity in the EHEC/SDS system, which suggest that the surfactant act as "connector" between hydrophobic sites on the polymer chains. In the case of ibuprofen, more than 200 mM is present at the higher values in reduced viscosity. Furthermore, the values of reduced viscosity for the EHEC/SDS system drop well below 1000 mL/g at higher SDS concentrations, whereas there is an increase in the reduced viscosity for the EHEC/ibuprofen system instead, above 1000 mL/g. One interpretation is that SDS molecules at higher amphiphile concentrations more effectively "dress" the hydrophobic parts of EHEC and hereby the intermolecular ties between the EHEC chains diminish, as compared to ibuprofen which has a lower surface activity and also is a sterically more hindered molecule with its aromatic ring.

The adsorption of ibuprofen to the two polymer fractions was determined by equilibrium dialysis according to the principle employed for the SDS/cellulose ether/water systems previously studied.[6,18−20,22,33] The adsorption isotherm expressed as the number of millimoles of ibuprofen bound per gram of EHEC, *y*, as a function of the ibuprofen concentration, is shown in Figure 3. Significant amounts of ibuprofen bind to EHEC at [IbuNa] ≥ 150 mM. There is a positive second derivative in the adsorption isotherm up to about 180 mM ibuprofen, and then there follows a steep cooperative binding to $y = 3$ at an ibuprofen concentration of just above 200 mM. After this, *y* levels off on a plateau and then decreases again after 350 mM ibuprofen. The adsorption isotherm of HPMC is similar to that of EHEC up to $y = 1.5$ and then decreases. At the maximum in *y*, about 15% at most of the total amount of ibuprofen is EHEC-bound ($c_p y = 30$, cf., eq 1). This is to be compared with the adsorption of SDS onto 1% EHEC which reaches a maximum of $y = 3$ when about 75% of the total amount of SDS present in the solution is adsorbed (unpublished results). There is a major difference between a polymer−surfactant system such as EHEC/SDS and the EHEC/ibuprofen system. The former usually shows an onset of surfactant−polymer aggregation with respect to the surfactant concentration (usually denoted cac, critical aggregation concentration) well below the cmc for the corresponding binary surfactant/water system.[5] The maximum in adsorption is here typically reached before any ordinary micelles are formed in the solution. The EHEC/ibuprofen system, on the other hand, reaches the maximum in *y* at concentrations exceeding the ordinary cmc. This suggests a weaker mechanism of binding in the latter system, in accordance with the argument that the value of cac is a measure of the thermodynamic strength of polymer−amphiphile adsorption, cac being lower for a stronger binding.[5] In short terms, SDS forms micelles onto EHEC polymer chains below the cmc of SDS, whereas ibuprofen first forms micelles into which EHEC distributes. There is, however, significant adsorption of ibuprofen onto EHEC from about 150 mM before free "ordinary" micelles of ibuprofen start to form in the solution, with a cooperative binding as a result. A small significant binding of ibuprofen onto EHEC is also observed below 100 mM ibuprofen. This suggests that premicellar ibuprofen clusters form on the EHEC chains, and the result is consistent with the fluorescence data discussed below. After the maximum, dialysis adsorption isotherms generally show a decrease in *y*, as is the case also for the EHEC/SDS/water system.[20] The reason for this cannot be fully explained, but the membrane dialysis system tends to equilibrate by increasing the concentration of amphiphile on the side of the dialysis membrane having no polymer, as soon as free micelles are present in the solution. Thus, although it is unclear whether the entire decrease in *y* is a true redistribution from bound to free micelles, the dialysis experiments in this higher concentration region monitor a change in interaction between ibuprofen and the cellulose ethers—stronger for EHEC than for HPMC in accord with the higher hydrophobicity of the former.

Fluorescence probe techniques have been utilized in this study to give information on micellar sizes and characteristics. The fine vibrational emission spectrum of pyrene is sensitive to the polarity of the immediate surroundings of the probe,[23] see the Experimental Section. The micropolarity index I_1/I_3 is presented as a function of the ibuprofen concentration in Figure 4. The binary ibuprofen/water system gives values of $I_1/I_3 \approx 1.8$ for low drug concentrations, indicating a polar probe environment close to that of water. At intermediate ibuprofen concentrations there is a steep drop in I_1/I_3 down to ≈1.0 to 1.1 which indicates formation of micelles. These values are comparable to those of pyrene dissolved in most common surfactant micelles.[23] The cmc, as taken at the inflection point of the sigmoidal drop of the curve, is about 180 mM. In the presence of 1%

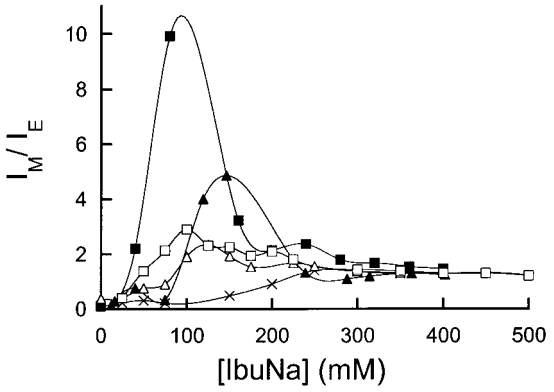

Figure 5—The microviscosity inex I_M/I_E of P3P as a function of the ibuprofen concentration, [IbuNa], at 20 °C. × no polymer present; ▲ 0.1% EHEC; ■ 0.5% EHEC; △ 0.1% HPMC, □ 0.5% HPMC.

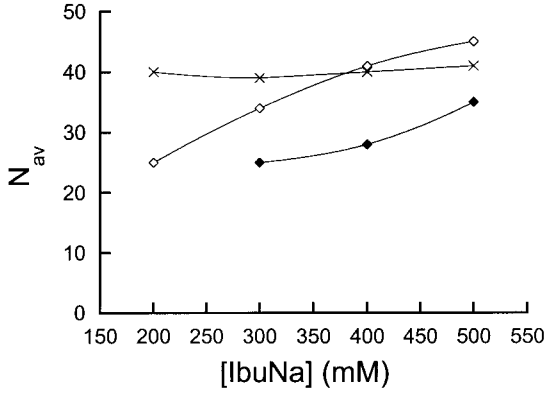

Figure 6—Average aggregation numbers of the total ensemble of ibuprofen micelles formed in solution, N_{av}, as a function of the ibuprofen concentration, [IbuNa], at 20 °C. × no polymer present; ◆ 1.0% EHEC; ◇ 1.0% HPMC.

polymer, the general trend with a drop in I_1/I_3 at cmc remains, but the absolute values are now lower. The HPMC sample gives $I_1/I_3 \approx 1.5$ at 25 mM ibuprofen and levels off at 0.9 at the higher drug concentrations. Hence, 1% HPMC mediates a more hydrophobic environment for the ensemble of pyrene molecules throughout the composition interval (25−500 mM ibuprofen). There is, for this curve, a significant decrease in I_1/I_3 in the ibuprofen concentration range 25−100 mM which can be interpreted as adsorption of ibuprofen onto HPMC in this composition interval. The more hydrophobic sample EHEC, fraction CST-103, gives even lower values of I_1/I_3 at ibuprofen concentrations below cmc than that of HPMC, suggesting that EHEC forms more polymer-dense mixed clusters with less water penetration. Pyrene thus monitors a complex interaction pattern of ibuprofen with both polymer samples starting at low ibuprofen concentrations in the range 25−50 mM.

The onset of polymer−ibuprofen interaction can also be investigated by the fluorescent microviscosity probe P3P. As further outlined in the Experimental Section, the intramolecular monomer-to-excimer emission intensity ratio, I_M/I_E, is a qualitative index of the microviscosity at the site of solubilization of the ensemble of probe molecules.[25] For a set of cellulose ethers of varying hydrophobicity, it was found that the onset of SDS−polymer interaction with respect to the surfactant concentration, here denoted c_1, as monitored by an abrupt increase in I_M/I_E, correlated with a similar abrupt decrease in I_1/I_3 for each polymer sample, as monitored by pyrene.[26] I_M/I_E is presented in Figure 5 as a function of the ibuprofen concentration in the absence as well as presence of polymer. The binary system ibuprofen/water displays an increase in I_M/I_E at cmc from about 0.2 to 1.5, an increase comparable in magnitude to that of SDS (up to about $I_M/I_E = 1$).[8] The reason for ibuprofen micelles being slightly more rigid than SDS micelles as monitored by P3P, might have its origin in the stiff aromatic ibuprofen molecule as compared to the more flexible hydrocarbon tail of SDS. Furthermore, the flat aromatic pyrene entities of P3P might associate to the aromatic ring of ibuprofen, with a decrease in the degrees of freedom for P3P. The ternary EHEC/ibuprofen/water and HPMC/ibuprofen/water systems display qualities similar to the corresponding polymer/SDS/water systems,[26] including a well-developed maximum in I_M/I_E right after c_1 and a lower plateau in I_M/I_E at higher amphiphile concentrations. The maximum in microviscosity corresponds to, as argued earlier,[8] mixed micelles or clusters with a high molar ratio polymer/ibuprofen which effectively hinders the molecular motion and excimer formation of P3P. At higher ibuprofen concentrations, the mixed micelles have a lower molar ratio polymer/ibuprofen—the mixed micelles now resemble free not polymer bound micelles—which increases the molecular mobility of P3P. Also, the fraction of micelles not bound to the polymer at higher ibuprofen concentrations is large, and much larger than in the EHEC/SDS case,[8] which tends to shift the value of I_M/I_E toward that of ordinary free micelles. The numerical value of the maximum of I_M/I_E for the 0.5% EHEC sample is about 10. This is more than three times the maximum value in I_M/I_E observed for the 0.5% HPMC sample, which is about 3. Consequently, as monitored by P3P, EHEC forms more rigid and dense mixed polymer−ibuprofen micelles than HPMC, in the lower ibuprofen concentration regime. This finding is in accord with the higher hydrophobicity of EHEC, and correlates with the values of I_M/I_E for the corresponding polymer/SDS/water systems.[26] P3P, like pyrene, monitors the onset of polymer−drug interaction to be in the range 25−50 mM ibuprofen for both polymer samples. Figure 5 also illustrates that a maximum in microviscosity does not need to be coupled to a maximum in bulk viscosity, cf., Figure 2. The former will definitely affect the transport properties of drug molecules in solution, but might pass undetected by only using conventional rheological methods.

The average aggregation numbers of ibuprofen micelles—the average number of ibuprofen molecules per micelle—were determined by a combination of static and time-resolved fluorescence quenching as described in the Experimental Section. In the model calculation of the aggregation numbers the cmc of ibuprofen is taken to be 180 mM throughout the calculation in accord with the data shown above. This assumption is probably not totally correct as there might be a redistribution of free ibuprofen monomers into micelles above the cmc, but the calculation still gives a good estimate of the micelle sizes and shows the effect of the presence of polymer in the system. As can be seen in Figure 6 where the average aggregation numbers of all micelles present in the system, N_{av}, are plotted as a function of the ibuprofen concentration, N_{av} for the binary system ibuprofen/water remains about 40 in the concentration range investigated. This is in accord with the start−stop process signifying micellization including a certain micelle size distribution for a certain solute, solvent, temperature, and ionic strength.[5] The ibuprofen micelles are comparable in size with many surfactant micelles, e.g., SDS, which have aggregation numbers in the range 60−70 as monitored by the same technique.[5] Turning next to the ternary 1% cellulose ether/ibuprofen/water systems, no aggregation numbers could be determined at 100 mM ibuprofen since not enough quencher could be solubilized in the clusters for accurate determinations. At 200 mM and 300 mM ibuprofen, the total micelle concentrations are significantly higher if 1% HPMC is present in the solutions as compared to the polymer-free case, cf., Table 1. This is

Table 1—Total Micelle Concentrations [micelle] (mM)

[IbuNa] (mM)	no polymer present	1% EHEC	1% HPMC
200	0.49	-	0.79
300	3.11	4.70	3.58
400	5.48	7.82	5.36
500	7.87	9.21	7.11

an indication of polymer-bound micelles which alter the micellar concentrations. The effect is smaller average aggregation numbers including both polymer-bound and free micelles, N_{av}, as presented in Figure 6. At 400 mM and 500 mM ibuprofen, the effect of HPMC on N_{av} diminish, suggesting the total ensemble of micelles at these high drug concentrations to be similar to the binary ibuprofen/water system, in accord with the P3P data of Figure 5. The more hydrophobic polymer sample EHEC CST-103 affects the micellar concentrations and hence N_{av} to an even larger degree, which seems correct as EHEC binds more ibuprofen ($y_{max} = 3$) than HPMC does ($y_{max} = 1.5$) as shown by the dialysis experiments. At higher ibuprofen concentrations, N_{av} for the EHEC/ibuprofen system also strives toward that of the binary system. The aggregation numbers of polymer-bound micelles are hence smaller than free micelles, an observation in line with the corresponding cellulose ether/SDS systems.[7,22] An illustrative example of this is the 300 mM ibuprofen/1% EHEC solution. The EHEC-bound ibuprofen concentration is, with $y = 3$ from Figure 3, 30 mM. This gives, with the cmc = 180 mM, 90 mM of ibuprofen incorporated into free micelles. With a total micelle concentration from Table 1 of 4.70 mM and $N_{av} = 40$ for free micelles, the average aggregation number of polymer-bound micelles becomes 12.

Conclusion

The aggregation behavior of ibuprofen in aqueous solution, with and without addition of interacting polymer, can be well-characterized by a combination of phase equilibrium data, adsorption isotherms, rheology measurements, and fluorescence probe investigations. It is shown that cmc of ibuprofen in pure water is 180 mM, and that above cmc, micelles are formed which resemble ordinary surfactant micelles, as monitored by fluorescence quenching and microviscosity measurements. In the presence of a cellulose ether, adsorption to the polymer occurs below cmc, but the strong cooperative part of the adsorption coincides with the normal cmc, in contrary to the normally accepted model for polymer−surfactant interaction.[5] The more complex interaction pattern of the ibuprofen−cellulose ether system might be mediated by the ionic strength which varies considerably in the investigated ibuprofen concentration interval (0−500 mM) and thus changes the system with changed drug concentration. The present study was undertaken to provide a background for transport studies in drug−polymer systems. Obviously the results obtained indicate that since, for instance, aggregation numbers and microfluidity of the mixed polymer−drug micelles can vary considerably as a function of composition these facts must be taken into account in order to correctly describe the irreversible process of mass transport in drug release from such systems.

References and Notes

1. Attwood, D.; Florence, A. T. *Surfactant Systems*; Chapman & Hall: Bristol, 1983.
2. Florence, A. T.; Attwood, D. *Physicochemical Principles of Pharmacy*, 3rd ed.; Macmillan: London, 1998.
3. Greminger, G. K. J.; Krumel, K. L. Alkyl and Hydroxyalkylcellulose. In *Handbook of Water-Soluble Gums and Resins*; Davidson, R. L., Ed.; McGraw-Hill: New York, 1980; p 3.
4. Persson, B.; Nilsson, S.; Sundelöf, L.-O. On the Characterization Principles of Some Technically Important Water Soluble Nonionic Cellulose Derivatives. Part II: Surface Tension and Interaction With a Surfactant. *Carbohydr. Polym.* **1996**, *29*, 119.
5. *Interactions of Surfactants with Polymers and Proteins*; Goddard, E. D., Ananthapadmanabhan, K. P., Eds.; CRC Press: Boca Raton, 1993.
6. Holmberg, C.; Nilsson, S.; Singh, S. K.; Sundelöf, L.-O. Hydrodynamic and Thermodynamic Aspects of the SDS-EHEC−Water System. *J. Phys. Chem.* **1992**, *96*, 871.
7. Nilsson, S.; Holmberg, C.; Sundelöf, L.-O. Aggregation numbers of SDS micelles formed on EHEC. A steady-state fluorescence quenching study. *Colloid Polym. Sci.* **1995**, *273*, 83.
8. Evertsson, H.; Nilsson, S. Microviscosity in Clusters of Ethyl Hydroxyethyl Cellulose and Sodium Dodecyl Sulfate Formed in Dilute Aqueous Solutions as Determined with Fluorescence Probe Techniques. *Macromolecules* **1997**, *30*, 2377.
9. Gaikar, V. G.; Latha, V. Hydrotropic Properties of Sodium Salt of Ibuprofen. *Drug Dev. Industr. Pharm.* **1997**, *23*, 309.
10. Fini, A.; Zecchi, V.; Rodriguez, L.; Tartarini, A. Solubility-Dissolution Relationship for Ibuprofen, Fenbufen and their Sodium Salts in Acid Medium. *Pharm. Acta Helv.* **1984**, *59*, 106.
11. Fini, A.; Zecchi, V.; Tartarini, A. Dissolution Profiles of NSAID Carboxylic Acids and their Salts of Different Counterions. *Pharm. Acta Helv.* **1985**, *60*, 58.
12. Fini, A.; Laus, M.; Orienti, I.; Zecchi, V. Dissolution and Partition Thermodynamic Functions of Some Nonsteroidal Antiinflammatory Drugs. *J. Pharm. Sci.* **1986**, *75*, 23.
13. Fini, A.; Fazio, G.; Feroci, G. Solubility and solubilization properties of nonsteroidal antiinflammatory drugs. *Int. J. Pharm.* **1995**, *126*, 95.
14. Paavola, A.; Yliruusi, J.; Rosenberg, P. Controlled release and dura mater permeability of lidocaine and ibuprofen from injectable poloxamer-based gels. *J. Controlled Release* **1998**, *52*, 169.
15. Reinwald, G.; Zimmermann, I. A Combined Calorimetric and Semiempirical Quantum Chemical Approach To Describe the Solution Thermodynamics of Drugs. *J. Pharm. Sci.* **1998**, *87*, 745.
16. Nilsson, S.; Sundelöf, L.-O.; Porsch, B. On the Characterization Principles of Some Technically Important Water Soluble Nonionic Cellulose Derivatives. *Carbohydr. Polym.* **1995**, *28*, 265.
17. Fischman, M. L.; Eirich, F. R. Interactions of Aqueous Poly(N-vinylpyrrolidone) with Sodium Dodecyl Sulphate I. Equilibrium Dialysis Measurements. *J. Phys. Chem.* **1971**, *75*, 3135.
18. Holmberg, C.; Sundelöf, L.-O. Temperature Dependence of Hydrodynamic Properties and Surfactant-Polymer Interaction in Solution. The EHEC/SDS/Water System. *Langmuir* **1996**, *12*, 883.
19. Holmberg, C. Phase conditions, hydrodynamic features and salt influence in the polymer-amphiphile interaction for the EHEC/SDS/water system. *Colloid Polym. Sci.* **1996**, *274*, 836.
20. Holmberg, C.; Nilsson, S.; Sundelöf, L.-O. Thermodynamic properties of surfactant/polymer/water systems with respect to clustering adsorption and intermolecular interaction as a function of temperature and polymer concentration. *Langmuir* **1997**, *13*, 1392.
21. Nilsson, S.; Holmberg, C.; Sundelöf, L.-O. Approach to hydrodynamic equilibrium and its time dependence in the system EHEC/SDS/Water. *Colloid Polym. Sci.* **1994**, *272*, 338.
22. Evertsson, H.; Nilsson, S.; Holmberg, C.; Sundelöf, L.-O. Temperature effects on the interactions between EHEC and SDS in dilute aqueous solutions. Steady-state fluorescence quenching and equilibrium dialysis investigations. *Langmuir* **1996**, *12*, 5781.
23. Kalyanasundaram, K.; Thomas, J. K. Environmental Effects on Vibronic Band Intensities in Pyrene Monomer Fluorescence and Their Application in Studies of Micellar Systems. *J. Am. Chem. Soc.* **1977**, *99*, 2039.
24. Evertsson, H.; Holmberg, C. Salt influence in the polymer-surfactant interaction in solution. A fluorescence probe investigation of the EHEC/SDS/water system. *Colloid Polym. Sci.* **1997**, *275*, 830.
25. Zachariasse, K. A. Intramolecular Excimer Formation With Diarylalkanes as a Microfluidity Probe for Sodium Dodecyl Sulphate Micelles. *Chem. Phys. Lett.* **1978**, *57*, 429.
26. Evertsson, H.; Nilsson, S. Microviscosity in Dilute Aqueous Solutions of SDS and Nonionic Cellulose Derivatives of

Different Hydrophobicity: Fluorescence Probe Investigations. *Carbohydr. Polym.* **1998**, *35*, 135.
27. Evertsson, H.; Nilsson, S.; Welch, C. J.; Sundelöf, L.-O. Molecular Dynamics in Dilute Aqueous Solutions of Ethyl-(hydroxyethyl)cellulose and Sodium Dodecyl Sulfate as Investigated by Proton NMR−Relaxation. *Langmuir* **1998**, *14*, 6403.
28. Infelta, P. P.; Grätzel, M.; Thomas, J. K. Luminescence Decay of Hydrophobic Molecules Solubilized in Aqueous Micellar Systems. A Kinetic Model. *J. Phys. Chem.* **1974**, *78*, 190.
29. Tachiya, M. Application of a Generating Function to Reaction Kinetics in Micelles. Kinetics of Quenching of Luminescent Probes in Micelles. *Chem. Phys. Lett.* **1975**, *33*, 289.
30. Turro, N. J.; Yekta, A. Luminescent Probes for Detergent Solutions. A Simple Procedure for Determination of the Mean Aggregation Number of Micelles. *J. Am. Chem. Soc.* **1978**, *100*, 5951.
31. Almgren, M.; Löfroth, J.-E. Determination of Micelle Aggregation Numbers and Micelle Fluidities from Time-Resolved Fluorescence Quenching Studies. *J. Colloid Interface Sci.* **1981**, *81*, 486.
32. Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, 1953.
33. Nilsson, S. Interactions between water soluble cellulose derivatives and surfactants. Part 1: The HPMC−SDS-water system. *Macromolecules* **1995**, *28*, 7837.

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