Interaction of (Hydroxypropylmethyl)cellulose with Anionic Surfactants

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Summary: The aggregation process between (hydroxypropylmethyl)cellulose (HPMC 0.20% m/m) and three anionic surfactants namely sodium cholate (CS), sodium deoxycholate (DC) and sodium dodecylsulphate (SDS), in aqueous dilute solutions, was investigated by fluorescence, electrical conductivity, dynamic light scattering (DLS) and small angle X-ray scattering (SAXS) techniques. Through fluorescence, the critical micelle concentration (CMC) and critical aggregation concentration (CAC) of the systems were obtained in good agreement with those obtained from conductivity. Also by means of conductivity measurements, once the experiments were undertaken at four temperatures, the thermodynamic parameters of the micellization process were calculated. From DLS, the relaxation time distribution functions were analyzed by REPES Routine, revealing that the surfactants bind to the polymer before CAC as well as the formation of free micelles at high surfactant content. The SAXS technique confirmed the existence of such free micelles.

Keywords: bile salts; conductivity; (hydroxypropylmethyl)cellulose; light scattering; SAXS

Introduction

Polymers are often used in pharmaceutical field to act in drug delivery systems, to give rheological properties to formulations or to stabilize emulsions and suspensions. The presence of surfactants in the system plays an important role as agents that are able to improve the system properties.[1]

It is well described in the literature that non ionic polymers, such as poly(vinylpirrolidone)[2] (PVP), poly(ethylene oxide)[3] (PEO) and (hydroxypropyl)cellulose[4] (HPC) interact strongly with anionic surfactants like sodium dodecylsulphate (SDS). The complex formation in these systems is characterized by a decrease in the critical aggregation concentration (CAC) if compared to critical micelle concentration (CMC) of the free surfactant and also by the fact that polymer/surfactant system acts as a polyelectrolyte. The major driving force for polymer/surfactant interaction is the stabilization of the interfaces between the hydrophobic polymer segments and water by association of these segments with the exposed hydrophobic parts of aggregate surfactants.[5]

In our research group and in a series of works[4,6–8] the interaction between non ionic cellulose ethers and anionic surfactants, such as bile salts and sodium dodecylsulphate, has been investigated either in dilute aqueous or concentrated solutions. Bile salts are natural anionic surfactants that are polyhydroxy derivatives from cholesterol. In contrast to classical surfactants, formed by long alkyl chains with polar headgroups, the bile salts exhibit a lipophilic surface, which is the convex side of the rigid steroid ring system, and a hydrophilic surface, which is the polyhydroxylated concave side of the molecule.

In our previous works, the aggregation between (hydroxypropyl)cellulose (HPC)

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and sodium cholate (CS), sodium deoxycholate (DC) and sodium dodecylsulphate (SDS) was studied in the absence[4] or in the presence[6] of added sodium chloride. It was verified that the interaction of HPC and the bile salts is weak.

In this paper, we present another cellulose ether derivative, namely (hydroxypropylmethyl)cellulose (HPMC) and its interaction with the same set of surfactants since the aggregation study of HPMC and bile salts has been unthoroughly studied in the last years. In this way, the investigation of the aggregation process between bile salts and HPMC may contribute to extend the comprehension about the role of surfactant and polymer structures in the formation of their aggregated systems.

Materials and Methods

The surfactants CS (99%), DC (99%), SDS (98%) were purchased from Acros Organics and used without further purification. After dialysis HPMC (Aldrich) presents $M_w = 3.4\ 10^5$ g mol^{-1}, radius of gyration $R_g = 71.5$ nm, hydrodynamic radius $R_H = 25.4$ nm and second virial coefficient $A_2 = 7.84\ 10^{-4}$ cm^3 mol g^{-2} (data obtained in water at 298 K through static and dynamic light scattering by Zimm-Plot extrapolation procedures, not shown) and refractive index increment, $dn/dc = 0.1371$ mL g^{-1} obtained by differential refractometry at 298 K and $\lambda = 620$ nm. A stock aqueous solution of HPMC was dialyzed 1 week (Membracel tubing, cut-off 12,000–16,000 g mol^{-1}, Viskase) against Milli-Q grade water (Millipore), filtered subsequently through 8 and 0.45 μm membrane filters (Millipore) and kept under refrigeration. The HPMC 0.20% m/m/surfactant samples were prepared starting from the highest concentration in surfactant and subsequent dilutions with HPMC 0.20% m/m aqueous solution down to the desired surfactant contents.

The pyrene (Py) emission spectra were run on a Hitachi F-4500 Spectrophotometer in the corrected spectrum mode with excitation wavelength set at 336 nm and 2.5 mm slit in the range 350–500 nm with cell holder thermostated by a circulating ethylene glycol bath at 298 ± 0.4 K. The Py concentration was kept as low as 5 10^{-6} mol L^{-1} to avoid excimer formation. The electrical conductivity experiments were carried out with an Oakton Con 100 Series Conductometer thermostated at 298 ± 0.1 K with a water bath for at least 10 min before the readings were taken. Milli-Q grade water had a specific conductivity of 1.3 μS cm^{-1}. Light scattering measurements have been undertaken on a Brookhaven Instruments goniometer, with a He-Ne Coherent laser at 632.8 nm. The samples were thermostated in a refractive index matching liquid (decaline) at 298 K. To remove dust from the solutions, they were filtered through 0.22 μm filter (Millipore) and centrifuged at 4,000 rpm for 2.5 h. SAXS measurements were performed with a synchroton radiation source at the Laboratório Nacional de Luz Síncrotron (LNLS-Campinas, SP, Brazil) with sample-detector distance 549.2 mm; $\lambda = 1.608$ Å, scattering vector ($\vec{q}$) range, 0.02–0.65 Å^{-1} and $T = 298 \pm 0.2$ K.

Results and Discussion

Fluorescence experiments were carried out to study the aggregation of HPMC 0.20% m/m/anionic surfactant systems by determining the hydrophobic index, I_1/I_3. It is well established that the I_1/I_3 of pyrene can be used to follow the aggregation phenomenon,[1,9] as well as to determine the critical micellization concentration (CMC) and/or critical aggregation concentration (CAC).

Illustrated in Figure 1 is the dependence of the hydrophobic index on surfactant concentration for the studied systems. A common characteristic for all curves is the decrease of I_1/I_3 with surfactant addition. This fact suggests that pyrene molecules are preferably solubilized into a less polar microenvironment due to aggregate formation.

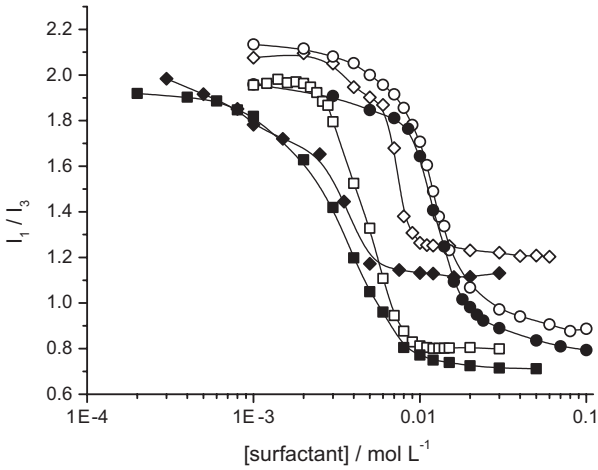

Figure 1.
Dependence of the ratio I_1/I_3 on surfactant concentration in absence (open symbols) or with HPMC 0.20% m/m (full symbols): CS (circles), DC (squares) and SDS (diamonds). Temperature = 298 K.

For a better understanding, the curves are divided into three regions, as it can be seen in Figure 2:

- Region I – first plateau: no evidences of hydrophobic pockets are found in this region;
- Region II – second plateau: initial decrease of I_1/I_3 until the beginning of the second plateau: the formation of hydrophobic microdomains occurs either by the self-association between surfactant molecules (pure surfactant systems) or by HPMC/surfactant aggregates;
- Region III – second plateau at high surfactant concentration: free micelle formation for surfactant/water systems. In the presence of HPMC it is reached the limit of surfactant adsorption onto the polymer, leading as well to free micelle formation.

Another information that can be obtained from the analysis of the curves

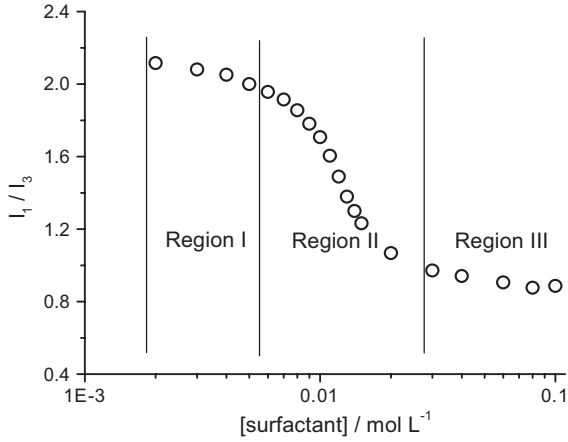

Figure 2.
Hydrophobic index as a function of surfactant concentration for CS/water system: delimitation of the three aggregation regions. Temperature = 298 K.

(Figure 1) is the value of CMC or CAC. The first is related to systems containing only surfactant whereas the other is associated with systems in which polymer is present. The results for CMC and CAC were taken as the inflection points of the I_1/I_3 curves (Figure 2, Region II). The data from fluorescence as well as from electrical conductivity measurements are displayed in Table 1.

The CMC values obtained for each surfactant at 298 K are shown in Table 1 in good agreement with literature data.[10–12a] In the presence of HPMC 0.20%, it is observed that all CAC values decrease in comparison to CMC denoting a polymer/surfactant interaction. Besides, the pronounced decrease assigned to HPMC/SDS system may indicate a strong association supported by other techniques used in this work. This phenomenon is related to a possible decrease of the electrostatic headgroup repulsion on the micelle surface due to reduction of the surface charge density because of the presence of the polymer.

Electrical conductivity experiments were also performed to evaluate the interaction HPMC/anionic surfactants. By using this technique, in aqueous surfactant solutions, the micellization process is revealed by a breakpoint in the profile of the curve conductivity *versus* surfactant concentration. When a polymer is added to the system, two breakpoints may be detected: the first one is related to the CAC and the second one, to the polymer saturation point (PSP).[13–15]

Table 1.
Critical concentrations from fluorescence and conductivity measurements. T = 298 K.

System	CMC or CAC (mol $L^{-1} \times 10^3$)	
	Fluorescence	Conductivity
HPMC 0.20%/SDS	3.7	4.0
SDS/water	7.7	8.3
HPMC 0.20%/CS	11.3	10.0
CS/water	11.8	11.5
HPMC 0.20%/DC	3.7	–
DC/water	4.3	–

The system HPMC/CS had been already studied by conductivity.[16] It was stated that no aggregation was found with this technique, in the presence or not of polymer. Nevertheless, our results have detected some interaction between these two compounds as well as between HPMC/DC, using fluorescence as technique (as seen before). Indeed, if one observes Table 1, the values obtained from fluorescence and conductivity are in accordance to each other for all systems in which it was possible the detection of CMC or CAC. As the discussion about the bile salt aggregation (pure systems) was already argued in terms of conductivity experiments in our previous paper,[4] we focus directly on the systems containing HPMC and surfactant. Thus, Figures 3 and 4 exemplify the study for HPMC 0.20%/SDS and HPMC 0.20%/CS systems at four temperatures.

Firstly, we should point out that the electrical conductivity experiments were carried out at four temperatures in order to determine the thermodynamic parameters of aggregation (ΔG^0_{mic}, ΔH^0_{mic} and T ΔS^0_{mic}). In this way, Table 2 summarizes the thermodynamic parameters as well as the critical concentrations obtained for HPMC 0.20%/SDS, SDS/water, HPMC 0.20%/CS and CS/water systems. For the other systems, ΔG^0_{mic}, ΔH^0_{mic} and $T\ \Delta S^0_{mic}$ were not calculated once it was not possible to establish their CMC or CAC by breakpoints in the conductivity plots. At 278 K, there are no results found for SDS/water system since the mentioned temperature is below the SDS Krafft point temperature.[12b]

The results on Table 2 clearly follow the same behavior observed for HPC 0.25% and the same set of surfactants:[4] the free energy of micellization is negative and apparently independent of temperature over the analyzed temperature range. The direct comparison between SDS/water and CS/water ΔG^0_{mic} values leads us to infer that the aggregation process for the alkylsulphate is favored. In turn, when HPMC is present, the free energy becomes more negative for both surfactants, revealing the

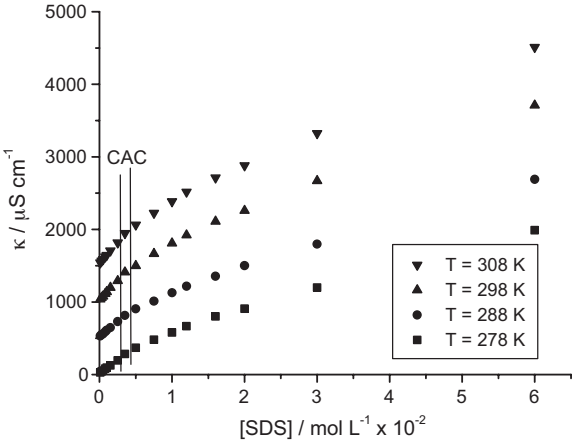

Figure 3.
Electrical conductivity as a function of SDS concentration at four temperatures for HPMC 0.20%/SDS systems. The plots have been shifted for a better visualization. The parallel bars indicate the region of critical aggregation concentration.

polymer character of stabilizing the aggregates. This behavior corroborates with the decrease of CAC related to CMC when HPMC is added to the system. Regarding the ΔH^0_{mic} values, they seem to be temperature dependent whereas the entropic contribution ($T\,\Delta S^0_{mic}$) is positive and follows the free energy trend related in terms of temperature dependence. According to the literature, such ΔH^0_{mic} behavior indicates that London-dispersion interactions possibly play an important role in the aggregation processes.[17]

Dynamic light scattering was another approach applied to study the binding of CS, DC and SDS to HPMC. The time correlation functions (not shown) obtained for each HPMC/surfactant system showed two correlation modes: a) a fast mode assigned to single polymer chain, intrachain polymer/surfactant aggregates or free micelles and b) a slow mode attributed to

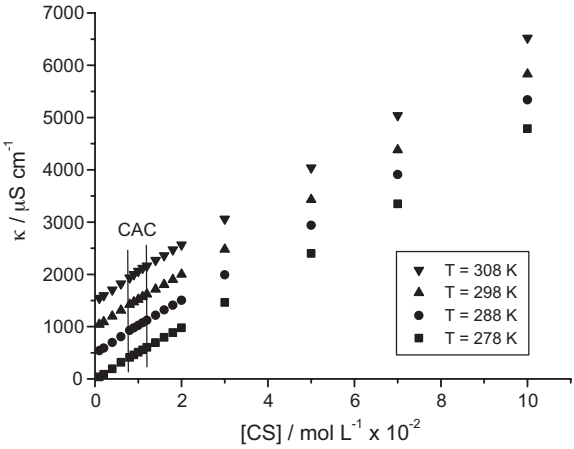

Figure 4.
Electrical conductivity as a function of CS concentration at four temperatures for HPMC 0.20%/CS systems. The plots have been shifted for a better visualization. The parallel bars indicate the region of critical aggregation concentration.

Table 2.
Thermodynamic parameters for some of the studied systems at different temperatures.

System	T/K	CMC or CAC (mol $L^{-1} \times 10^3$)	ΔG^o_{mic} (kJ mol^{-1})	ΔH^o_{mic} (kJ mol^{-1})	$T\,\Delta S^o_{mic}$ (kJ mol^{-1})
HPMC 0.20%/SDS	278	3.2	−37.2	−9.0	28.2
	288	3.5	−37.6	−9.5	28.1
	298	4.0	−37.5	−10.4	27.1
	308	4.3	−38.1	−10.8	27.3
SDS/water	278	–	–	–	–
	288	8.7	−34.8	−4.4	30.4
	298	8.3	−35.7	−4.7	31.0
	308	8.6	−36.4	−4.9	31.5
HPMC 0.20%/CS	278	8.7	−26.2	−8.1	18.1
	288	9.4	−26.3	−8.4	17.9
	298	10.0	−26.8	−9.3	17.5
	308	11.5	−27.1	−9.7	17.4
CS/water	278	12.6	−23.5	−7.4	16.1
	288	8.7	−24.1	−7.5	16.6
	298	11.5	−24.8	−8.3	16.5
	308	12.6	−25.3	−8.8	16.5

polymer cluster and interchain polymer/surfactant complexes. All systems demonstrated to be diffusive.[8] The study of the hydrodynamic radius (R_H) of the systems plotted as a function of the surfactant concentration contributes to the understanding of the aggregation process (Figure 5, fast mode). One should point out that the R_H values were obtained by extrapolation to zero angle.

The hydrodynamic radius profile of the three systems followed the viscosity behavior[8] (not shown): there is a minimum value of R_H in the vicinity of CAC for the bile salts with subsequent increase. On the other hand, for HPMC/SDS system the opposite occurs: the R_H curve shows a maximum, followed by a decrease. This decrease can be also seen for bile salts. This fact is an evidence of the beginning of free

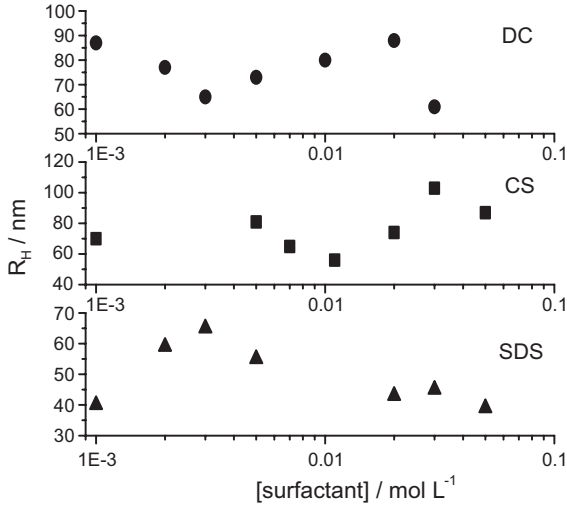

Figure 5.
Hydrodynamic radius (R_H), corresponding to the fast mode, as a function of the surfactant concentration for all studied systems.

micelle formation. The analysis of the relaxation time distributions through REPES routine[18] corroborates with this interpretation.

In this way, Figures 6 to 8 show the relaxation time distributions for the HPMC/surfactant systems. Each set of curves is delimited by CAC, i.e., the first three curves (from bottom to top) are associated to the pre-aggregation range, whereas the others refer to the post-aggregation range. The bottom curve is always pure HPMC 0.20% m/m.

In the pre-aggregation range, the influence of the three surfactants on the polymer dynamics can be easily observed. The addition of $[CS] = 3\ 10^{-3}$ mol L^{-1}, $[DC] = 10^{-3}$ mol L^{-1} and $[SDS] = 10^{-3}$ mol L^{-1} changes the distribution curve of HPMC. The mentioned curve becomes narrower and it is shifted to shorter correlation times. Besides, the HPMC fraction located at longer times is shifted to shorter ones in the presence of CS or DC, while it is dissolved when SDS is the amphiphilic molecule.

As the surfactant concentration increases, the system dynamics changes. For instance, at $[DC] = 3\ 10^{-3}$ mol L^{-1}, which is not far from CAC, the former single peak splits into two, being dominant the peak at longer correlation times. This may be understood as the beginning of HPMC/DC complex, in spite of the concentration lower than CAC. At $[DC] = 10^{-2}$ mol L^{-1}, both correlation modes contribute equally to the dynamics. For $[DC] > 10^{-2}$ mol L^{-1}, the fast mode prevails, probably due to the appearance of free micelles.

In turn, for HPMC/CS, the fast mode dominates the dynamics along the concentration range. It is possible to detect once again the peak corresponding to free micelles, at shorter times and higher CS concentrations. Regarding the HPMC/SDS system, at $[SDS] = 10^{-3}$ mol L^{-1}, it is verified that the dynamics of HPMC is affected: the curve is shifted to shorter times. This behavior may be observed until $[SDS] < 3\ 10^{-3}$ mol L^{-1}, because at this concentration the dynamics of the system

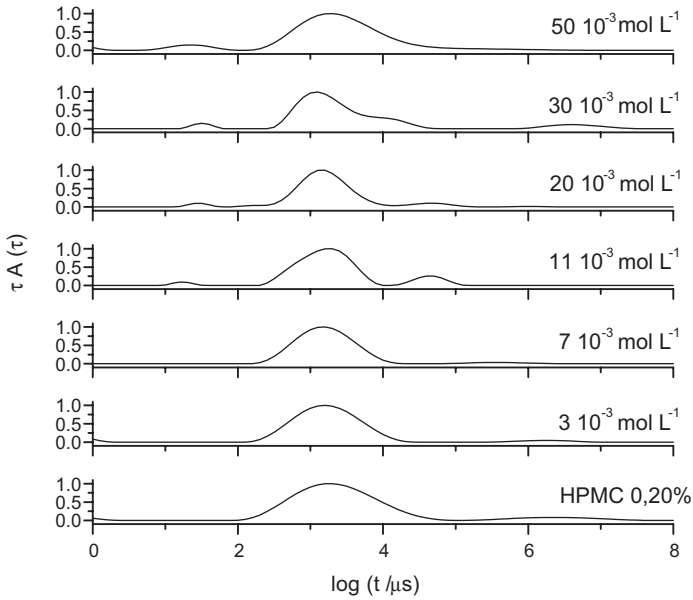

Figure 6.
Relaxation time distributions for the systems HPMC 0.20%/CS. The surfactant concentration is indicated in each plot. Scattering angle = 45°. Temperature = 298 K.

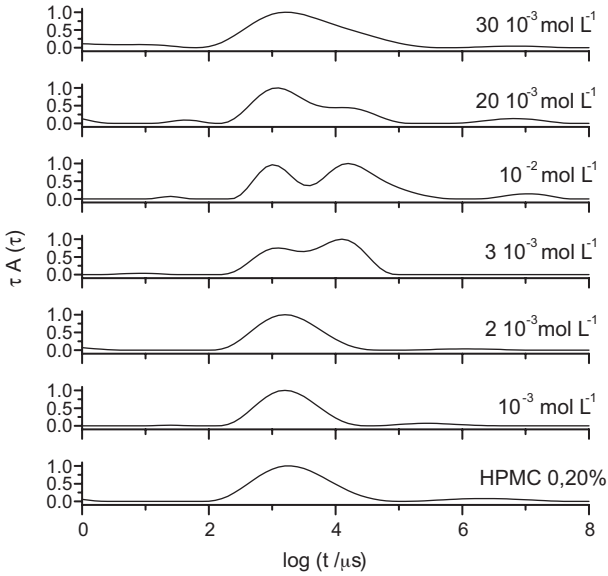

Figure 7.
Relaxation time distributions for the systems HPMC 0.20%/DC. The surfactant concentration is indicated in each plot. Scattering angle = 45°. Temperature = 298 K.

becomes slower. Subsequent additions of SDS widen the distribution. The peak related to free micelles in noticed at [SDS] = 20 10^{-3} mol L^{-1} and becomes evident at [SDS] = 50 10^{-3} mol L^{-1}.

It is worth commenting that the peak at shorter correlation times (found in the same region) and at high surfactant content appears for all systems. The calculated R_H for the characteristic times is about 1–3 nm, corresponding to the value of free micelles as confirmed by SAXS (see below).

Thus, SAXS measurements were performed in order to verify the existence of

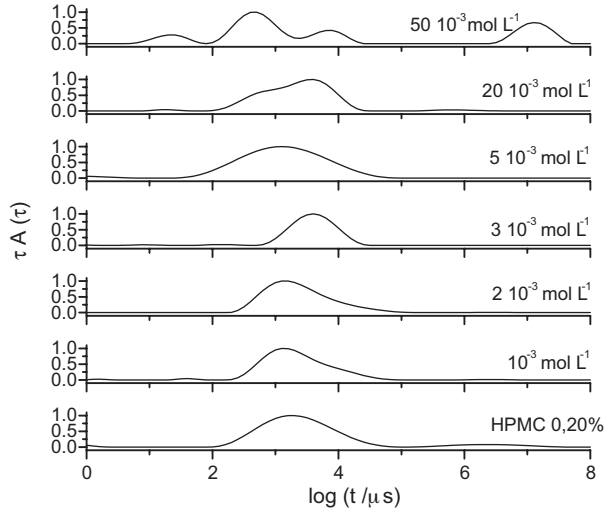

Figure 8.
Relaxation time distributions for the systems HPMC 0.20%/SDS. The surfactant concentration is indicated in each plot. Scattering angle = 45°. Temperature = 298 K.

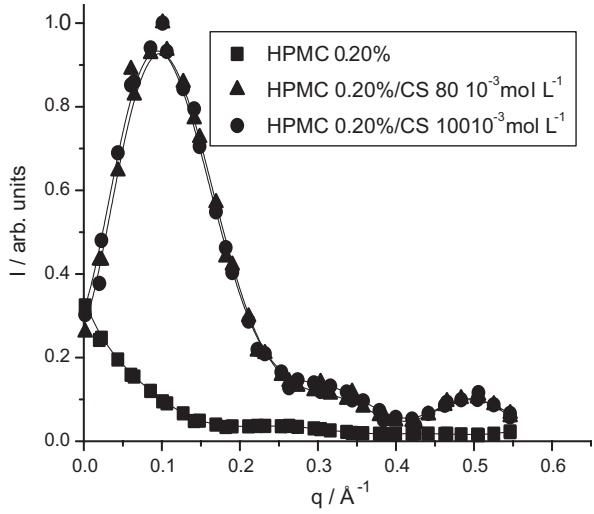

Figure 9.
SAXS profiles for the systems HPMC 0.20%/CS. Temperature = 298 K.

free micelles for HPMC 0.20%/surfactant systems at high surfactant concentration. The same set of surfactants was also analyzed by means of SAXS technique but in the absence of polymer. Figure 9 shows a representative SAXS profile for HPMC/CS system at two different concentrations of sodium cholate.

If one observes Figure 9, the curve attributed to polymer without CS does not show any peak, as expected. However, in the presence of high amounts of CS, a peak characteristic of micelle formation is present. It is possible to evaluate the diameter of the structures taking into account the equation[19]

$$L = \frac{2\pi}{\vec{q}_{\max}} \quad (1)$$

where L is the diameter of the structure and $\vec{q}_{\max}$ represents the scattering vector at the highest intensity position. The diameter results obtained by equation (1) applied to the systems HPMC/surfactant and surfactant/water are displayed in Table 3.

If one compares the results, one verifies that the diameter values attributed to free micelles in the absence of polymer are, within the experimental error, close to those found in the presence of HPMC. Based on this evidence, it can be inferred that free micelles are formed in the HPMC/surfactant systems at high surfactant concentrations. This fact had been already evidenced by dynamic light scattering measurements, so the SAXS technique ratifies this finding.

Table 3.
Diameters obtained for free surfactant micelles through SAXS technique in presence or in the absence of polymer.

[surfactant] mol $L^{-1} \times 10^3$	Micelle diameter (nm)	
	HPMC 0.20%	Absence of polymer
CS 80	6.61	6.61
CS 100	6.68	6.23
DC 30	9.24	9.31
DC 40	8.97	8.97
SDS 30	3.32	3.39
SDS 40	3.25	3.36

Conclusions

The interaction between HPMC 0.20% m/m and different anionic surfactants (SDS, CS and DC) has been investigated by fluorescence, electrical conductivity, light scattering and small angle X-ray scattering techniques. It was observed that each surfactant contributed differently to the aggregation process with HPMC as evidenced by

changes in the values of critical surfactant concentration (CAC) with respect to critical micellization concentration (CMC). Electrical conductivity measurements confirmed that HPMC/bile salts indeed interact. Nevertheless, HPMC/SDS system has shown higher stability than HPMC/bile salts, as demonstrated by free energy results (lower ΔG^0_{mic} values). By means of dynamic light scattering (DLS), it was verified the existence of two correlation modes (denoted as fast mode and slow mode). The fast mode was attributed to single polymer chain, intrachain polymer surfactant aggregates or free micelles; the slow mode was assigned to polymer clusters and interchain polymer/surfactant complexes. In addition, the relaxation time distribution showed the influence of the surfactants on the polymer dynamics. An important experimental fact was that such influence was noticed even at surfactant concentrations lower than CAC, contradicting polymer/surfactant models widely accepted. Both DLS and SAXS techniques revealed the presence of free micelles at high surfactant contents for HPMC/surfactant systems. Based on the overall results, an aggregation mechanism between HPMC and the surfactants used in this work is proposed as follows: a) attachment of surfactant unimers to the HPMC chain leading to the formation of aggregation nuclei; and b) subsequent binding of surfactant micelle-like aggregates on it.

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