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Poly(acrylic acid) microgels (carbopol® 934)/ surfactant interactions in aqueous media

Part I: Nonionic surfactants

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Abstract

The interaction between Tween 80 and Pluronic F-127 with carbopol in water was studied as a function of surfactant concentration. 0.25% carbopol microgels dispersions showed a continuous decrease in transmittance, viscosity and conductivity when surfactant concentration ranged from 0.01–0.02% to 0.50% Tween 80 or from 0.03–0.06% to 0.30% Pluronic F-127. These limit values can be considered as the critical association concentration and the saturation binding concentration, respectively. In this concentration range, a strong rise in pH (from 3.18 to 3.50) suggested that surfactant–polymer binding occurred mainly through a stoichiometric hydrogen-bonding interaction between the oxyethylene and carboxylic groups. In the presence of carbopol, the concentration of Tween 80 at the air/water interface decreases as the surfactant is adsorbed onto the polymer and drawn into the bulk solution. In contrast, the interaction with the polymer seems to change the conformation of the expanded chains of Pluronic F-127, making it easier for more molecules of surfactant to be at the interface and increasing the thickness of the interfacial surfactant layer. Fluorescence probes indicated that the carbopol network presents a more apolar medium than pure water, and the differences in the hydrophile–lipophile balance (HLB) of each surfactant were responsible for the lower I_I/I_{III} values obtained with Tween 80/carbopol systems. Microcalorimetry titration data made it possible to conclude that Tween 80/carbopol interaction, at 298 K, is an enthalpy-driven process due to stabilization of Tween 80 units inside the polymer network. In contrast, Pluronic F-127/carbopol association (endothermic process) occurs owing to a gain in entropy when polymer–surfactant interaction allows the restoration of free water hydrogen-bonding structure, resembling the micellization process.

Keywords: Carbopol; Tween 80; Pluronic F-127; Poly(acrylic acid)/surfactant interactions; Microcalorimetry

1. Introduction

Polymer–surfactant association is influenced by many factors including their ionic character, the hydrophobicity of the polymer and the non-polar tail of the surfactant (Rosen et al., 1998; Marques et al., 1999), the structural conformation and flexiblity of the polymer (Ritaco et al., 2000), or the presence of additives (Tsianou and Alexandridis, 1999) and salts (Rosen et al., 1998). In general, polymer–surfactant systems show a typical phase diagram with three regions depending on the relative proportions of the components (Goldraich et al., 1997; Guerrini et al., 1998). Below the critical aggregation concentration (cac), no changes are appreciable. Above the cac but below critical micellar concentration (cmc), if the polymer concentration is lower than its entanglement

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concentration, the surfactant favors the intrapolymeric interactions (each aggregate involves one polymer molecule), which causes the coiling of the polymer chain and a decrease in viscosity (Goddard, 1993). Oppositely, for polymer concentration higher than the entanglement concentration, the surfactant can act as a binding bridge among different polymer chains (interpolymeric complex), which promotes the appearance of a three-dimensional network and increases the viscosity. Above the saturation level of binding, the surfactant will form micelles that can solubilize hydrophobic regions of the polymer and the complexes, decreasing the consistency of the network and the viscosity of the system (Hansson and Lindman, 1996). In addition to viscosity, several other techniques have been used to determine the cac. However, in some cases opposite results were obtained (Benkhira et al., 2000).

The association processes between linear poly(acrylic acid) polymers and surfactants have been studied by adsorption (Kiefer et al., 1993; Shimizu, 1994), surface tension (Bromberg et al., 2000), fluorescence (Anghel et al., 1994; Oliveira et al., 1996; Schillén et al., 2000), dye solubilization (Anghel et al., 1994), and conductivity (Anghel et al., 1994; Anghel et al., 1999) methods. When the surfactant is anionic, the interaction is mainly hydrophobic and is favored when the polymer is not ionized. To maintain the electroneutrality conditions, the surfactant is accompanied by its counterions, which increase the osmotic pressure inside the aggregates and cause their swelling (Philippova et al., 1998). In the case of a cationic surfactant, the association process with poly(acrylic acid) may result in a phase separation when the carboxylic groups are neutralized by the cationic groups of the surfactant (Goldraich et al., 1997; Anthony et al., 1998). The interaction with a nonionic surfactant is usually weak except for the association of poly(acrylic acid) with ethoxylated surfactants (Anghel et al., 1994; Galatanu et al., 2000; Lin and Sung, 2000; Robb and Stevenson, 2000). In these systems, hydrogen bonding between the carboxylic groups and the oxygen of the ethyleneoxide chain contributes to the aggregation.

Carbopol microgels, which are constituted by poly(acrylic acid) cross-linked with allylsucrose or allylpentaerythritol, have numerous pharmaceutical and cosmetical applications thanks to an important thickening ability both in aqueous solutions and in polar organic solvents. In aqueous medium, an increase in pH causes repulsion among the carboxylic groups and swelling of the microgels to give an extensive gel-like structure. In non-aqueous media, the presence of a hydroxyl donor can expand the microgels through the establishment of hydrogen bonds with the carboxylic groups (Dittgen et al., 1997). The concomitant presence of surfactants in the formulations, as solubilizers or stabilizers, and in the physiological medium leads to considerable interest in the study of carbopol-surfactant interactions. The knowledge of these interactions can be useful to modulate the rheological pH-dependence of carbopol microgels and its performance as drug delivery systems (Barreiro-Iglesias et al., 2001; Paulsson and Edsman, 2001).

Although a large number of studies have examined linear poly(acrylic acid) polymers-surfactant systems, much less attention has been paid to cross-linked networks (Cole et al., 1990; Philippova et al., 1996; Ashbaugh et al., 2000; Hansson et al., 2000; Barreiro-Iglesias et al., 2001). Simovic et al. (1999) and Lin and Sung (2000) analysed the rheological behaviour of carbopol/Tween 80 and carbopol/Pluronic F-127 dispersions with high surfactant concentrations. These studies showed that, although Tween 80 caused almost no change in the viscosity, Pluronic increased it strongly. In a previous paper (Barreiro-Iglesias et al., 2002), we observed, using infrared spectroscopy and differential scanning calorimetry of films, that carbopol interaction with these surfactants depends markedly on their weight ratio and that, in fact, hydrogen bonding formation occurs with both surfactants. The aim of this work is to obtain a clearer picture of the mechanisms of interaction between carbopol and these two surfactants and to characterize the structure of the complexes formed.

2. Experimental

2.1. Materials

Carbopol® 934NF (62.6% carboxylic groups, molecular weight 3×10^6 Da) was provided by BFGoodrich Europe, UK. Polyoxyethylene 20 sorbitan monoleate (Tween® 80), polyoxyethylene–polyoxypropylene–polyoxyethylene triblock copolymer

(Pluronic® F-127) were from Sigma. Orange OT (an oil soluble dye) and pyrene (Py) were from Aldrich Chemical Co. Ultra-pure water obtained by reverse osmosis (MilliQ®, Millipore Spain) was used. The other chemicals were of analytical grade.

2.2. Preparation of carbopol/surfactant dispersions

Carbopol/surfactant samples were prepared by mixing, under stirring, concentrated carbopol and surfactant aqueous solutions at the appropriate ratio, and dilution with ultrapure water to obtain a constant carbopol concentration (0.25% (w/w)) and a wide range of surfactant concentrations (0.001–2.0% (w/w)). The systems were prepared on a surfactant percent basis rather than in molarity due to the large differences in molecular weight between Tween 80 (MW = 1310) and Pluronic F-127 (MW = 12,600). In the range of Tween 80 concentrations studied, equimolar solutions of Pluronic F-127 would be too viscous (Wesemeyer et al., 1993). The samples were left to stand at room temperature at least 24 h before measurements. All subsequent experiments were carried out in triplicate at 298.0 K.

2.3. pH

The pH measurements were made with a pHmeter Crison, model GLP22 (Barcelona, Spain), equipped with a viscous sensor (Ag/AgCl) no. 52-21.

2.4. Cloudiness

The cloudiness of dispersions was determined by measuring trasmittance at 800 nm (Shimadzu UV-240, Japan) against a blank of carbopol dispersion without surfactant.

2.5. Viscosity

Determinations of specific viscosity of carbopol-surfactant dispersions were carried out in a Cannon-Fenske capillary viscometer.

2.6. Surface tension

Surface tension measurements were made by the platinum ring method using a Lauda Tensiometer TD1 (Lauda-Königshofen, Germany) applying the needed density corrections. The concentration of surfactant at the interface (Γ) in the presence and absence of polymer was estimated applying the modified Gibbs adsorption equation (Rosen, 1989):

$$\mathrm{d}\gamma = -RT\Gamma d\ln C \tag{1}$$

in which γ is the surface tension (mJ/m^2) of a surfactant solution of molar concentration C, R is the gas constant (8.31 J/mol K), T is the absolute temperature, and Γ is the surface excess of surfactant molecules or the concentration of surfactant at the interface (mol/1000 m^2). From the surface excess concentration, the area per molecule at the interface, in square angstroms, was calculated as follows:

$$A_s = \frac{10^{23}}{N\Gamma} \tag{2}$$

where N is the Avogadro's number.

2.7. Conductivity

Conductance measurements were made in a Conductivity Meter model CDM2e (Radiometer Copenhagen, Denmark) equipped with a Crison platinum sensor (Barcelona, Spain).

2.8. Dye solubilization

An excess of Orange OT was added to a solution of surfactant with or without polymer. The system was mixed with a magnetic stirrer and stored at 298.0 K for 72 h. The non-solubilized dye was separated off by centrifugation, and the absorbance of the supernatant was determined spectrophotometrically at 495 nm (Shimadzu UV-240, Japan) against a blank of carbopol dispersion without surfactant, to subtract the small solubilizing effect due to carbopol itself.

2.9. Steady-state fluorescence measurements

Pyrene (Py) emission spectra (λ = 350–450 nm) were recorded in a Perkin-Elmer LS50B fluorescence spectrophotometer (Buckinghamshire, UK), with the excitation wavelength set to 336 nm and slits set to 5 and 2.5 for excitation and emission, respectively. Pyrene (Py) was used as a probe at 10^{-6} M, concentration low enough to prevent excimer formation in water. The samples were prepared by addition of Py solution to polymer/surfactant or surfactant only dispersions, and stored at 298.0 K for 48 h. The ratio of the intensity at the first (I_{I} at 373 nm) and the third (I_{III} at 384 m) vibronic peaks was used as an index of the local hydrophobicity of the polymer/surfactant aggregates (Oliveira et al., 1996).

2.10. Titration microcalorimetry

Calorimetric experiments were performed in duplicate using a Tronac-450 isoperibol microcalorimeter and Tronac FS101 calorimetry software (Tronac Inc., Orem, Utah). In each experiment, a 47.5 ml carbopol solution with a concentration of 0.25% (w/w) was placed in a dewar reaction vessel, and a relatively concentrated surfactant solution (15%) was loaded into a 2 ml calibrated buret. The entire assembly was then immersed into a constant temperature water bath (298.0 K). After thermal equilibration, the surfactant solution was delivered at a constant rate of 0.3332 ml/min into the reaction vessel, in which a stirrer mixed the two solutions rapidly. The rise or decrease in the temperature of the system was monitored using a thermistor, and later reproduced using a heating coil in the reaction vessel. The apparent enthalpy was calculated from the applied current and voltage and the heating time. Calibration of the system was assured by titration of tris(hydroxymethyl)aminomethane with HCl. As a blank, a diluted HCl aqueous solution of the same pH as carbopol solution (pH 3) was used instead of carbopol dispersion. To obtain the heat associated to carbopol ionization, the carbopol dispersion was titrated with ammonium acetate (0.046 M) to produce the same increase in pH as the addition of the surfactant solutions. The integral binding heat for the polymer/surfactant aggregation (Q_{agg}) process was estimated by subtracting from the measured heat produced by addition of surfactant to the carbopol dispersion (Q_{p}), the heat effects due to the dilution/demicellization of the surfactant in the HCl aqueous solution used as a blank (Q_{d}) and due to the change in the ionization degree of carbopol carboxylic groups (Q_{ion}) (Eatough et al., 1974; Killman and Melchior, 1990; Irwin et al., 1993).

$$Q_{\mathrm{agg}} = Q_{\mathrm{p}} - Q_{\mathrm{d}} - Q_{\mathrm{ion}} \qquad (3)$$

The enthalpy of carbopol dilution (final concentration was 3% lower) was negligible. The final concentration of Pluronic F-127 in the dewar was well below that required for micellar formation at the temperature of the experiment. Therefore, no interference due to phase transition should be expected in the estimation of the enthalpy (Irwin et al., 1993). From the integral heats of the reaction at different times (at least 10 points were used), ΔH_{agg} and the apparent binding equilibrium constant (K_{agg}) were estimated, using FS101 software, by iterative convergence applying the least squares technique (Eatough et al., 1974). Using K_{agg}, the Gibbs energy changes (ΔG_{agg}) per mole surfactant adsorbed was estimated.

$$\Delta G_{\mathrm{agg}} = -RT \ln K_{\mathrm{agg}} \qquad (4)$$

3. Results and discussion

3.1. Cloudiness and viscosity

During sample preparation, an important change in the aspect and consistency of the systems depending on the amount of surfactant added was observed. Fig. 1 shows that for both nonionic surfactants a strong decrease in transmittance and viscosity occurs as the surfactant proportion in the sample increases. Around 0.2% surfactant, macroscopic aggregates were shown in the 0.25% carbopol dispersion and viscosity could not be measured. A further increase in surfactant did not modify the transmittance but the aggregates were not perceptible, and the viscosity could be measured again. Carbopol/Tween 80 systems had a minimum in viscosity for 0.6% Tween 80, while carbopol/Pluronic F-127 showed the minimum at 0.3% surfactant. The decrease in viscosity may be attributed to intrapolymeric interactions favored by surfactant binding, which cause a shrinking of the polymer microgels (Fig. 2). Changes in the intrinsic viscosity of carbopol in the absence and presence of Tween 80 and Pluronic F-127 were reported previously (Barreiro-Iglesias et al., 2001). At acid pH, carbopol intrinsic viscosity was 5.56 ± 0.75 dl/g. When Tween 80 or Pluronic F-127 was added to the medium at a concentration below cmc, intrinsic viscosity was reduced to 0.98 ± 0.01 or 0.75 ± 0.15 dl/g, respectively. Changes in intrinsic viscosity are directly

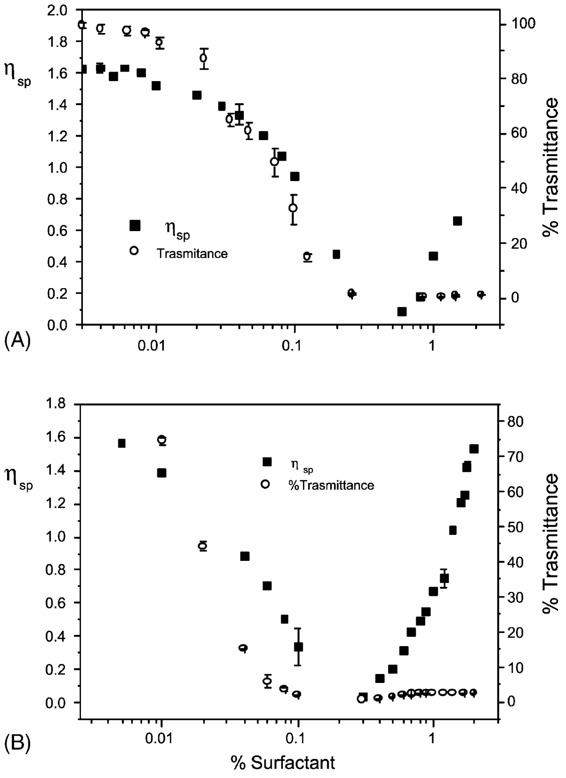

Fig. 1. Effect of Tween 80 (A) and Pluronic F-127 (B) concentration on viscosity and cloudiness of 0.25% carbopol solutions.

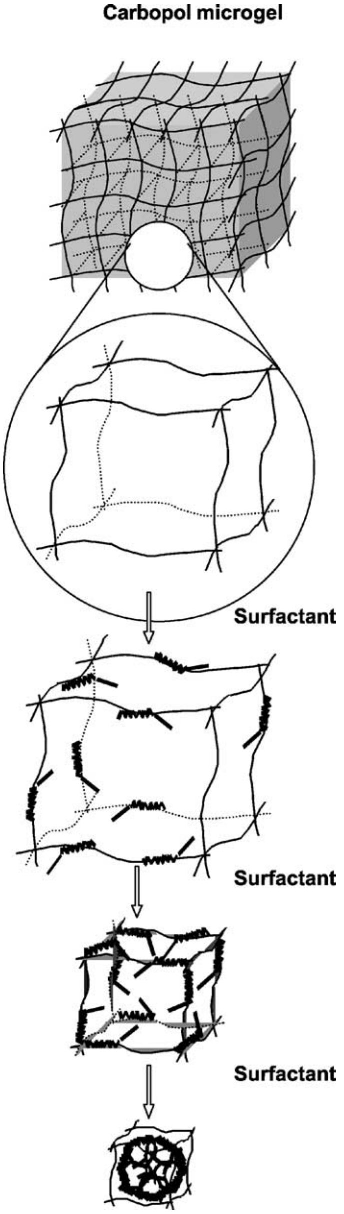

Fig. 2. Schematic representation of the changes in carbopol microgels volume caused by association process of a nonionic surfactant. Carbopol microgels size ranged from 800 to 12000 nm (BF Goodrich, 1994) while nonionic surfactant micelles ranged from 2 to 8 nm (Wanka et al., 1994).

related to the variation in the hydrodynamic volume of the polymer. Fig. 2 is an attempt to explain graphically the decrease in viscosity (Fig. 1) caused by surfactant absorption. The scheme is also consistent with the data obtained using the techniques described below. Above saturation, surfactant aggregates may involve several carbopol microgels and free micelles appear, which may be responsible for the increase in viscosity. Previous studies performed on linear poly(acrylic acid) and hexaethylene glycol monododecyl ether or octaethylene glycol monododecyl ether showed a similar pattern (Anghel et al., 1994). The surfactant concentration at which the viscosity begins to diminish is related to the cac, while the viscosity minimum may correspond to the saturation binding.

Considering the number of ethyleneoxide groups per molecule of each surfactant (Porter, 1994; Alexandridis et al., 1994), 0.5% Tween 80 gives 0.0763 mol ethyleneoxide per liter while 0.3% Pluronic F-127 provides 0.0476 mol ethyleneoxide per liter. These values are close to the 0.0348 mol carboxylic groups contained in 1 l of 0.25% carbopol solution. This observation suggests an almost stoichiometric hydroxyl/carboxyl binding in the saturation region.

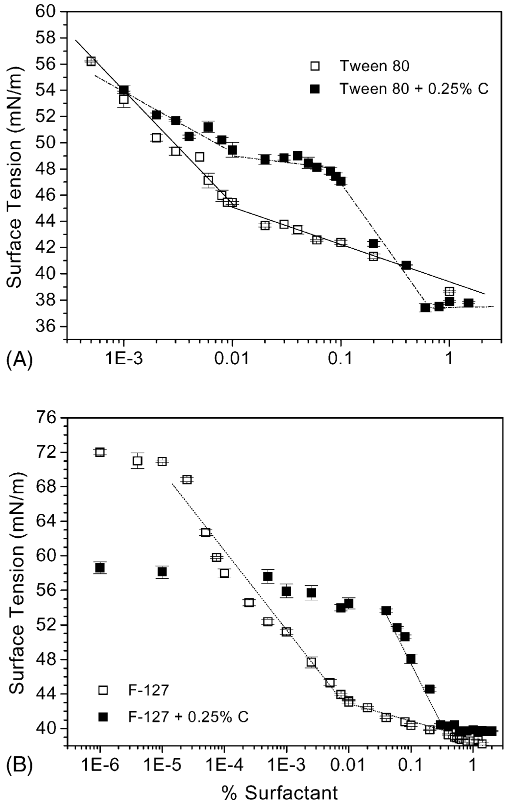

Fig. 3. Surface tension of aqueous solutions of Tween 80 (A) and Pluronic F-127 (B) in the absence and presence of 0.25% carbopol.

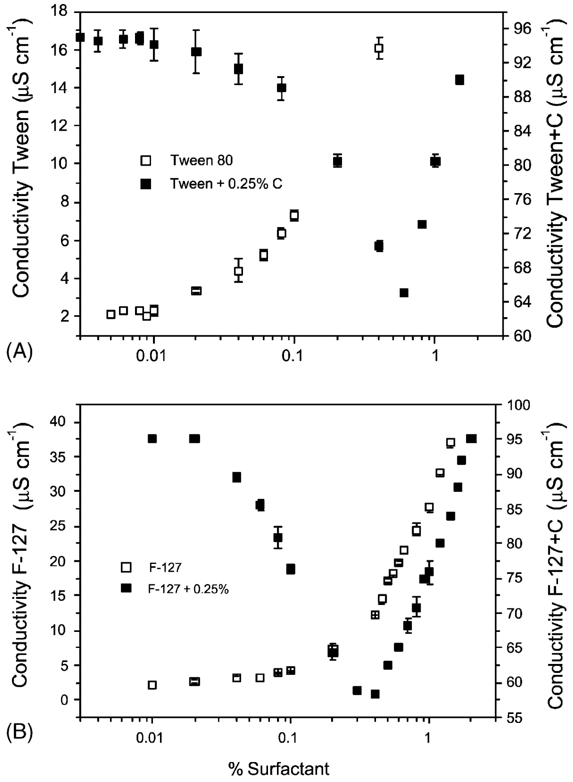

Fig. 4. Conductivity of aqueous solutions of Tween 80 (A) and Pluronic F-127 (B) in the absence and presence of 0.25% carbopol.

3.2. Surface tension, conductivity, and pH

Both surfactant and carbopol/surfactant dispersions were analyzed simultaneously in order to discriminate the effects of carbopol/surfactant interaction. The cmc for Tween 80 and Pluronic F-127 in pure water can be established by surface tension and conductivity to be around 0.02 and 0.50%, respectively (Figs. 3 and 4). In general, when the surface tension of a surfactant solution is plotted against the logarithm of the surfactant concentration, the plot shows an initial curved segment, for very low surfactant concentrations, followed by a linear segment, along which there is a sharp decrease in surface tension up to the cmc of the surfactant is reached. In this region the surface excess is constant as the bulk concentration increases, and the surface area occupied per surfactant molecule may be calculated using Gibbs equation (Eqs. (1) and (2)) (Rosen, 1989). In the case of Tween 80 systems, this region corresponds to 0.001–0.01% surfactant (Fig. 3A). However, for Pluronic F-127 only solutions two points of inflection were observed, at 0.02 and 0.50% (Fig. 3B). These two breaks in the curves have been attributed to changes in the size and shape of Pluronic aggregates (Prasad et al., 1979) or to the inherent broad molecular distribution of the copolymers (Wanka et al., 1994). The last inflexion point is coincident with the value identified, in this paper, as cmc using other techniques, and with the values previously reported by different authors (Alexandridis et al., 1994). According to Bahadur and Pandya (1992), for this surfactant the Gibbs adsorption equation was applied to the surface tension values obtained at concentrations below the first inflection point.

The surface tension plots of 0.25% carbopol/Tween 80 systems showed several regions. Below the cac, surface tension was higher than for the surfactant alone. The cac (0.01%) can be identified by the beginning of an almost flat region, which corresponds to the situation when the surfactant added is bound to the polymer. After this region, the excess of surfactant remains free, which decreases surface tension. In the case of Pluronic F-127, surface tension values in the presence of 0.25% carbopol remained above the values obtained for the surfactant alone. An increase in surface tension values of the final region was also found by Maloney and Huber (1994) in solutions of polyethyleneglycol nonionic surfactants in the presence of linear poly(acrylic acid)s, and was attributed to a disturbance of the interfacial surfactant layer by coadsorption of the polymer. Compared to linear poly(acrylic acid), the surface activity of carbopol was greater and caused a stronger modification in the surface tension of surfactant solutions. Surface tension measurements of several poly(acrylic acid) solutions in a similar range of concentrations resulted in values of 67–68 mN/m (Maloney and Huber, 1994), while 0.25% carbopol solution presented 60 mN/m. Additionally, in the presence of linear poly(acrylic acid), the surface tension of nonionic surfactant solutions and their concentration dependence remain essentially unaffected (Anghel et al., 1994; Maloney and Huber, 1994; Anghel et al., 1999). The cross-linked network of carbopol microgels may provide a more hydrophobic microenvironment, promoting nonionic surfactant–polymer interactions.

In the case of Tween 80 (Fig. 3A), the concentration dependence of the surface tension in the presence of 0.25% carbopol presented an initially lower slope than for the surfactant alone. In contrast, in the case of Pluronic F-127, the decrease in surface tension was greater. From these slopes and applying Eq. (1), the surface excess of surfactant molecules or the concentration of surfactant at the interface (Γ) and the area per molecule at the interface were calculated. As can be seen in Table 1, molecular areas of both surfactants were similar in the absence of carbopol but the effect of the presence of the polymer was opposite.

In the presence of carbopol, the concentration of Tween 80 at the air/water interface decreases as the surfactant is adsorbed onto the polymer and drawn into the bulk solution. This explains the high surface tension during the plateau region. In contrast, the interaction with the polymer seems to make it easier for more Pluronic F-127 molecules to be at the interface. It has been reported that the large area values of Pluronic surfactants are due to the hydrated coiled chains of poly(ethylene oxide) (Prasad et al., 1979; Wanka et al., 1994). In the case of Pluronic F-127, the molecular area showed in Table 1 was similar to the value found by Bahadur and Pandya (1992) for Pluronic P-94 (128 Å^2 interface area/molecule), in spite of having a different number of poly(ethylene oxide) units at each side; 24 in the case of Pluronic P-94 versus 100 in Pluronic F-127 (Alexandridis et al., 1994). When the long hydrated poly(ethylene oxide) chains interact with the carbopol microgels, the surfactant may change its conformation to surround the polymer. This folding would be responsible for a reduction in the area occupied per molecule and for an increase in the thickness of the interfacial surfactant layer, which justifies the higher surface tension values compared to those of the surfactant alone in solution (Maloney and Huber, 1994).

The conductivity plots (Figs. 4A and B) showed that surfactant micelles have greater mobility than the corresponding surfactant monomers and that the high conductivity of carbopol decreases strongly as the surfactant is added to the medium. The minimum in conductivity was reached when using 0.6% Tween 80 or 0.4% Pluronic F-127. Above these concentrations, free surfactant micelles could be formed and conductivity increased again. The lower conductivity of the

Table 1
Surface excess and area per molecule of Tween 80 and Pluronic F-127 aqueous dispersions in the presence and absence of 0.25% carbopol; mean value (standard deviation)

System	Surface excess (mol/m^2)	Area per molecule (Å^2)
Tween 80	1.43×10^{-6} (0.07×10^{-6})	116 (6)
Tween 80 + carbopol	0.71×10^{-6} (0.09×10^{-6})	233 (32)
Pluronic F-127	1.29×10^{-6} (0.06×10^{-6})	128 (6)
Pluronic F-127 + carbopol	2.34×10^{-6} (0.18×10^{-6})	71 (5)

Gibbs equation (Eq. (1)), correlation coefficients (r) > 0.99.

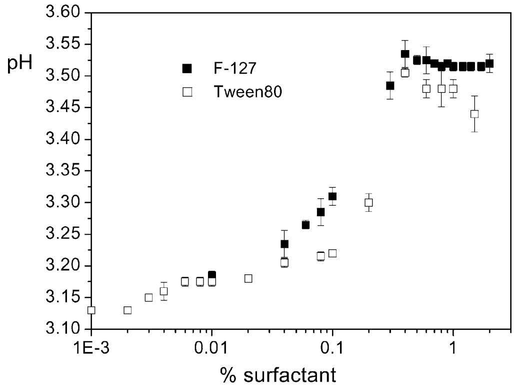

Fig. 5. pH changes observed in 0.25% carbopol solutions after addition of different amounts of nonionic surfactant.

polymer–surfactant aggregates may be partially related to the binding mechanism. If hydrogen-bonding interaction occurs, the degree of dissociation of the carbopol carboxylic groups decreases and fewer ions remain free in the medium (Anghel et al., 1994). This hypothesis was clearly confirmed by the changes in pH observed in the samples (Fig. 5).

To corroborate that the increase in pH is due to the polymer–surfactant interaction and not to the mixing of solutions of different pHs (surfactant solutions have a pH close to neutrality), a control experiment consisting of adding each pure surfactant directly to the carbopol solution was carried out, and the same change in pH was observed. In both cases, pH raised from 3.18 to 3.50 when the concentration of any of both surfactants increased from 0.01 to 0.30%, although the pattern depended on the surfactant showing the above commented differences in the cac and saturation concentration. The final plateau region, reached at 0.3% surfactant, may also indicate that above this surfactant concentration, further binding is driven mostly by hydrophobic interactions of the surfactant chains (Anghel et al., 1999).

The strength of the interaction with carbopol can be estimated as the free energy per mole surfactant for the reaction: free micelle ↔ polymer-bound micelle, as follows (Wang et al., 1997; Singh and Nilsson, 1999):

$$\Delta G_{\mathrm{i}} = RT \ln(\mathrm{cac}/\mathrm{cmc}) \tag{5}$$

where cac is the critical aggregation concentration and cmc the critical micellar concentration of the surfactant estimated by the techniques described above.

Table 2
Critical association concentration (cac), critical micellar concentration (cmc) and free energy of interaction per mole of surfactant (ΔG_{i}) in 0.25% carbopol solution

Surfactant	cac (mM)	cmc (mM)	ΔG_{i} (kJ/mol)
Tween 80	0.076	0.153	−1.716
Pluronic F-127	0.048	0.397	−5.250

Table 2 illustrates the greater strength of the interaction between carbopol and Pluronic F-127.

3.3. Dye solubilization and fluorescence probe measurements

One of the most important properties of surfactants that is directly related to micelle formation is solubilization of hydrophobic substances (Rosen, 1989). The hydrophobicity inside surfactant–polymer aggregates is usually measured by the changes in the emission spectra of pyrene in aqueous solution (Oliveira et al., 1996). Solubilization of pyrene into a hydrophobic environment is detected by the decrease in $I_{\mathrm{I}}/I_{\mathrm{III}}$ ratio. The changes in $I_{\mathrm{I}}/I_{\mathrm{III}}$ as a function of surfactant concentration (Fig. 6) showed that carbopol provides a more hydrophobic environment than pure water. Upon addition of increasing amounts of surfactant, there was an initial flat region until a sharp fall of the $I_{\mathrm{I}}/I_{\mathrm{III}}$ ratio occurred and then it remained constant again. The decrease in $I_{\mathrm{I}}/I_{\mathrm{III}}$ began at 0.002% Tween 80 or 0.10% Pluronic F-127, while the final plateau was obtained with 0.02% Tween 80 or 0.50% Pluronic F-127. These values again demonstrate the different cac and binding saturation concentration of both surfactants. The final $I_{\mathrm{I}}/I_{\mathrm{III}}$ value was also different, showing that the polarity sensed by pyrene differs significantly whether it is solubilized in Tween 80/carbopol aggregates or Pluronic F-127/carbopol aggregates. This effect is probably caused by the higher hydrophile–lipophile balance of Pluronic F-127 (HLB = 22) compared to Tween 80 (HLB = 15) (Porter, 1994). In consequence, their capacity to solubilize hydrophobic substances may be different.

Orange OT solubilization could not be put into practice in the case of Pluronic F-127 since the resulting system was too cloudy to measure Orange OT absorbance. In the case of Tween 80, as was expected,

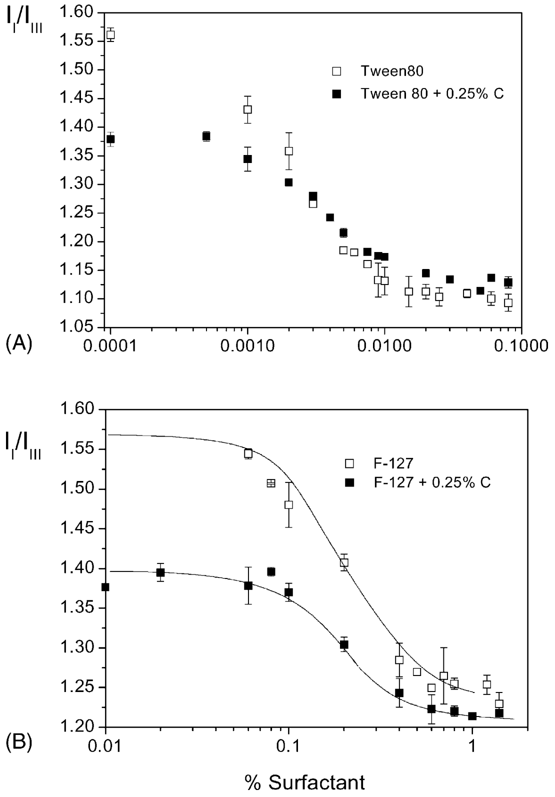

Fig. 6. Ratio of the first to third vibronic peaks of pyrene as a function of Tween 80 (A) and Pluronic F-127 (B) concentration in the absence and presence of 0.25% carbopol.

the presence of carbopol improved strongly the solubilizing properties of the system (Fig. 7).

3.4. Microcalorimetric titration

The thermodynamics of the interaction between the nonionic surfactants and carbopol was investigated using isoperibol titration microcalorimetry at 298.0 K. Recent studies have shown that calorimetry may provide detailed information about polymer–surfactant interactions (Kevelam et al., 1996; Wang et al., 1997; Singh and Nilsson, 1999). The changes in temperature measured after addition of a concentrated surfactant solution to a polymer solution can be regarded as the sum of the following contributions (Singh and Nilsson, 1999):

(a) Dilution of surfactant and demicellization process;
(b) Dilution of polymer;

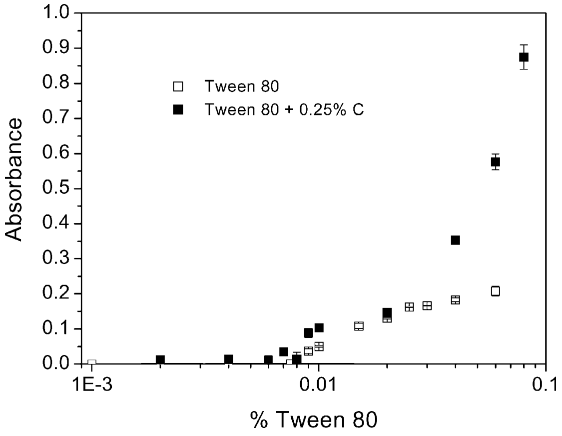

Fig. 7. Orange OT absorbance recorded in Tween 80 solution alone or containing 0.25% carbopol.

(c) Binding between surfactant and polymer, which may be accompanied by changes in solvation, conformation, and ionization degree of both components;
(d) Interactions between aggregates through adjacent surfactant or polymer molecules.

Fig. 8 shows the calorimetric titration profiles for carbopol solutions with Tween 80 (Fig. 8A) and Pluronic F-127 (Fig. 8B) along with the corresponding dilution curves of each surfactant in an aqueous solution of the same pH as carbopol dispersion (HCl aq, pH 3). Both surfactants are in micellar form in the 15% (w/w) solution placed in the buret. After injection into the HCl aqueous solution, the micelles break up and the monomers separate. In both cases the demicellization process was exothermic (enthalpy change negative), especially for Pluronic F-127, and the demicellization enthalpy decreased as the concentration in the dewar approached the cmc. Differently from most ionic surfactants, the micellization of polyoxyalkylene surfactants at room temperature is strongly endothermic (Kevelam et al., 1996). The micellization process, although enthalpically unfavorable, occurs spontaneously due to entropy-driven hydrophobic interactions, in which core (polyoxypropylene)-shell (polyoxyethylene) structures are formed (Alexandridis et al., 1994). In the case of Pluronic surfactants, the exothermic dilution process is attributed to the result of hydrogen-bonding formation between the triblock copolymer and water after breakage of water–water

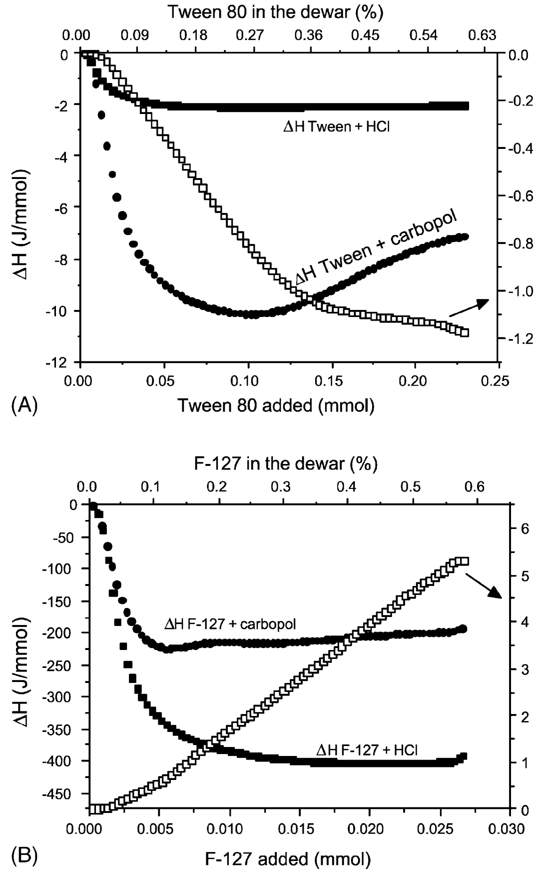

Fig. 8. Calorimetric titration curves observed during addition of small volumes of 15% Tween 80 (A) or Pluronic F-127 (B) into a dewar containing 0.25% carbopol solution. The corresponding dilution plots of each surfactant into diluted HCl solution (pH 3) are also given. Open circles represent the difference between the heat evolved in the presence and absence of carbopol, Q_{agg}.

and surfactant–surfactant hydrogen-bonds (Irwin et al., 1993). The apparent enthalpy change observed for demicellization of Pluronic F-127 ($\Delta H_d = -410$ kJ/mol) is in agreement with previously reported micellization enthalpies obtained using differential scanning calorimetry (Chu and Zhou, 1996). No data were found for Tween 80. Although the structure of Tween 80 is clearly different, its lower demicellization enthalpy may be attributed to the lack of segments as hydrophobic as polyoxypropylene.

In the presence of carbopol, exothermic peaks were also observed. The apparent enthalpy for Tween 80/carbopol interaction was more exothermic than the dilution of the surfactant. In contrast, in the case of Pluronic F-127 the heat evolved in the dewar containing carbopol was lower than the values obtained in pure water, suggesting that the binding process is endothermic. The heat changes observed during the calorimetric titration include all the processes that occur during the addition of surfactant solution to carbopol solution; i.e. dilution of surfactant and carbopol solutions, change in the ionization degree of carbopol, binding, changes in conformation of both polymer and surfactant molecules, ... All those processes, except the dilution effect (negligible in the case of carbopol), are characteristic of the interaction process under given conditions and should be taken into account. The addition of the surfactant solution causes a small increase in pH (Fig. 5). The heat associated to the ionization process was estimated by titration with ammonium acetate. The enthalpy of carbopol ionization was small (−0.770 kJ/mol acid groups) and close to the values reported for different carboxylic weak acids (Eatough et al., 1974). The integral heat of reaction, Q_{agg}, was estimated as the difference between the heat evolved in the presence of carbopol and the sum of the heats associated to the dilution/demicellization of the surfactant and the ionization process of carbopol carboxylic groups.

The initial flat region in Q_{agg} (Fig. 8) corresponds to a surfactant concentration below the cac. Once cac is reached (0.01% Tween 80 and 0.06% Pluronic F-127), an almost constant decrease (exothermic) or increase (endothermic) in Q_{agg} was observed for Tween 80 and Pluronic F-127, respectively. Above certain surfactant concentration, the binding reaches the saturation and no changes in Q_{agg} were observed. The data were reproducible and variation lower than 2% were observed. The analysis of the slope using iterative software made it possible to obtain the binding constant and the thermodynamic parameters summarized in Table 3. The surfactant–polymer interaction

Table 3
Thermodynamic parameters for nonionic surfactant–carbopol aggregation, expressed per mole of surfactant and mole of polymer

Surfactant	K_{agg}	ΔG_{agg} (kJ/mol)	ΔH_{agg} (kJ/mol)
Tween 80	33.11	−8.643	−243256
Pluronic F-127	17.38	−7.051	+505267

Standard deviations were in all cases lower than 2%.

process is in general a cooperative binding process in which the binding constant (K_{agg}) may change as the surfactant is adsorbed (Goddard, 1993). Although in the analysis of heats of reaction, Tronac FS-101 software assumed a constant value for K_{agg}, it was proved previously (Eatough et al., 1974) that this process is accurate and that the value obtained is a reliable best apparent K_{agg}. The different order of magnitude of ΔG_{agg} and ΔH_{agg} impeded a precise estimation of ΔS_{agg}. Nevertheless, the results showed in Fig. 8 and Table 3 suggest that Tween 80/carbopol interaction is an enthalpy-driven process, while Pluronic F-127/carbopol association (endothermic) should occur thanks to the gain in entropy. The aggregation process to some extent resembles the micellization process, especially for Pluronic F-127. In the case of Tween 80, the exothermic surfactant–polymer interaction may be attributed to an increase in stability of Tween 80 monomers when they adsorb onto carbopol (Kevelam et al., 1996).

The values obtained for ΔG_{agg} were higher than for ΔG_{i}, and both were in the same order of magnitude as those obtained for nonionic polymers interacting with nonionic or ionic surfactants through hydrogen-bonding, van der Waals or London-dispersion forces (Wang et al., 1997; Singh and Nilsson, 1999).

4. Conclusions

Complex formation between Tween 80 or Pluronic F-127 with carbopol occurs mainly through hydrogen-bond interactions and is accompanied by important changes in the conformation of both components. The cross-linked network of carbopol seems to create a more favorable microenvironment than linear poly(acrylic acids) for interacting with nonionic surfactants. The initial adsorption of surfactant onto carbopol microgels favors polymeric interactions. Those interactions, in detriment of polymer–water and surfactant–water interactions, collapse the polymer network when an almost stoichiometric relationship between the carbopol carboxylic groups and the surfactant ethyleneoxide groups is reached. An excess of surfactant contributes to partially solubilize those aggregates. These observations explain the previous reported changes in viscous and elastic moduli of these systems (Barreiro-Iglesias et al., 2001). The results also suggest that Tween 80 is drawn into the bulk solution by the carbopol microgels, while in the case of Pluronic F-127 coadsorption into the interfacial layer is also possible. The higher molecular weight and core-shell conformation of Pluronic F-127 compared to Tween 80 is also responsible for the different enthalpy–entropy compensation behavior of the aggregation process. Enthalpically driven complexation, such as in the case of the small Tween 80, is characteristic of a tight host–guest inclusion through nonpolar interactions, which results in a strong entropy loss (Wang et al., 1997). The complex formed in the case of carbopol–Pluronic F-127 resembles the micellization process of this surfactant and may not be so tight, resulting in favorable entropy. There is an enthalpic cost to introduce the nonpolar regions of polymer in surfactant clusters and there may be a small entropic cost due to the localization of the chains in the micelle. However, this is compensated by the entropy gain from a decrease in the degree of structuring of the water molecules around the hydrophobic segments, which restore the water hydrogen-bonding structure, increasing the water entropy.

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References

Alexandridis, P., Holzwarth, J.E., Hatton, T.A., 1994. Micellization of poly(ethylene oxide)-poly(propylene oxide)- poly(ethylene oxide) triblock copolymers in aqueous solutions: thermodynamics of copolymer association. Macromolecules 27, 2414–2425.

Anghel, D.F., Saito, S., Iovescu, A., Baran, A., 1994. Some critical points in the interaction between homogeneous non-ionic surfactants and poly(acrylic acid). Colloids Surfaces A 90, 89–94.

Anghel, D.F., Winnik, F.M., Galatanu, N., 1999. Effect of the surfactant head group length on the interactions between polyethylene glycol monononylphenyl ethers and poly(acrylic acid). Colloids Surfaces A 149, 339–345.

Anthony, O., Marque, C.M., Richetti, P., 1998. Bulk and surface behavior of cationic guars solutions of oppositely charged surfactant. Langmuir 14, 6086–6095.

Ashbaugh, H.S., Piculell, L., Lindman, B., 2000. Interactions of cationic/nonionic surfactant mixtures with an anionic hydrogel: adsorption equilibrium and thermodynamics modeling. Langmuir 16, 2529–2538.

Bahadur, P., Pandya, K., 1992. Aggregation behavior of Pluronic P-94 in water. Langmuir 8, 2666–2670.

Barreiro-Iglesias, R., Alvarez-Lorenzo, C., Concheiro, A., 2001. Incorporation of small quantities of surfactants as a way to improve the rheological and diffusional behavior of carbopol gels. J. Control. Release 77, 59–75.

Barreiro-Iglesias, R., Alvarez-Lorenzo, C., Concheiro, A., 2002. Thermal and FTIR characterization of films obtained from carbopol/surfactant aqueous solutions. J. Therm. Anal. Calorim. 68, 479–488.

Benkhira, A., Lachhab, T., Bagassi, M., Francois, J., 2000. Interactions of polyethers with a cationic surfactant. Polymer 41, 2471–2480.

Goodrich, B.F., 1994. Bulletin 17, Brecksville, Ohio.

Bromberg, L., Temchenko, M., Colby, R.H., 2000. Interactions among hydrophobically modified polyelectrolytes and surfactants of the same charge. Langmuir 16, 2609–2614.

Chu, B., Zhou, Z., 1996. Physical chemistry of polyoxyalkylene block copolymer surfactants. In: Nace, V.M. (Ed.), Nonionic surfactants. Polyoxyalkylene block copolymers, Marcel Dekker Inc., New York, pp. 67–143.

Cole, M.L., Whateley, T.L., Harrison, P.J., 1990. Interaction of non-ionic block co-polymeric (poloxamer) surfactants with poly(acrylic acid) and the application in the stabilisation of multiple emulsions, J. Pharm. Pharmacol. 42, p. 136.

Dittgen, M., Durrani, M., Lehmann, K., 1997. Acrylic polymers. A review of pharmaceutical applications. STP Pharma Sci. 7, 403–437.

Eatough, D.J., Christensen, J.J., Izatt, R.M., 1974. Experiments in Thermometric Titration and Titration Calorimetry, Brigham Young University Press, Provo, pp. 8–36.

Galatanu, A.N., Chronakis, I.S., Anghel, D.F., Khan, A., 2000. Ternary phase diagram of the Triton X-100/poly(acrylic acid)/water system. Langmuir 16, 4922–4928.

Goddard, E.D., 1993. Polymer–surfactant interactions. In: Goddard, E.D., Ananthapadmanabhan, K.P. (Eds.), Interactions of surfactants with polymers and proteins, CRC Press, Boca Raton, pp. 123–169.

Goldraich, M., Schwartz, J.R., Burns, J.L., Talmon, Y., 1997. Microstructures formed in a mixed system of cationic polymer and an anionic surfactant. Colloids Surfaces A 125, 231–244.

Guerrini, M.M., Negulescu, I.I., Daly, W.H., 1998. Interactions of aminoalkylcarbamoyl cellulosics and sodium dodecyl sulfate. J. Appl. Polym. Sci. 68, 1091–1097.

Hansson, P., Lindman, B., 1996. Surfactant–polymer interactions. Curr. Opin. Colloid Interface Sci. 1, 604–613.

Hansson, P., Schneider, S., Lindman, B., 2000. Macroscopic phase separation in a polyelectrolyte gel interacting with oppositely charged surfactant: correlation between anomalous deswelling and microstructure. Progr. Colloid Polym. Sci. 115, 342–346.

Irwin, J.J., Beezer, A.E., Mitchell, J.C., Buckton, M.G., Chowdhry, B.Z., Eagland, D., Crowther, N.J., 1993. Isothermal stability of dilute aqueous solutions of block copolymers of poly(oxyethylene)- poly(oxypropylene)-poly(oxyethylene): a microcalorimetric study of pluronic F87 and pluronic F88. J. Phys. Chem. 97, 2034–2036.

Kevelam, J., van Breemen, J.F.L., Blokzijl, W., Engberts, J.B.F.N., 1996. Polymer–surfactant interactions studied by titration microcalorimetry: influence of polymer hydrophobicity, electrostatic forces, and surfactant aggregational state. Langmuir 12, 4709–4717.

Kiefer, J.J., Somasundaran, P., Ananthapadmanabhan, K.P., 1993. Interaction of tetradecyltrimethylammonium bromide with poly(acrylic acid) and poly(methacrylic acid). Effect of charge density. Langmuir 9, 1187–1192.

Killman, K., Melchior, W., 1990. Microcalorimetric adsorption enthalpies of ethylene oxide and propylene oxide copolymers from carbon tetrachloride and water on pyrogenic silica. Progr. Colloid. Polym. Sci. 83, 84–95.

Lin, H.R., Sung, K.C., 2000. Carbopol/pluronic phase change solutions for ophthalmic drug delivery. J. Control. Release 69, 379–388.

Maloney, C., Huber, K., 1994. Mixtures of polyacrylic acid and nonionic surfactants at the water/air interface. J. Colloid. Interface Sci. 164, 463–470.

Marques, E.F., Regev, O., Khan, A., Miguel, M.G., Lindman, B., 1999. Interactions between catanionic vesicles and oppositely charged polyelectrolytes-phase behavior and phase structure. Macromolecules 32, 6626–6637.

Oliveira, V.A., Tiera, M.J., Neumann, M.G., 1996. Interaction of cationic surfactants with acrylic acid-ethylmethacrylate copolymers. Langmuir 12, 607–612.

Paulsson, M., Edsman, K., 2001. Controlled drug release from gels using surfactant aggregates: I. Effect of lipophilic interactions for a series of uncharged substances. J. Pharm. Sci. 90, 1216–1225.

Philippova, O.E., Chtcheglova, L.A., Karybiants, N.S., Khokhlov, A.R., 1998. Two mechanisms of gel/surfactant binding. Polym. Gels Networks 6, 409–421.

Philippova, O.E., Hourdet, D., Audebert, R., Khokhlov, A.R., 1996. Interaction of hydrophobically modified poly(acrylic acid) hydrogels with ionic surfactants. Macromolecules 29, 2822–2830.

Porter, M.R., 1994. Handbook of Surfactants, 2nd ed. Blackie Academic & Professional, London.

Prasad, K.N., Luong, T.T., Florence, A.T., Paris, J., Vaution, C., Seiller, M., Puisieux, F., 1979. Surface activity and association of ABA polyoxyethylene-polyoxypropylene block copolymers in aqueous solution. J. Colloids Interface Sci. 69, 225–232.

Ritaco, H., Albouy, P.A., Bhattacharyya, A., Langevin, D., 2000. Influence of the polymer backbone rigidity on polyelectrolyte-surfactant complexes at the air/water interface. Phys. Chem. Chem. Phys. 2, 5243–5251.

Robb, I.D., Stevenson, P., 2000. Interaction between poly(acrylic acid) and an ethoxylated nonionic surfactant. Langmuir 16, 7168–7172.

Rosen, M.J., 1989. Surfactants and Interfacial Phenomena, 2nd ed. Wiley, New York, pp. 64–83.

Rosen, O., Sjöström, J., Piculell, L., 1998. Responsive polymer gels based on hydrophobically modified cellulose ethers and their interactions with ionic surfactants. Langmuir 14, 5795–5801.

Schillén, K., Anghel, D.F., Miguel, M.G., Lindman, B., 2000. Association of naphthalene-labeled poly(acrylic acid) and interaction with cationic surfactants. Fluorescence studies. Langmuir 16, 10528–10539.

Shimizu, T., 1994. Changes of pH and counterion activity during the binding process of cationic surfactants to carboxylic polyions. Colloids Surfaces A 84, 239–248.

Simovic, S., Tamburic, S., Milic-Askrabic, J., Rajic, D., 1999. An investigation into interactions between polyacrylic polymers and a non-ionic surfactant: an emulsion preformulation study. Int. J. Pharm. 184, 207–217.

Singh, S.K., Nilsson, S., 1999. Thermodynamics of interaction between some cellulose ethers and sodium dodecylsulfate by titration microcalorimetry. J. Colloid Interface Sci. 213, 133–151.

Tsianou, M., Alexandridis, P., 1999. Control of the rheological properties in solution of a polyelectrolyte and an oppositely charged surfactant by the addition of cyclodextrins. Langmuir 15, 8105–8112.

Wang, Y., Han, B., Yan, H., Kwak, J.C.T., 1997. Microcalorimetry study of interaction between ionic surfactants and hydrophobically modified polymers in aqueous solutions. Langmuir 13, 3119–3123.

Wanka, G., Hoffman, H., Ulbricht, W., 1994. Phase diagrams and aggregation behavior of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) triblock copolymers in aqueous solutions. Macromolecules 27, 4145–4149.

Wesemeyer, H., Muller, B.W., Muller, R.H., 1993. Adsorption of ethoxylated surfactants on nanoparticles. Part 2. Determination of adsorption enthalpy by microcalorimetry. Int. J. Pharm. 89, 33–40.