Journal of Thermal Analysis and Calorimetry, Vol. 82 (2005) 499–505

CHITOSAN/SODIUM DODECYLSULFATE INTERACTIONS
Calorimetric titration and consequences on the behaviour of solutions and hydrogel beads

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The thermodynamics of the interaction of chitosan and sodium dodecylsulfate, SDS, was characterised by titration microcalorimetry to gain an insight into the binding process of amphiphilic molecules to this biocompatible polymer and its consequences on the behaviour of the solutions and chemically cross-linked hydrogels of chitosan. 0.2 M acetic acid was used as solvent medium, without or with 0.9% NaCl, in order to evaluate the influence of the ionic and hydrophobic interactions with two chitosans of different molecular mass and degree of deacetylation, DD. The critical micellar concentration, CMC, of SDS was ten times lower in the presence of the salt (0.35 *vs.* 3.5 mM, as estimated by surface tension measurements). Binding to chitosan (at 0.25%) began at concentrations significantly lower than CMC (critical aggregation concentration, CAC=0.035–0.17 mM) and saturation was reached at around 10 mM SDS, which corresponds to a positive/negative charges ratio of about 1. The process was in all cases enthalpy-driven (strongly exothermic) and, in the absence of the salt, also entropically favourable. The Gibbs free energy of interaction values were slightly greater for the chitosan with lower DD but greater molecular mass. The addition of increasing amounts of SDS resulted in a continuous decrease in the viscosity of chitosan solutions above the CAC, which ended in a macroscopic coacervation when around 1/3 of the positive charges were neutralised. In the same range of SDS concentrations, the hydrogel beads showed a continuous decrease in the swelling degree and a final collapsed state. The scarce tendency to redissolution or hydrogel reswelling in the presence of greater SDS concentrations can be attributed to that the binding process is mainly caused by the ionic interaction and did not go beyond the neutralisation point.

Keywords: *chitosan, isoperibol microcalorimetry, polymer/surfactant interactions, SDS, surface tension*

Introduction

Chitosan, partially deacetylated chitin, is attracting new fields of applications owing to its biocompatible and highly versatile structure [1, 2]. Chitosan is constituted by 2-acetamido-2-deoxy-β-*D*-glucopyranose, GlcNAc, and 2-amino-2-deoxy-β-*D*-glucopyranose, GlcN, residues, which relative mole ratio and sequence distribution strongly condition the properties of this biopolymer. The amino and hydroxyl groups can be also specifically modified to prepare alkylated derivatives [3] or more complex macrostructures [4]. Additionally, due to its gel- and film-forming properties, chitosan based systems are being extensively studied as drug and gene carriers [5].

The charge density along the chains and, therefore, the flexibility of chitosan can be tailored by changing the deacetylation degree, DD. These properties, together with the hydrophobicity of the backbone, may play an important role on its interactions with amphiphilic molecules, such as surfactants and certain drugs. Despite the quite random distribution of ionic and nonionic pyranoses, the binding of anionic surfactants has been shown to follow cooperative models when the content in GlcNAc residues is low. Wei and Hudson [6] observed, using selective electrodes, that the interaction of chitosan hydrobromide salts (DD of 76–92%) with sodium dodecylsulfate, SDS, becomes less cooperative and, in consequence, the amount sorbed decreases, as more nonionic GlcNAc residues separate the ionic sites. Compared to free chains in solution, the cooperativity was enhanced in cross-linked chitosan films [7]. The initially bound surfactant ions can assist the binding of subsequent surfactant molecules probably by formation of hemimicelle-type clusters or aggregates inside the polymer network [8, 9]. In a neutral medium, where chitosan amino groups are not ionised (water dispersions), Prado *et al*. [10] observed an endothermic interaction process with SDS prompted by hydrophobic sorption.

Polymer-surfactant complex formation can significantly alter the properties of solutions and hydrogels, which opens interesting possibilities for modulating their performance in different fields such as cosmetics, pharmacy [11, 12] or even robotics [13]. Many drugs and biological macromolecules (e.g. proteins) have an amphiphilic character and/or a polymeric

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1388–6150/$20.00

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structure, which enhances the importance of knowing about polymer/surfactant associations from both theoretical and practical points of view. The viscoelastic character of polymer solutions and the volume of gel pieces have been shown to be dramatically altered by the presence of amphiphilic molecules [14, 15].

The aim of this study is to gain an insight into the thermodynamics of the interaction of chitosan and SDS, in a good-solvent acidic medium in which the amino groups are ionised, and its repercussions on the properties of chitosan systems. SDS, in addition to be a common surfactant, is used as a microbicide in the acidic vaginal environment; some of the formulations being gels made of acrylic bioadhesive polymers that enhance the permanence on the application site [16]. Since bioadhesive properties of chitosan are well known, its potential utility in this field is evident. Additionally, surfactants can be involved in the preparation of polymer beads and microparticles [17]. To carry out this work, two chitosan brands of different DD were chosen and diluted acetic acid was used as solvent medium in order to evaluate the influence of DD on the ionic and hydrophobic interactions with SDS. The presence of salts, at isoosmotic concentration with physiological fluids, was also considered.

Experimental

Materials and methods

Materials

Two commercially available chitosan brands were used; Chit-F from Georges S. Daras S.A. (France, chitosan 222, batch 991012) and Chit-I from Marine Chemicals (India, batch MI/OA/270/FC/99/4294). SDS was from Sigma Aldrich Chemical Co., USA. Glutaraldehyde (25% in water) was from Merck Co., Germany. Purified water by reverse osmosis (MilliQ®, Millipore Spain) with a resistivity above 1.82 MΩ cm was used.

Structural characterization of chitosan

Infrared spectroscopy: IR spectra were recorded over the range 400–4000 cm^{-1}, in a Bruker IFS 66V FT-IR spectrometer (Germany), using the potassium bromide pellet technique.

Degree of deacetylation: The elemental composition was determined using a Carlo-Erba 1108 Elemental Analyzer (Fisons Instruments). Since carbon/nitrogen ratio (C/N) varies from 5.145 in completely N-deacetylated chitosan to 6.861 in the fully N-acetylated chitin [18], the degree of deacetylation was calculated according to:

$$DD = 100 - \frac{C/N - 5.145}{6.861 - 5.145} \cdot 100 \quad (1)$$

Intrinsic viscosity, mean molecular mass and overlapping concentration: The viscosity of chitosan solutions in 0.5 M acetic acid/0.25 M NaCl (0.02, 0.04, 0.06, 0.08 or 0.10 g dL^{-1}) at 25°C was measured in a Cannon-Fenske capillary viscometer (Afora Spain, six determinations per concentration). Intrinsic viscosity ([η]) was estimated by fitting Martin's equation to the results thus obtained. Mean molecular masses were then estimated from the [η] values using the Mark–Houwink equation with constants K and a set to $2.14 \cdot 10^{-3}$ and 0.657, respectively [19]. Overlapping concentration was estimated as the reciprocal of the intrinsic viscosity [20].

Interaction of chitosan with SDS in solution

Preparation of the solutions: Chitosan/SDS solutions were prepared by mixing, under stirring, concentrated chitosan and surfactant solutions (both prepared in 0.2 M acetic acid) at the appropriate ratio, and posterior dilution with acetic acid to obtain a constant chitosan concentration (0.25 mass%) and a wide range of surfactant concentrations (0.003–34.7 mM). Similarly, other chitosan/SDS solutions set was prepared using as solvent medium NaCl 0.9% solutions in acetic acid 0.2 M. The systems were left to stand for 24 h before characterization. All measurements were carried out at 37°C.

pH: The pH measurements were made with a pH-meter Crison, model GLP22 (Barcelona, Spain), equipped with a sensor for viscous samples (Ag/AgCl n° 52-21).

Cloudiness: The cloudiness of solutions was determined by measuring transmittance at 800 nm (Shimadzu UV-240, Japan) against a blank of chitosan solution without surfactant.

Viscosity: Determinations of specific viscosity of chitosan-SDS solutions were carried out in a Cannon–Fenske capillary viscometer (Afora, Spain).

Surface tension: Surface tension measurements were made using the platinum ring method with a Lauda Tensiometer TD1 (Lauda-Königshofen, Germany) applying the necessary density corrections [9].

Titration microcalorimetry: Calorimetric experiments were performed in duplicate using a Tronac-450 isoperibol microcalorimeter and Tronac FS101 calorimetry software (Tronac Inc., Orem, Utah), as described previously [9]. Calibration of the system was assured by titration of tris(hydroxymethyl)aminomethane with HCl ($\Delta H = -48 \pm 1$ kJ mol^{-1}). Briefly, in each experiment, a 47.5 mL chitosan (0.25 mass%) solution in 0.2 M acetic acid, with or without 0.9% NaCl, was placed in a dewar reaction vessel, and a relatively concentrated

surfactant solution (520 mM) was loaded into a 2 mL calibrated buret. The entire assembly was then immersed into a constant temperature water bath (37°C). After thermal equilibration, the surfactant solution was delivered at a constant rate of 0.3332 mL min^{-1} 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 current and voltage applied and the heating time. As a blank, 0.2 M acetic acid was used instead of chitosan solution. The enthalpy of the chitosan dilution (final concentration was 3% lower) was negligible. The enthalpy of micellization (ΔH_{mic}) and of aggregation (ΔH_{agg}) were estimated directly, from the plots of the recorded enthalpy *vs.* surfactant concentration, at the critical micellar concentration (CMC) and critical aggregation concentration (CAC), respectively, and the enthalpy associated to the polymer/surfactant interaction (ΔHi) was estimated from

$$\Delta Hi=\Delta H_{agg}-\Delta H_{mic} \quad (2)$$

Similarly, ΔG_{mic}, ΔG_{agg} and ΔGi were calculated using the following expressions [21, 22]:

$$\Delta G_{mic}=(1+K)RT\ln(CMC) \quad (3)$$

$$\Delta G_{agg}=(1+K)RT\ln(CAC) \quad (4)$$

$$\Delta Gi=\Delta G_{agg}-\Delta G_{mic} \quad (5)$$

where K is the effective micellar charge fraction of SDS, which is approximately 0.85 [21]. Values of the entropy, ΔS_{mic}, ΔS_{agg} and ΔSi were then derived from the appropriate values of ΔH and ΔG.

Interaction of chitosan hydrogels with SDS

Preparation of the beads: Hydrogel beads were prepared by simultaneous cross-linking/insolubilisation as previously reported [23]. Briefly, 10 g of chitosan solution (1.5 mass% in 0.2 M acetic acid) were mixed with 0.090 mL glutaraldehyde (25% in water) for 30 s and, then, were dropwise added to a NaOH 1.5 M solution. After 15 min in this solution, the beads obtained were washed for several days with ultrapure water.

Swelling in SDS solutions: Swollen beads were immersed in SDS solutions of different concentration. The degree of swelling of the beads in each medium was followed using a zoom stereo microscope Olympus (SZ-6045-TR-F) equipped with a color videocamera DP12 (Olympus, Japan). The areas of the projected surface of the particles, analysed with DP-SOFT software, were referred as percentage of those of freshly prepared beads.

Results and discussion

Some structural parameters of the two chitosan brands are shown in Table 1. Chit-F presents a lower degree of deacetylation (DD) and a greater molecular mass than Chit-I. The differences in DD were also clearly seen in the FTIR spectra (data not shown); Chit-F featuring sharper amide bands at 1659 and at 1559 cm^{-1}, and a less intense primary amine band at 1597 cm^{-1} [1, 23, 24]. This means that Chit-I has more free amino groups in its structure and a higher overlapping concentration, as estimated from the inverse of the intrinsic viscosity (0.169% *vs.* 0.105% for Chit-F), and its solutions are notably less viscous. Owing to the influence of being below or above the overlapping concentration on the intensity and repercussions of the interactions with surfactants [12, 25], we selected for the study a fix polymer concentration of 0.25%, to ensure that both chitosans were above the overlapping concentration. The 0.2 M acetic acid medium provides a good solvent and an almost constant pH of around 3.2–3.4, at which chitosan behaves as a cationic polyelectrolyte [18].

Interaction of chitosan solutions with SDS

As SDS concentration increased, the chitosan solutions underwent a typical phase separation [26]; large aggregates were observed to begin to be formed at different SDS concentrations depending on chitosan grade and NaCl concentration in the medium. In Chit-I solutions, coacervation began at around 3.47 mM SDS in both the absence or the presence of the salt; redissolution was only observed above 17.34 mM SDS in 0.9% NaCl medium. In Chit-F solutions, coacervation was induced by 0.34 mM SDS in both media and redissolution was not observed, in any case, even increasing SDS concentration up to 34.7 mM. This behaviour can be attributed to different critical aggregation and saturation concentrations, CAC and SC, respectively.

The surface tension values obtained for SDS solutions in 0.2 M acetic acid without and with 0.9% NaCl are shown in Fig. 1. The critical micellar concentration, CMC, of SDS was ten times lower in the presence of the

Table 1 Structural characteristics of the chitosans; mean (standard deviation)

Chitosan	N/%	C/N	DD/%	Intrinsic viscosity/dL g^{-1}	Molecular mass
Chit-F	7.07	5.55	76.2	9.55 (1.00)	359000 (11000)
Chit-I	7.84	5.41	84.6	5.90 (0.91)	172000 (10000)

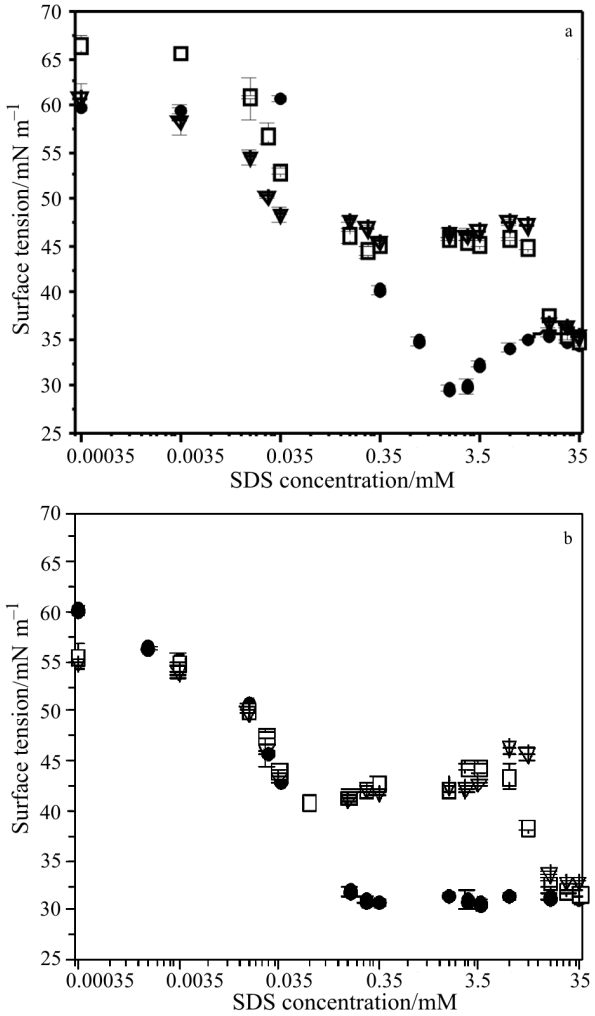

Fig. 1 Effect of SDS concentration on surface tension of 0.25% chitosan solutions in 0.2 M acetic acid, a – without and b – with 0.9% NaCl. Legend: ● – medium without chitosan, □ – Chit-I and ▽ – Chit-F

salt (0.34 *vs*. 3.4 mM), as expected from the increase in the ionic strength of the medium [27, 28]. In the presence of chitosan, a plateau region, which determined the CAC, began at concentrations below CMC. The presence of more SDS caused the surface tension to reach the values observed for the surfactant only solutions. The value at which the plateau region ends and converges on SDS solution values is considered the saturation concentration, SC (Table 2). Considering the content in free amino groups (deacetylated) of each polymer, the CAC for Chit-I corresponds to a positive/negative charges mole ratio of 85 and 68, in the absence and presence of 0.9% NaCl, respectively. For Chit-F, this ratio was around 278 and 55 under the same conditions. In the SC, the positive/negative charges ratio was of about 1, for both polymers and conditions. Therefore, the surfactant begins to absorb onto the polymer at a concentration well below the CMC, and the process ends at the surfactant concentration needed to neutralise all amino groups of chitosan. For other cationic polysaccharides, such as cationic cellulose ethers, the SC was above the amount needed to neutralise the charges of the polymer, suggesting the concomitance of both electrostatic and hydrophobic polymer/SDS interactions [15]. In the case of chitosan, under the conditions of the experiments, the SC values obtained indicate that the SDS binding stops near the charge neutralisation conditions. This explains that chitosan-SDS complexes show a weak tendency for redispersion at greater SDS concentration, as found also by Dèdinaitè and Ernstsson [29]. In contrast, in most polyelectrolyte-surfactant systems, surfactant can be bound to the complexes and redissolution is complete due to repulsion between recharged complexes [15].

The chitosan/SDS sorption behaviour was macroscopically evidenced as a sharp decrease in the viscosity of the solutions once the CAC was reached (Fig. 2). No recovery of the viscosity was observed at SDS concentrations above SC.

To obtain information about the thermodynamics of surfactant micellization and polymer–surfactant aggregation, microcalorimetric measurements were carried out. Microcalorimetry has a growing interest in pharmaceutical development [30–32] and microcalorimetric titrations are particularly useful to analyse interactions in water medium among different substances [9, 21, 22, 28]. Figure 3 shows the apparent enthalpies associated to the demicellization, the interaction with chitosan, and the micellization of SDS in 0.25% chitosan solutions without (a) or with (b) 0.9% NaCl. Before being added to the dewar, SDS was at 520 mM in the burette, i.e. above its CMC. Therefore, when the surfactant solution was slowly added to the acetic acid solution, the micelles broke up until the concentration in the dewar reached CMC. In subsequent addition, micelles were only diluted in a solution of micelles. SDS demicellization process was endothermic, especially in the absence of salt, while micelle dilution was slightly exothermic. The apparent

Table 2 Critical aggregation concentration (CAC), saturation concentration (SC), and thermodynamic parameters for SDS-chitosan aggregation in 0.2 M acetic acid

Chitosan	CAC/ mM	CS/ mM	ΔH_{agg}/ kJ mol^{-1}	ΔHi/ kJ mol^{-1}	ΔG_{agg}/ kJ mol^{-1}	ΔGi/ kJ mol^{-1}	ΔS_{agg}/ J mol^{-1} K^{-1}	ΔSi/ J mol^{-1} K^{-1}
Chit-F	0.139	10.4	–4.5	–11.0	–9.4	–15.3	+15.8	+14.0
Chit-I	0.035	10.4	–4.0	–10.5	–16.0	–21.9	+38.7	+37.0

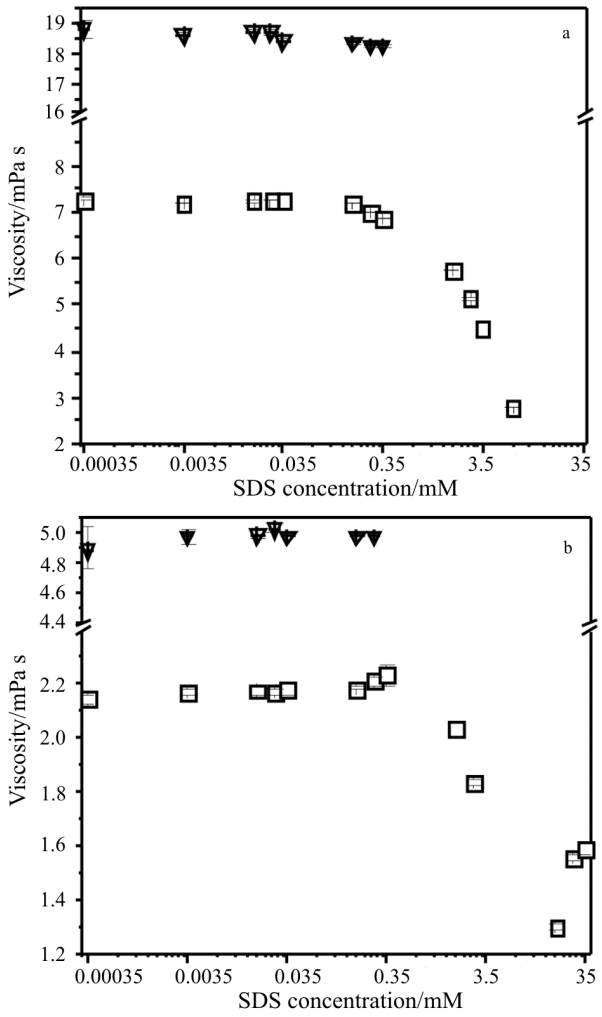

Fig. 2 Effect of SDS concentration on viscosity of 0.25% chitosan solutions in 0.2 M acetic acid, a – without and b – with 0.9% NaCl. Legend: □ – Chit-I and ▽ – Chit-F

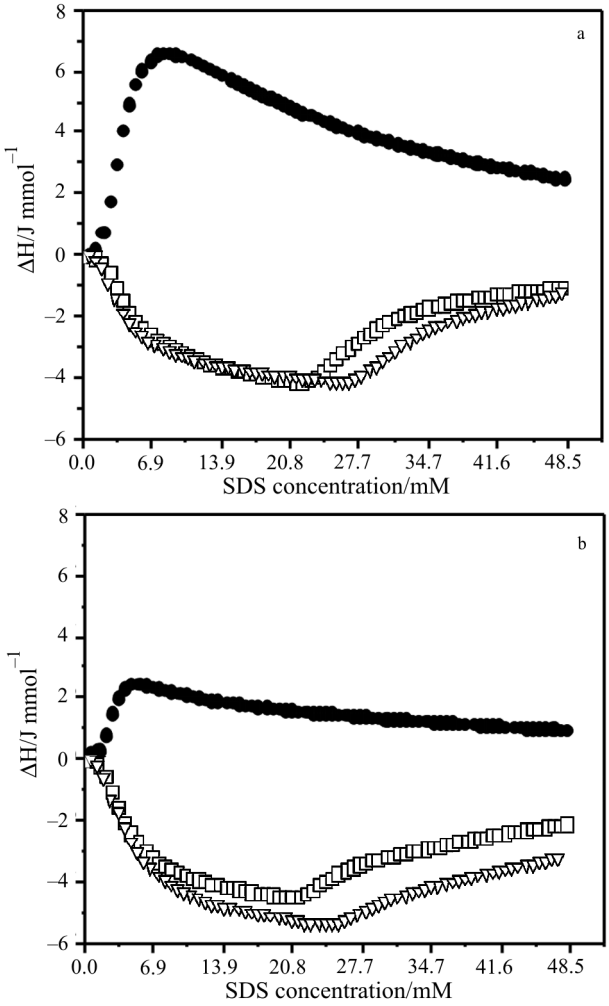

Fig. 3 Calorimetric titration curves recorded during addition of small volumes of 15% SDS into a dewar containing chitosan solutions in 0.2 M acetic acid, a – without and b – with 0.9% NaCl. Legend: □ – Chit-I and ▽ – Chit-F. The corresponding dilution plots of ● – SDS into 0.2 M acetic acid solutions are also given

enthalpy of micellization of SDS in acetic acid solution without salt (ΔH_{mic}= –6.5 kJ mol^{-1}) was greater than in the presence of 0.9% NaCl (ΔH_{mic}= –2.3 kJ mol^{-1}). This may be explained by the higher associative capacity of this surfactant in the presence of salts (lower CMC), which implies that the dilution process is accompanied by the breakage of a lower number of micelles than in the absence of NaCl. In consequence, the endothermic process reaches the maximum at lower SDS concentrations in the presence of salts [28].

When the SDS solution was added to chitosan solutions, the initial endothermic step almost disappeared, which indicates that as the micelles break up, the surfactant units interact electrostatically with the polymer, which is a strongly exothermic process. In the presence of Chit-I, the maximum binding enthalpy was reached around 12–14 mM SDS. In the case of Chit-F, the maximum heat evolved corresponded to a slightly greater concentration, 14–15 mM. Nevertheless, the enthalpy associated to the interaction process was similar for both chitosan brands (Tables 2 and 3).

The results shown in Fig. 3 and Tables 2 and 3 indicate that, for both chitosans, the interaction with SDS is enthalpy-driven and, in the absence of salt, is also entropically favourable. This results in a greater free energy of interaction in acid medium without NaCl. The decrease in affinity in the presence of 0.9% NaCl (i.e. greater CAC and lower ΔHi and ΔGi) is explained by the screening effect of the counterions [6]. Nevertheless, it is also important to note that a salt concentration isoosmotic with most biological media, is not enough to hinder the strong ionic interaction.

In any medium, Chit-F showed a slightly greater affinity for SDS than Chit-I. The former has a greater molecular mass and more hydrophobic sites (less

Table 3 Critical aggregation concentration (CAC), saturation concentration (SC), and thermodynamic parameters for SDS-chitosan aggregation in acetic acid 0.2 M with NaCl 0.9%

Chitosan	CAC/ mM	CS/ mM	ΔH_{agg}/ kJ mol^{-1}	ΔHi/ kJ mol^{-1}	ΔG_{agg}/ kJ mol^{-1}	ΔGi/ kJ mol^{-1}	ΔS_{agg}/ J mol^{-1} K^{-1}	ΔSi/ J mol^{-1} K^{-1}
Chit-F	0.173	10.4	–4.5	–6.8	–8.3	–3.3	+12.4	–11.3
Chit-I	0.173	10.4	–5.5	–7.8	–8.3	–3.3	+9.2	–14.5

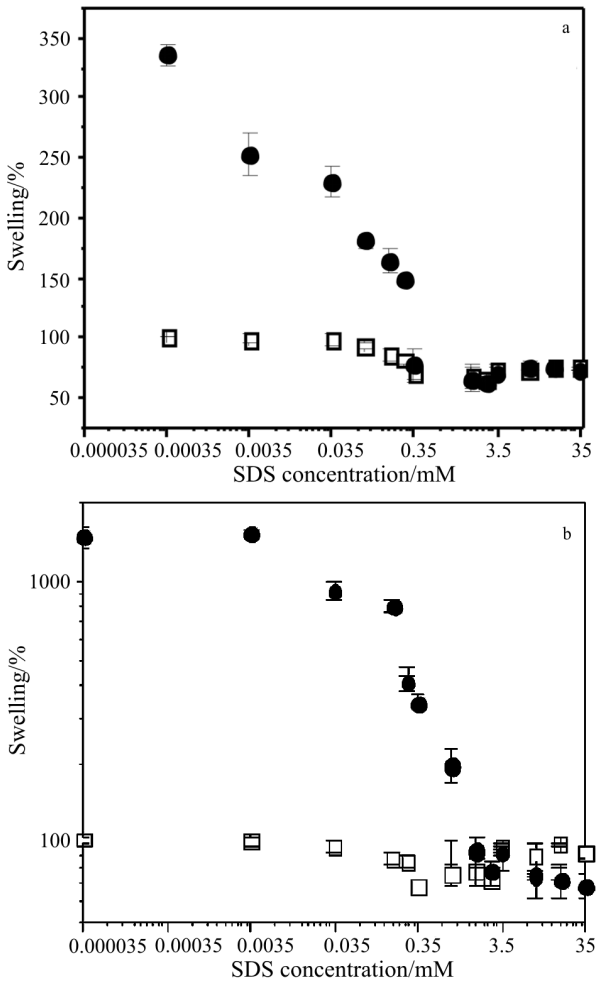

Fig. 4 Effect of SDS concentration on the swelling degree of chitosan beads made of a – Chit- I or b – Chit-F. Before the experiment, the beads were swollen □ – in water or ● – in 0.1 N HCl

N-deacetylated groups), which may induce a more cooperative binding owing to the establishment of hydrophobic interactions with the surfactant. This explains the higher contribution of the entropic component to the interaction with this chitosan [10, 28].

This interaction behaviour is clearly different from that previously reported for SDS with dispersions of chitin and chitosan in water (amino groups not ionised), with which only hydrophobic bonds with the surfactant can be established and, in consequence, the process is strongly endothermic and entropically driven [10]. Increasing the proportion of ionic groups in the polymer (when immersed in acetic acid), a more intense binding of oppositely charged surfactant occurs, and the process changes from being entropically driven to enthalpically driven. This explains the opposite calorimetric behaviour of chitosan in water and in acetic acid. Similarly, SDS association to non-ionic hydroxyethylcellulose is endothermic [22] but to the cationic derivatives of this cellulose ether, which are strongly ionised in water, is exothermic [15].

Interaction of chitosan hydrogels with SDS

Chitosan beads have a notable interest as drug carriers. The content in water and, in consequence, the volume of the beads may be dramatically altered by the presence of the surface-active substances, both common surfactants or amphiphilic drugs. This can affect their drug loading/release performance. Additionally, the monitoring of volume phase-transition of hydrogels in the presence of surfactants provides quick and useful information to predict the interaction process in solution [14, 15, 33]. To carry out the experiments, the beads were prepared as described elsewhere [23] and swollen in water or in HCl 0.2 M. Then they were transferred to SDS solutions of different concentrations. In acidic medium, the beads were significantly more swollen than in water owing to the ionisation of chitosan amino and imine (C=N) groups (Fig. 4). In any case, above a SDS concentration of 0.17 mM a strong decrease in volume was observed. In the region of 0.35–3.5 mM the minimum in volume was reached.

During surfactant absorption three simultaneous process can occur: a) water flow from inside the hydrogel towards the surrounding medium, or vice versa, owing to differences in osmotic pressure; b) surfactant diffusion towards the inside of the hydrogel due to a chemical gradient; and c) polymer-surfactant binding [33]. The neutralisation of the protonised amino groups of chitosan beads by SDS molecules decreases the osmotic pressure inside the bead, which shrinks. The SDS concentration at which the decrease in volume becomes apparent is coincident with the CAC observed in the solutions (Figs 1 and 2). Some recovery in volume was only observed for beads swollen in water at SDS concentration close to its CMC (8.7 mM). This behaviour may be attributed to the hydrophobic adsorption of surfactant micelles by the hydrogel [15, 33].

Conclusions

SDS association with chitosan in solution, with or without NaCl, begins at concentrations significantly lower than CMC and saturation is mainly reached when the positively charged amino groups of the polymer are neutralised. The association was in all cases enthalpy-driven and, in the absence of the salt, also entropically favourable. The influence of the DD and molecular mass of chitosan, in the range evaluated, was little relevant. Only slightly greater Gibbs free energy of interaction values were observed for Chit-F (lower DD and greater molecular mass). The addition of increasing amounts of SDS resulted in a continuous decrease in the viscosity of chitosan solutions above the CAC, until when 1/3 of the polymer amino groups were neutralised. At this point, a macroscopic coacervation occurred. In the same region of SDS concentrations, the hydrogels showed a continuous decrease in the swelling degree and a final collapsed state, respectively. The results obtained indicate that the ionic interactions are the main contribution to the chitosan/SDS association, and that the tendency to redissolution or hydrogel reswelling owing to further sorption of SDS is scarce.

Acknowledgements

This work was financed by the Xunta de Galicia, Spain (PGIDIT02BTF20302PR, PGIDIT03PXIC20303PN) and by the Ministerio de Ciencia y Tecnología, Spain (SAF2002-03440; RYC 2001/8).

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DOI: 10.1007/s10973-005-7244-0