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CALORIMETRIC APPROACH TO TETRONIC/WATER INTERACTIONS

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Tetronic® comprises X-shaped copolymers formed by four poly(propylene oxide) (PPO) and poly(ethylene oxide) (PEO) block chains bonded to an ethylene diamine central group. Micellization behaviour of three representative Tetronics (T304, T904 and T1307) was characterized to gain an insight into the interactions between the copolymer unimers and the state of water in their solutions. The enthalpy of demicellization, recorded at 37°C in an isoperibol microcalorimeter, indicated that the process was in all cases exothermic and the enthalpy ranked in the order T1307≥T904>>T304. Micellization is entropy-driven owing to hydrophobic interactions between the PPO chains.

DSC analysis showed that the crystallization and melting peaks of the free water remaining in T304 and T904 solutions were progressively shifted toward lower temperatures as the surfactant proportion increased, owing to a colligative effect. Bound water corresponded to 3 water molecules per EO repeating unit. In the case of T1307, which has longer PEO chains, a splitting of the melting peak was observed, one peak appearing around 0ºC due to free water and another at –15°C due to interfacial water. As T1307 proportion raised, the enthalpy of the former decreased, whilst the enthalpy of the latter increased. In 40% T1307 solutions, interfacial water overcame the proportion of free water; there being 1 interfacial and 3 bound water molecules per EO repeating unit. Gaussian deconvolution of FTIR spectra also enabled to characterize the evolution of free water as a function of Tetronic proportion. The dependence of micellization and water interaction behaviour on Tetronics structure should be taken into account to use these copolymers as drug solubilizers and micellar carriers.

Keywords: *bound water, DSC, free water, FTIR, interfacial water, isoperibol calorimetry, micellization enthalpy, poloxamine surfactants, poly(propylene oxide)-poly(ethylene oxide) block copolymers*

Introduction

The Tetronic® is a family of surfactants based on X-shaped copolymers formed by four poly(propylene oxide) (PPO) and poly(ethylene oxide) (PEO) block chains bonded to an ethylene diamine central group. The sizes of both the PEO and PPO blocks can be independently modified giving rise to a wide range of HLB values. These surfactants, also known as poloxamines or Synperonics and first introduced in the 1950's by BASF (New Jersey, USA), are well-known as wetting agents, dispersants, thickeners, and emulsifiers for different industrial purposes. Tetronics have mainly found application in the industry of petroleum for the preparation of drilling well fluids and the phase-separation of naturally occurring water-oil emulsions [1]. Tetronics play an important role in the withdrawing of water, since otherwise the high salt content and tendency to form emulsions of greater viscosity than that of the dehydrated oil would provoke corrosion and engineering problems. Although less studied in the biomedical and pharmaceutical fields, Tetronics have also been evaluated at relatively lower concentrations, at which they are non-toxic, as matrices for tissue engineering [2], excipients for transdermal administration [3], and components in nanoparticle engineering [4]. Surface-adsorbed Tetronic can provide steric stabilization and modify the biodistribution of orally or parenterally administered drug-loaded nanoparticles [5, 6]. For any of these purposes, the efficacy of a surfactant is intimately linked to its ability to interact with water, which determines the solubility, the free/bound water ratio, and the self-associative phenomena. In the case of Tetronics the paucity of data is notable. There is only some information regarding micellization in aqueous solutions of Tetronic 908 obtained by photon correlation spectroscopy [7], Tetronic 701 by DSC [8, 9], and Tetronic 704 by nuclear magnetic resonance and fluorescence spectroscopy [10].

The aim of this work was to characterize the micellization/demicellization processes by isoperibol microcalorimetry of several Tetronics, of different total and relative contents in PEO and PPO blocks, and to determine the state of the water and the microstructure of the surfactant solutions by DSC and FTIR analysis [11, 12]. This information is essential for foreseeing the potential of Tetronics as drug

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solubilizers and micellar carriers [13–15], field in which they have not been explored yet. It has been recently shown that aqueous solutions containing colloidal vesicles, such as micellar systems or microemulsions, have composition-dependent freezing temperatures and that the smaller the diameter of the droplets, the lower the freezing temperature is [16, 17]. Therefore, a detailed DSC analysis of the behaviour of the surfactant-based system during the cooling was carried out to obtain information about the microstructure of Tetronic solutions [16].

Experimental

Materials

Tetronic® 304, 904 and 1307 ($((OE_aOP_b)_2NCH_2CH_2N(OP_bOE_a)_2)$) were from BASF Corporation (New Jersey, USA) and used as received. Purified water (resistivity>18.2 MΩcm; MilliQ®, Millipore Spain) obtained by reverse osmosis was used.

Methods

Isoperibol microcalorimetry

Experiments were performed in triplicate using a Tronac-450 isoperibol microcalorimeter and Tronac FS101 calorimetry software (Tronac Inc., Orem, Utah). In each experiment, 47.5 mL of water were placed in a Dewar reaction vessel, and a relatively concentrated surfactant solution (10%) was loaded into a 2 mL calibrated buret. The entire assembly was then immersed into a constant temperature water bath (310.0 K). 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. The change 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.

Surface tension measurements

Surface tension of 10% Tetronic solutions in water was determined by the platinum ring method, using a Lauda Tensiometer TD1 (Lauda-Königshofen,Germany) and applying the required density corrections.

Differential scanning calorimetry (DSC)

Tetronic solutions were prepared, at various proportions, by vigorous mixing of both components in hermetically closed vials, and then stored at room temperature for 24 h before examination. The experiments were carried out, in triplicate, using a DSC Q100 (TA Instruments, New Castle, DE, USA) with a refrigerated cooling accessory. Nitrogen was used as purge gas at a flow rate of 50 mL min^{-1}. The calorimeter was calibrated for baseline using no pans, for cell constant and for temperature using indium (melting point 156.61°C, enthalpy of fusion 28.71 J g^{-1}), and for heat capacity using sapphire standards. Samples were sealed in the aluminium pans and then cooled to –45°C and heated to 70°C, at 5°C min^{-1}, to determine the amounts of free water and freezing (interfacial) water [18, 19]. The total content in water of the sample relates to the three water states (non-freezing water, W_{nf}, freezing bound water or interfacial water, W_{fb}, and free water, W_f) as follows [19]:

$$EWC(\%) = W_{nf}(\%) + W_{fb}(\%) + W_f(\%) \qquad (1)$$

The enthalpy of the melting/freezing peaks was referred to the proportion of water of each sample.

FTIR spectroscopy

The FTIR spectra of Tetronic solutions prepared as indicated above were recorded in ATR mode in the mid-IR range (4000–400 cm^{-1}) with a Mattson Cygnus-100 spectrophotometer with a resolution of 0.25 cm^{-1}, with 1000 scans per spectrum. The spectrum of pure Tetronic was used as reference in the absorbance calculations to extract its bands and to achieve only the spectrum of the water. Gaussian curve fitting was achieved with Microcal Origin 6.0 (Microcal Software Inc., Northampton MA, USA). The 3000–3800 cm^{-1} region was deconvoluted in three Gaussian curves (centred at 3330, 3450 and 3570 cm^{-1}) to estimate the contribution of the different water states to the area of this band [11].

Results and discussion

Tetronic micellization

Three Tetronic varieties were used for the study: T304 and T904 have similar HLB values (12–18) but different molecular masses; T1307 is significantly more hydrophilic (HLB>24) and presents the greatest molecular mass owing to its longer PEO and PPO blocks [20] (Table 1). Isoperibol microcalorimetry provided information about both the critical micellar concentration (CMC) of the copolymers and the energy associated to micellization. Before being added to the Dewar, the surfactant concentration in the buret (10 mass/mass%) was above the CMC, as confirmed by the low values of surface tension (<38 mN m^{-1}).

Table 1 Characteristics of the Tetronic varieties and micellization data obtained at 37°C

Tetronic	*Mw*	a	b	ΔH_{mic}/J mmol^{-1}	CMC/M
304	1650	3	4	+14.8	$2\cdot10^{-3}$
904	6700	15	17	+168	$1.5\cdot10^{-4}$
1307	18000	72	23	+208	$9.5\cdot10^{-5}$

[a]: number of EO units per PEO block; [b]: number of PO units per PPO block

Therefore, when the Tetronic solution was slowly added into water, the micelles broke up until the concentration in the Dewar reached the CMC. Then, micelles were only diluted in a solution of micelles. The demicellization process of all of these surfactants was exothermic (negative enthalpy change), although remarkable differences in enthalpy and CMC were observed depending on the copolymer variety analyzed (Fig. 1). The demicellization of T904 and T1307 was strongly more exothermic than that of T304 (Table 1). The exothermic dilution process is explained by the hydrogen-bonding formation between the PEO blocks and water, after breakage of water-water and surfactant-surfactant hydrogen-bonds [21]. The calorimetric profiles (Fig. 1) indicate that micellization is endothermic and entropy-driven. This behaviour was previously observed for other structurally related surfactants such as Pluronics [22, 23]. T304 requires a remarkably greater concentration to induce the self-associative process and, once the micelles are formed, they are easily broken by dilution. This is explained by the notably smaller length of its PPO and PEO chains.

States of water by DSC

The state of water in a surfactant solution as well as the microstructure of the system can be characterized by DSC, analyzing the enthalpy and the temperature of the water freezing in the cooling curve, and of ice melting in the heating curve [16, 17, 19, 24]. We firstly recorded the DSC pattern of the pure Tetronics in order to detect potential overlapping with phase-transition peaks of the surfactants (Fig. 2). T304 is a liquid at room temperature and does not show any freezing peak in the range of temperatures evaluated (up to –45°C). T904, which has a paste-like consistency, solidifies at 13.9°C, presenting a small exothermic peak, and then during the heating run shows two endothermic peaks at 24 and 32°C, which are related, respectively, to the softening and melting events. The variety of greater molecular mass, T1307, is solid at room temperature and just presents a deep melting peak at 52°C. Therefore, none of these events should interfere with the freezing/melting peaks of water in the surfactant solutions.

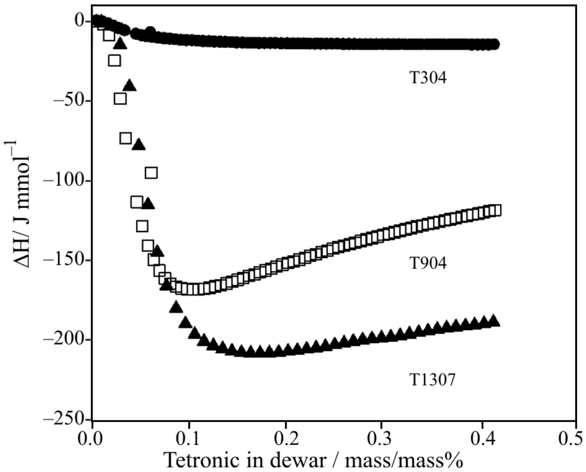

Fig. 1 Calorimetric profiles of the demicellization process of 10% Tetronic solutions when added into water at 310 K

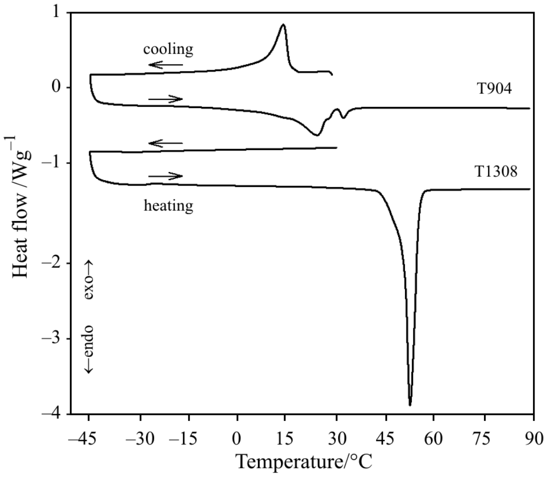

Fig. 2 DSC scans of Tetronics 904 and 1307. The data of Tetronic 1307 were shifted 1.0 W g^{-1} down in the Y-scale for a better visualization

A temperature of –40°C is commonly used as a reference to differentiate two water categories: free and bound water [25]. The water that achieves complete freezing at this reference temperature is termed free water (W_f) and it is usually quantified from the enthalpy change of the melting peak occurring around 0°C. The analysis of pure water under our experimental conditions reported a melting enthalpy of 350 J g^{-1}, which is in agreement with literature values [26]. However, in the quantification of the free water of Tetronic samples some difficulties arose. The freezing and melting peaks of water in the T304 and the T904 solutions progressively shifted toward lower temperatures as the proportion of Tetronic increased (from 0 to 40 mass/mass%) (Figs 3 and 4). As can be seen in Fig. 3 for the 50% T304 solution, the exothermic peak of crystallization (with maximum at –30°C) did not appeared during the cooling ramp, but when the heating began. The same occurred for 50% T904 system. This means that the sample has to be exposed for an extra-time at very low temperatures in order that some water can freeze. Samples prepared with 65% or more content in T304 or T904 did not show any freezing or melting peak. Water may be nonfreezable (W_{nf}) because it is bound to the surfactant through strong interactions, or exists in clusters (centered on hydrophilic groups) too small to act as a nucleus for ice formation or the stretched water is too viscous at low temperature, which results in vitrification instead of crystallization [16].

In the case of T1307, instead of recording a single peak, the melting peak split in two: one peak around 0°C with an enthalpy that decreased as T1307 proportion raised, and another peak at –15°C that, by contrast, progressively increased. The same behaviour was observed for the freezing peak, i.e. whilst the change in enthalpy of the main freezing peak at –12°C decreased as T1307 proportion increased, a secondary exothermic peak of much lower enthalpy appeared at around –30°C once the heating began

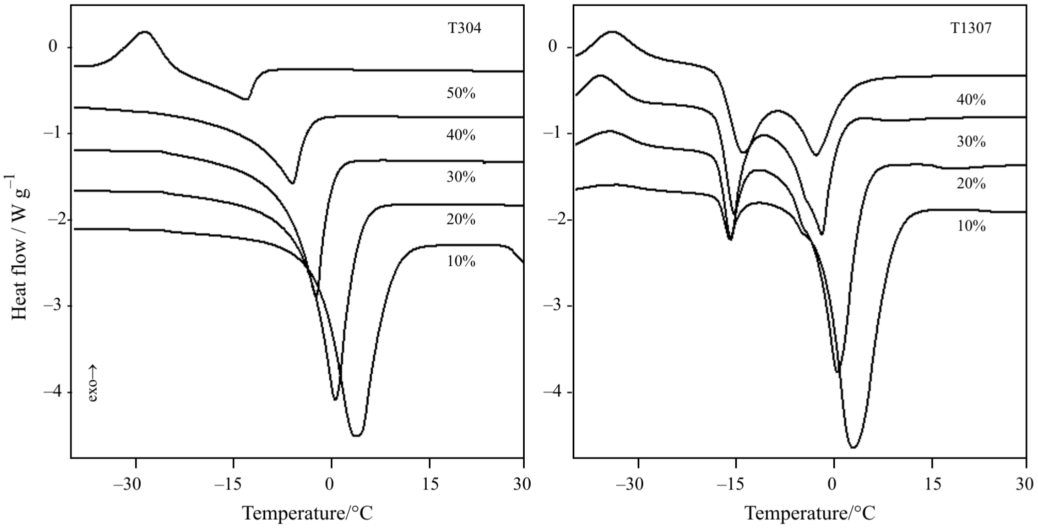

Fig. 3 DSC scans of aqueous systems prepared with the Tetronic proportions (mass/mass%) indicated in the plots. The scans were consecutively shifted 0.5 W g^{-1} down in the Y-scale for a better visualization

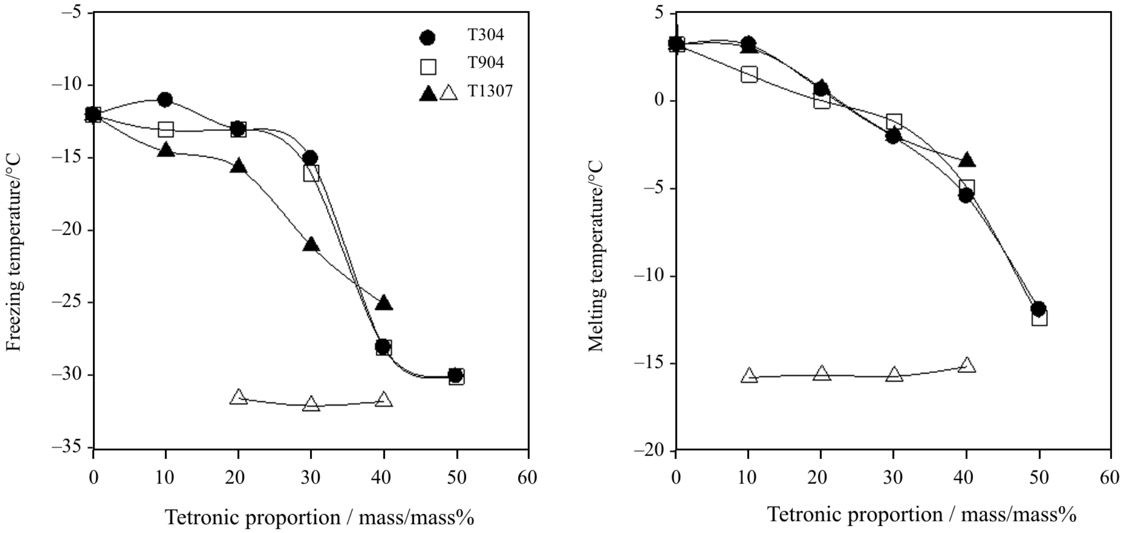

Fig. 4 Dependence of the freezing and melting temperatures on the proportion of Tetronic in aqueous solution (standard deviations of the size of the symbols). In the case of T1307, the solid and open symbols correspond to free water (W_f) and interfacial water (W_{fb}), respectively

(Figs 3 and 4). Systems with a T1307 proportion above 40% were not homogeneous, probably because of their extremely high viscosity and insufficient amount of water to fully hydrate the polymer and, therefore, were not analyzed.

The shifts in freezing and melting temperatures in surfactant solutions are in general attributed to the following factors: *i*) the colligative effect of the surfactant on the free or bulk water; *ii*) the presence of freezing-bound (interfacial) water associated to the hydrophilic surfaces of the surfactant microstructures; and *iii*) changes in size of the water domains when the surfactant concentration is sufficiently high [16, 19]. None of these factors can be disregarded in the case of Tetronic solutions. Polyoxyethylene-based non-ionic surfactants, such as PEGs, may depress the freezing and the melting point of free water below the value predicted for an ideal solution. This is particularly relevant for PEOs of low molecular mass, which can cause the free water to be supercooled at temperatures between –16 to –22°C [16]. Tetronics have, in addition to the PEO groups, amine groups in the surfactant core that raise the pH of the solutions up to 8.9–9.3. Therefore, a colligative effect may explain the progressive shift in the freezing and melting temperatures of water in the solutions prepared with the two lowest molecular mass varieties T304 and T904, but not the splitting of the peaks of T1307.

Tetronics offer to water various types of binding sites: the ethylene oxide (EO), the terminal hydroxyl groups (OH) of PEO, the propylene oxide (PO) and the amine groups. Studies carried out with PEG 600 (with 13 EO groups), revealed that two molecules of water can interact with each EO group ($N_{\mathrm{W/EO}}=2$) and another two can bind the terminal OH group, these being the two last molecules which were the most weakly bound and the first to detach from the surfactant [19, 27]. Various kinds of interfacial water (W_{fb}) have become apparent in some systems as small melting peaks at temperatures below 0°C or as shoulders of the bulk melting peak. A detailed DSC study of the behaviour of 20 to 50% PEOs (molecular mass ranging between 1000 and 20000 Da) aqueous solutions revealed that during the heating of frozen samples from –90 to 110°C various events occur: *i*) a glass-to-rubber transition at –80°C; *ii*) an exothermic crystallization at –50°C, and *iii*) two endothermic peaks, one in a temperature range of –14 to –22°C and the other at 0°C [28]. The latter was assigned to the melting of ice, whereas the former was interpreted as caused by the melting of the polymer hydrate containing two to three water molecules per polymer repeating unit [28, 29]. It is interesting to note that the melting temperature of this interfacial water was found to be dependent on the polymer molecular mass; a minimum of 8 oxyethylene units being required for detecting interfacial water [16]. This behaviour is related to the helicoidal structure adopted by large PEO chains, in which loosely-bound water molecules can be shared between adjacent segments of a single chain. This may explain the absence of the interfacial water signal in the T304 and T904 systems, owing to the shorter PEO chains compared to those of T1307. By contrast, interfacial water was evident even in the most diluted solution of T1307 (10%). As can be deduced from Fig. 3, the greater the content in T1307, the greater the change in enthalpy associated to interfacial water and also its relative proportion regarding the change in enthalpy of free water. From the enthalpies of both types of melting peaks, we have estimated the proportions of free and interfacial water in the T1307 solutions shown in Fig. 5.

A plot on the dependence of the heat of melting around 0°C on surfactant concentration gave a straight line, intercepting at 350 J g^{-1} that corresponded to the enthalpy of pure water. Similarly, the amount of water associated to this peak linearly decreased as the surfactant proportion increased and the interception occurred at 100% water. This indeed confirmed that the melting peak at 0°C corresponds to free water. Extrapolation of this line indicates that T1307 aqueous systems with surfactant concentration above 45% have no free water. This value is lower than that the ca. 65% found for T304 and T904. As shown in Fig. 5, the amount of bound water is 3 to 4 times that of interfacial water. A similar proportion has been reported for Brij 97-based microemulsions [19]. This means that there are fewer binding sites available for the formation of interfacial water or that they are not sterically accessible. One possibility could be that interfacial water corresponds to the second hydration layer of the EO groups. It has been re-

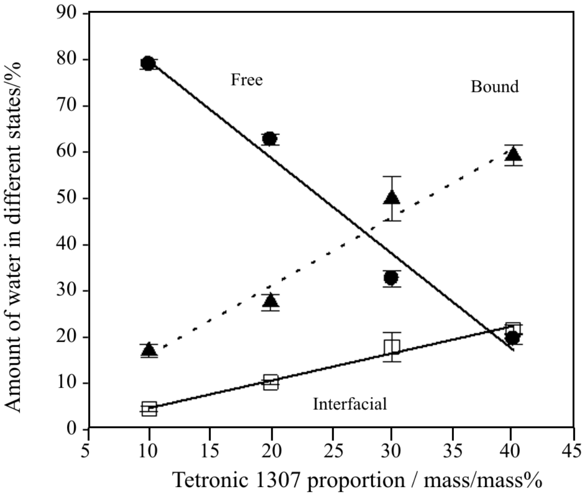

Fig. 5 Evolution of free, interfacial and bound water content on the proportion of Tetronic 1307 in the solution

ported that the lower limit of the thickness of the interfacial layer to cause a decrease in melting temperature is 0.54±0.10 nm, i.e. the equivalent to one water molecule thickness [30], and that the upper limit is between 5 and 10 nm, i.e. cooperativity of hydrogen-bonding extends up to 36 water molecules, the differences in properties between bound and bulk water being still significant [31]. The Tetronics selected for the study greatly differed in their total and relative contents in EO groups. Taking into account only the content in PEO groups of each Tetronic, in T304 and T904 there are 3.3 molecules of water bound per EO repeating unit. Since also the terminal hydroxyl groups of PEO chains and the diamine central group can strongly interact with water, the number of water molecules bound per EO repeating unit can be estimated to be 3. This value is in agreement with those found for several PEO based non ionic surfactants [16, 28, 30]. In the case of T1307, the systems containing 40% surfactant have 1 interfacial water molecule and 3 bound water molecules per EO repeating unit. The same number of interfacial water molecules was found for the other T1307 proportions evaluated, which agrees with the thickness of the interfacial water layer reported for other poly(ethylene oxide) polymers (0.5 nm, i.e. one water molecule) [30].

The analysis of the freezing peaks can also provide information about the size and shape of the water domains. In addition to the freezing peak that appeared during cooling of T1307 solutions due to the free water, a crystallization peak at –30°C was recorded during the first steps of heating, which can be attributed to the freezing of the interfacial water (Figs 3 and 4). This behaviour is explained by the fact that PEG hydrate solidifies much more slowly than free water but interfacial water cannot remain supercooled in contact with frozen water and, then, crystallizes [16]. Bogdanov and Mihailov [28] have postulated that hydrated PEG is frozen in an amorphous state which, when the temperature is raised, undergoes a glass-to-rubber transition that allows interfacial water to crystallize. Different kinds of emulsions have also shown two freezing peaks. For example, semisolid W/O emulsions stabilized by silicone surfactants showed freezing peaks at –20°C (bulk water) and –40°C (dispersed water). The finer and more monodisperse the emulsion, the more intense the peak at –40°C was [32]. Similarly, in W/O/W emulsions the water at the outer phase froze at –15°C whereas the water corresponding to the dispersed micro-sized droplets trapped in the oil globules froze at –41°C [33]. In the case of T1307, interfacial water may be mechanically trapped in the PEO chains, as reported for structurally related surfactants [34].

FTIR analysis

The Tetronic solutions were also analyzed by FTIR to obtain complementary information about the states of water [11, 35]. For this purpose the region between 3700 and 2700 cm^{-1} is the most interesting (Fig. 6). As can be seen for T304, pure anhydrous Tetronics present a C–H stretching mode region at 2800–3000 cm^{-1}, with three bands. The band with maximum at 2880 cm^{-1} can be attributed to the CH_2 symmetric and asymmetric stretching modes; and the bands at 2930 and 2970 cm^{-1} are due to the CH_3 symmetric and antisymmetric stretching modes [36]. The intensity ratio of the peaks at 2880 and at 2930 cm^{-1} (I_{2880}/I_{2930}) is sensitive to the physical state of hydrocarbon chains and can be used as a parameter

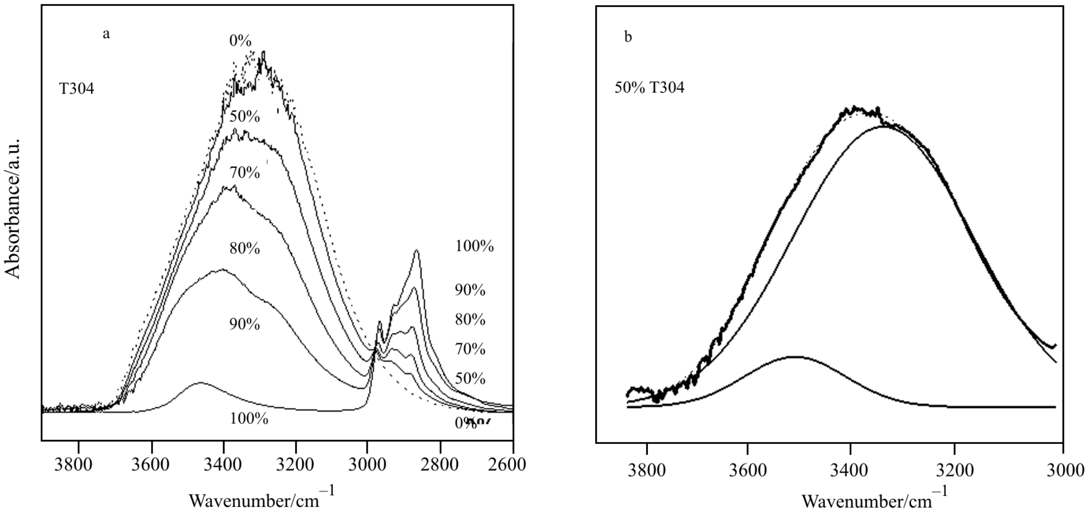

Fig. 6 FTIR spectra of a – aqueous systems prepared with the Tetronic proportions (mass/mass%) indicated in the plot; the intensity of the band 3200–3600 cm^{-1} progressively increases, whilst the intensity of the band 2800–3000 cm^{-1} diminishes, as the T304 proportion decreases. b – Gaussian deconvolution of the band 3200–3600 cm^{-1} of a system containing 50 mass/mass% T304

indicative of the degree of disorder of the copolymer. As can be seen in Fig. 6, the I_{2880}/I_{2930} decreased as the content in water of the samples increased. Similar effect on the peak height ratio was observed for other PEO-PPO-PEO surfactants and correlated with a higher population of gauche conformers in the micelle systems [35]. Thus, the decrease of the I_{2880}/I_{2930} of Tetronic in the aqueous solutions indicates that the copolymer molecules effectively interact with water, likely forming hydrogen bonds, which results in a decrease in copolymer intermolecular interactions and, therefore, a more disorder structure. The gauche conformer has a larger dipole moment and is, therefore, more soluble in water.

The dominant feature of the IR spectrum of water is the band relative to the OH stretching in the 3000–3800 cm^{-1}. To quantify the changes in this band in the Tetronic aqueous solutions, this region was deconvoluted in two or three Gaussian curves as previously proposed for the analysis of other micellar and microemulsion systems [11, 36]. The different Gaussian contributions are due to different water populations associated with a particular type of hydrogen bond. The band centered at 3300 cm^{-1} represents the so-called network water molecules, which can fully develop their ability to establish hydrogen bonds. The band centered at 3450 cm^{-1} corresponds to an intermediate state of water in which the molecules are somewhat connected to other water molecules forming short aggregates (larger than dimers or trimers but lower than the network). The band centered at 3570 cm^{-1} is ascribed to multimer water that consist of water molecules poorly connected between themselves, standing as free monomers, dimers or trimers. Once the spectrum of the water used for preparing the systems was deconvoluted, these areas represented the 90, 6.5 and 3.5% of the total area, respectively.

Tetronics show a quite low intensity band in this spectral region, which should not interfere in the analysis of the Tetronic aqueous solutions. The Gaussian deconvolution of the spectrum of T304:water systems was best fit to the sum of two areas (Fig. 6): the one with the greatest area was always centered at ca. 3300 cm^{-1}, which can be then attributed to free water; whilst the second one was progressively shifted from 3570 cm^{-1} (for 10% T304 systems) to 3470 cm^{-1} (for systems containing more than 50% T304). Figure 7 shows the evolution of the area of each peak referred to the total area as the content in T304 raises. As can be observed, the 60% content in T304 can be considered as a critical point: above such concentration a plateau exists; below that the area corresponding to the free water progressively increases as the total content in water raises. These results clearly correlate with those obtained by DSC. The other two Tetronic varieties could only be analyzed by FTIR up to 20% concentration since the solutions containing greater proportions were too viscous for a homogeneous spreading on the SeZn crystal of the ATR.

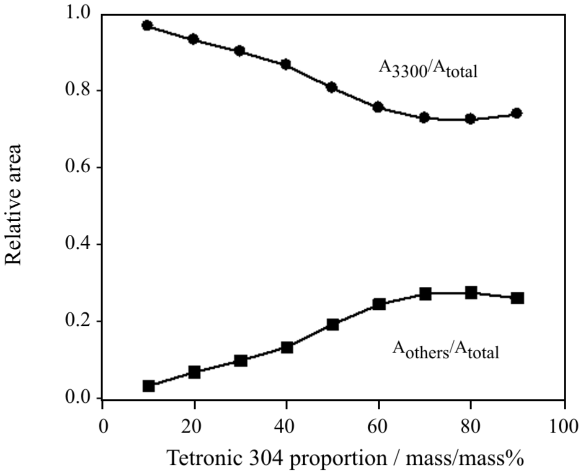

Fig. 7 Evolution of the relative areas of the deconvoluted peaks of FTIR spectra of T304 aqueous systems as a function of the content in water

Conclusions

The Tetronic varieties analyzed greatly differ in micellization enthalpy, CMC, proportion of water in each state and the maximum amount of water that the copolymer can bind. The variety of shorter PPO blocks, T304, has the lowest micellization enthalpy and greatest CMC, which indicates that these blocks are principally responsible for the self-association. By contrast, the length of the PEO chains determines the existence of interfacial water. All Tetronic varieties can bound 3 water molecules per EO repeating unit, but only T1307 presents an additional monomolecular layer of interfacial water. This means that more than 15 units of EO per block are required for visualizing the presence of interfacial water, which can be related to the possibility of PEO blocks adopting helicoidal conformation. These results show the influence of Tetronic structure on the micellization process and water interaction, which should be taken into account when these copolymers are used in drug formulation.

Acknowledgements

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