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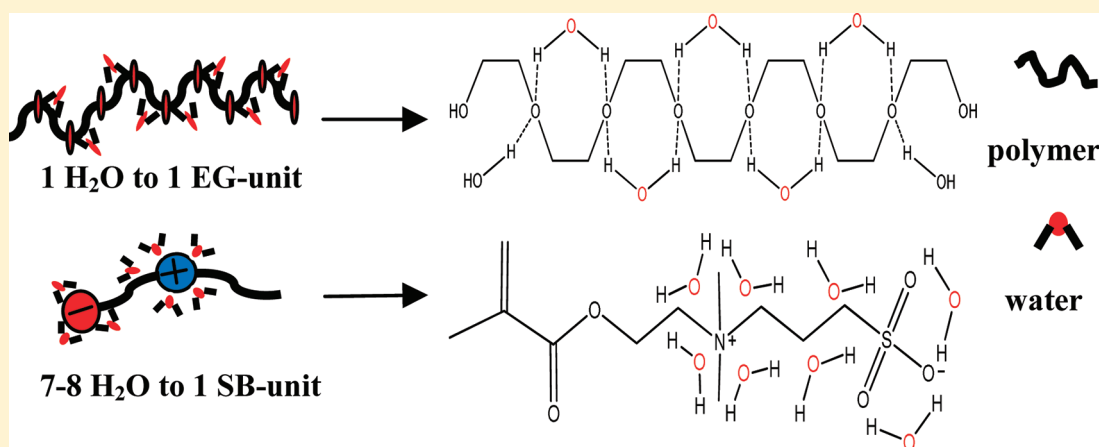
Investigation of the Hydration of Nonfouling Material Poly(sulfobetaine methacrylate) by Low-Field Nuclear Magnetic Resonance

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ABSTRACT: The strong surface hydration layer of nonfouling materials plays a key role in their resistance to nonspecific protein adsorption. Poly(sulfobetaine methacrylate) (polySBMA) is an effective material that can resist nonspecific protein adsorption and cell adhesion. About eight water molecules are tightly bound with one sulfobetaine (SB) unit, and additional water molecules over 8:1 ratio mainly swell the polySBMA matrix, which is obtained through the measurement of T_2 relaxation time by low-field nuclear magnetic resonance (LF-NMR). This result was also supported by the endothermic behavior of water/polySBMA mixtures measured by differential scanning calorimetry (DSC). Furthermore, by comparing both results of polySBMA and poly(ethylene glycol) (PEG), it is found that (1) the hydrated water molecules on the SB unit are more tightly bound than on the ethylene glycol (EG) unit before saturation, and (2) the additional water molecules after forming the hydration layer in polySBMA solutions show higher freedom than those in PEG. These results might illustrate the reason for higher resistance of zwitterionic materials to nonspecific protein adsorptions compared to that of PEGs.

INTRODUCTION

Zwitterionic-based materials such as polySBMA and hydrophilic/neutral poly(ethylene glycol) (PEG) are two main classes of nonfouling materials that resist nonspecific protein adsorption and cell adhesion.^{1–4} They have been used widely for many applications, including tissue engineering, drug delivery systems, medical diagnosis, and implant coatings.^{2,5–10}

However, it is difficult to compare the capability of resistance to nonspecific protein adsorption of these materials, which might directly relate to the coating thickness or proper molecular weight to form a resistant layer to prevent protein adsorption on surfaces. Thus, a straightforward method to score the grade of the resistance to nonspecific protein adsorption

can make advances in both the understanding of the mechanism of resistance to nonspecific protein adsorption and the systematic design of new materials.

The present discussion on the factors that determine the nonfouling ability of the materials is focused on the intrinsic strong hydration structures between the materials surfaces and protein.^{11–17} Thus, it is proposed that the number, structural properties, and dynamic properties of the water molecules near the nonfouling materials might reflect the capability of

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resistance to protein. Lots of previous investigations have suggested that these properties of the hydration layer on polymer chains are very important information to analyze the origin of the repulsing force to protein and have major effects on the degree of protein adsorption after contact with body fluid for a long period.^{12,13,18,19} It is well-known that hydrophilic and neutral PEG chains could only form the hydration layer via hydrogen bonding, while the zwitterionic-based polymer forms the hydration layer via strong electrostatic interaction.^{3,20–22} A careful comparison between the hydration characteristics of these two main classes of nonfouling materials can benefit us to understand the nonfouling mechanism and also to design new nonfouling material.

NMR is a direct approach to characterize the changes of the water molecule motion in polymer/water mixtures and solutions.^{15,23,24} We recently developed a new method to characterize the number and structural properties of the water molecules bound to PEG chains by inverting the signals of spin–spin relaxation time (T_2) obtained by low-field nuclear magnetic resonance (LF-NMR) through Carr–Purcell–Meiboom–Gill (CPMG) consequence. Multiple components of water molecules and PEGs in PEG/water mixtures can be quantified, and also the mobility of each component can be characterized through a multiexponential inversion algorithm of the T_2 of PEG/water mixtures. Results show an excellent agreement of the number of bound water molecules on the ethylene glycol (EG) unit with some other research papers.^{20,25} In this work, we will compare the different hydration characteristics of polySBMA and PEG chains through this NMR technology, as well as, their behavior of heating thermograms through differential scanning calorimetry (DSC) to tell the difference in hydration characteristics of the two typical nonfouling materials.

MATERIALS AND METHODS

Materials. The PEG polymers, PEG(2000) (molecular weight (MW) = 2000), PEG(20 000), and PEG(200 000), were purchased from J&K Chemical. [2-(Methacryloyloxy)ethyl]dimethyl(3-sulfo-propyl)-ammonium hydroxide (sulfobetaine methacrylate, or SBMA) macromonomer was purchased from Monomer–Polymer & Dajac Laboratories, Inc., United States. Ammonium persulfate (APS) and ethanol (absolute; 200 proof) were purchased from Sigma-Aldrich. Water used in experiments was purified using a Millipore water purification system with a minimum resistivity of 18.0 MΩ·cm.

Methods. Preparation of Zwitterionic polySBMA Polymers in Aqueous Solution. A total solid content of 15 wt % for the different molar ratios of SBMA monomer and APS initiator (Table 1) was dissolved in 15 mL of deionized water, and nitrogen was bubbled through to remove residual oxygen. The reaction was stirred under positive nitrogen pressure for 6 h at 70 °C. After polymerization, the resulting reaction solution was cooled to 4 °C for 3 h and then added slowly into ethanol and redissolved into deionized water repeatedly to precipitate the polymer out of the reaction solution and to remove residual reagents.

Preparation of polySBMA/H₂O Mixture. The different MWs of polySBMA were prepared by the same procedure and labeled 1–7 from low MW to high MW. In brief, 0.5 g of polymer with varied amount of H₂O was added into each glass tube (φ15 mm). The concentrations of H₂O were 100, 140, 180, 220, 260, 300, 340, and 380 μL. The samples were incubated in an oven at 32 °C overnight to reach equilibrium.

NMR Measurement. NMR relaxation measurements were performed using the same method as we used to detect the water behavior with PEG¹⁵ on a Niumag Bench-top Pulsed NMR Analyzer PQ001 (Niumag Electric Corporation, Shang, China) operating at a resonance frequency for protons of 21 MHz (0.5 T). Sample was

Table 1. Characteristic Data of Zwitterionic polySBMA Homopolymers

sample ID	reaction molar ratios ^a [SBMA]/[APS]	M_w (g/mol) ^b	M_w/M_n
SBMA-1	100:1	23 165	1.53
SBMA-2	220:1	55 411	1.84
SBMA-3	295:1	67 608	1.62
SBMA-4	470:1	114 709	2.13
SBMA-5	495:1	119 090	2.03
SBMA-6	580:1	137 581	1.87
SBMA-7	880:1	213 775	2.28

^aReaction molar ratios of SBMA monomer and APS initiator used with fixed total solid content of 15 wt % in the prepared reaction solution. ^bWeight-average molecular weights (M_w) and molecular weight distributions (M_w/M_n) were estimated by GPC and calibrated with PEO.

inserted in the NMR probe. Spin–Spin relaxation time, T_2 , was measured using the CPMG sequence.²⁶ The maximum point of every second echo was accumulated using a 90° pulse of 17 μs and a 180° pulse of 34 μs. The delay between the 180° pulses, τ , was 500 μs. The amplitude of every second echo was measured, a total of 18 000 points were collected, and scans were coded using a repetition time, T_R , of 3 s. The relaxation measurements were performed at 32 °C.

With regard to almost all samples, the relaxation signal can always be expressed in multiexponential form. In this paper, the spin–spin T_2 relaxation time inversion spectrum was performed following the equation below:²⁶

$$M(t) = \sum_i P_i \exp\left(-\frac{t}{T_{2i}}\right) \quad (1)$$

here P_i is the signal intensity of the i component whose spin–spin relaxation time is T_{2i} .

DSC Measurement. The samples of polymer–water solution with sulfobetaine (SB) units versus H₂O molecules of about 1:4, 1:6, 1:8, and 1:10 were characterized to make comparison with the results by NMR technique; additionally, polymer without water was used as a control sample.

A 6–9 mg material was placed in an aluminum pan, and then the pan was hermetically sealed. An empty aluminum pan was used as the control. Measurements were performed using TA Q200. During the cooling and heating experiments, the sample cell was purged with nitrogen gas at a flow rate of 50 mL/min. The samples were initially cooled from room temperature to −40 °C at a rate of 5 °C/min and then heated to 80 °C at the same rate.

RESULTS AND DISCUSSION

To study the hydration properties of the polySBMA polymers, seven samples with different molecular weights (1–7) were prepared from various molar ratios of monomer to initiator in the reaction solutions. The molecular-weight distributions of the synthesized polySBMA polymers were calculated from the gel permeation chromatography (GPC) data using the OmniSEC software from Viscotek and are shown in Table 1. All polymer samples have similar molecular-weight distributions (i.e., $M_w/M_n = 1.8 \pm 0.2$).

Hydration of polySBMA Polymers. The inversion spectra of the NMR measurement of polySBMA/H₂O mixtures with equilibrated different amounts of water are shown in Figure 1. Comparing with the inversion spectra of PEG/H₂O mixtures that use the same methods,¹⁵ the inversion spectra of polySBMA/H₂O exhibited only one big peak in Figure 1, which means that the T_2 of the polySBMA component is too short to be detected in our NMR measurement, and the only

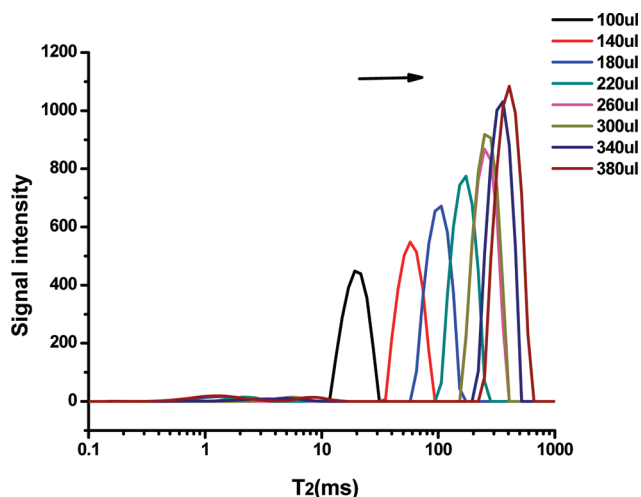


Figure 1. T_2 inversion spectra (signal intensity versus corresponding relaxation time) for varied amounts of polySBMA(55411)/H₂O mixtures with the amount of H₂O ranging from 100 to 380 μ L. The signal intensity represents the number of protons in the corresponding relaxation time. The right shift of the T_2 's of the water component indicates the mobility increase of the water molecules.

peak belongs to the water component. As shown in Figure 1, as more and more water is added to the polymers, the T_2 of the water component gradually moves to the right and becomes bigger and bigger, indicating that the bound water molecules are the least mobile owing to their direct attachment to the chain segments via electrostatic interactions, and the additional water could enhance the mobility of water molecules.

The amounts of bound water on the different MW polySBMAs are analyzed by the same method of the PEG in our previous paper (Figures 2 and 3).¹⁵ Figure 3 is the plot of the first derivative of $1/T_2$ versus the mass ratio of polySBMA versus water and polySBMA ($m_p/(m_p + m_w)$), where m_p is the mass of polySBMA and m_w is the total mass of added water. It shows that the constant value after $m_p/(m_p + m_w)$ is above 0.65 and below 0.7, which means that the surfaces of polySBMA are

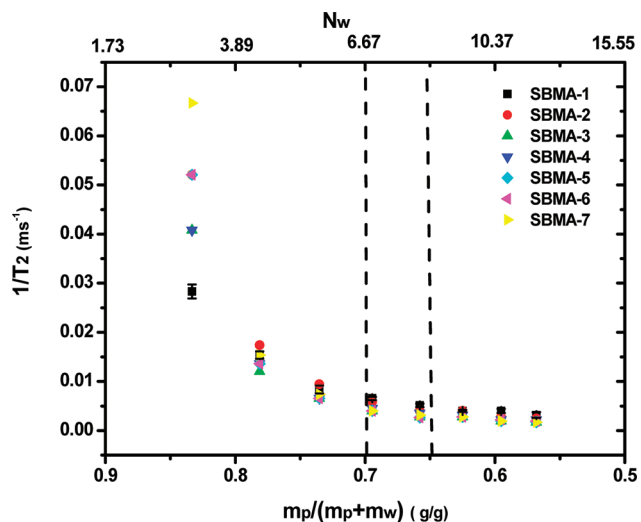


Figure 2. The reciprocal of T_2 of the water component in the inversion spectrum, $1/T_2$ (ms^{-1}), of polySBMA (1–7)/H₂O mixtures versus polymer concentration ($m_p/(m_w + m_p)$) (g/g). N_w is the number of added water molecules per SB-unit.

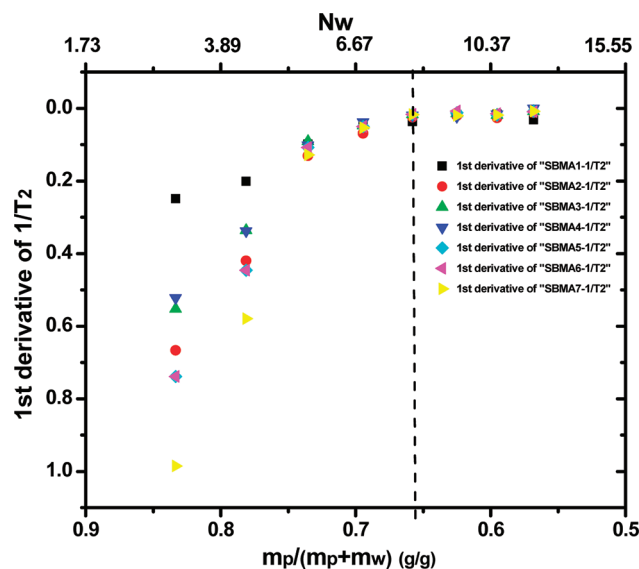


Figure 3. First derivative of $1/T_2$ (ms^{-1}) of the polySBMA (1–7)/H₂O mixtures to polymer concentration ($m_p/(m_w + m_p)$) (g/g). The constant value after $m_p/(m_p + m_w)$ is above 0.65 and below 0.7, which means that the surfaces of polySBMA are close to being saturated, and additional water molecules mainly dilute the polySBMA/water complexes.

close to being saturated when the H₂O/SB molar ratio reaches between 6.67 and 8. In another words, the constant value also points out that the surface of each SB unit possesses a hydration layer formed by 6.67–8 water molecules. Comparing with the one water molecule to EG-unit via hydration bond, zwitterionic-based materials hold a higher amount of bound water molecules via the electrostatic interaction. This value agrees well with the result by computer simulation of 7.86.¹³

In addition, the maximum hydration capacity of the SB unit detected by NMR is well supported by typical DSC heating thermograms of polySBMA (MW = 55 411) with different water content. Four water contents, having number ratios of H₂O:SB of 4:1, 6:1, 8:1, and 10:1, and also polySBMA without water were chosen for comparison. In Figure 4, first, no thermal transition was observed during the heating experiments of the

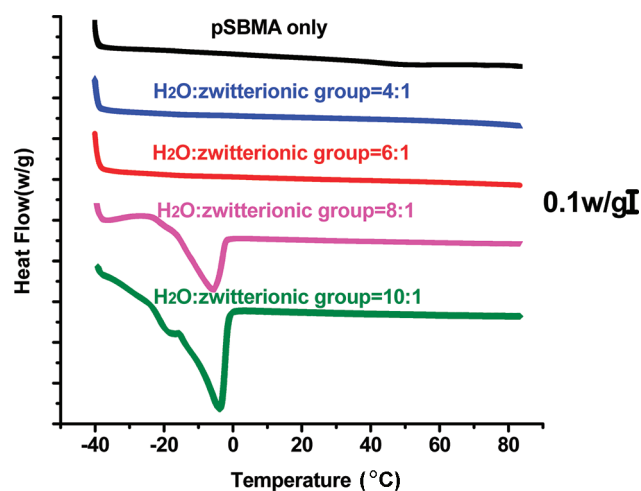


Figure 4. DSC thermograms of polySBMA(55 411)/H₂O mixtures at a heating rate of 5 $^{\circ}\text{C}/\text{min}$ for different water contents. The values indicate the H₂O:SB-unit molar ratios.

only polySBMA from -40 to 80 °C, which means the polymer chains have no contribution to the endothermic behavior. Second, no thermal transition was observed during the heating experiments when the number of $\text{H}_2\text{O}:\text{SB}$ equals 4:1, 6:1, which indicates that all the water molecules are tightly bound to the polymers, which is also called nonfreezable water.¹² The water/polySBMA mixture acts as one complex in this temperature range. It is believed that this kind of nonfreezable water is caused by the tightly bound water molecules on polymer chains via electrostatic interaction with a positively charged group ($\text{N}^+(\text{CH}_3)_3$) and a negatively charged group (SO_3^-). Third, the thermal transitions were observed when the number of $\text{H}_2\text{O}:\text{SB}$ equals 8:1 and 10:1, which suggests that the freezable water exists when all binding sites of the polymers are close to being saturated by water molecules, and freezable water give the transition over the temperature range similar to that of the ice-to-water transition for bulk water. Thus, the turning point of different phase transition behavior of $\text{H}_2\text{O}/\text{SB}$ of $\text{H}_2\text{O}/\text{polySBMA}$ mixtures is between 6:1 and 8:1 $\text{H}_2\text{O}:\text{SB}$ ratio. In conclusion, the heating thermo-grams of the $\text{H}_2\text{O}/\text{polySBMA}$ mixture give a similar range of $\text{H}_2\text{O}:\text{SB}$ ratio from mainly tightly bound to partially bound water molecules on polySBMA, which is consistent with the results obtained by NMR measurement.

Comparison of the Hydration of polySBMA and PEG.

Many studies have shown that the hydration of a material plays a key role in its nonfouling property. It was found that the nonfouling materials that gain a strong repulsive force to protein mainly arise from the interaction between the water molecules around protein and polymers.^{12,27,28} In this work, the structural and dynamic properties through the mobility of water molecule indicated by T_2 of water molecules from the water layer of polySBMA polymers were analyzed to obtain a better understanding of the origin of the nonfouling property. Additionally, the PEG/ H_2O mixtures were used for comparison. In order to make comparison with the PEG/ H_2O mixtures, the $1/T_2$ of water molecules on PEG and polySBMA polymers versus the same ratios of hydration layer are plotted in Figure 5. It is shown that the $1/T_2$'s of water molecules on polySBMA are bigger than those on PEG polymers in almost the whole experimental range. The much smaller T_2 of water molecules in the polySBMA/ H_2O mixture compared to that in the PEG/ H_2O mixture indicates that the water molecules bound to polySBMA polymers were much tighter than those bound to PEG polymers, especially in the low water/polymer range. This suggests that the zwitterionic-based materials have a stronger ability to hold the water molecules compared to PEG polymers at the same hydration degree, and the zwitterionic-based materials generate a stronger hydration layer via electrostatic interaction than PEG via hydration bond in this low water/polymer range. It is believed that extremely tighter holding of the first 3–4 water molecules on the SB unit than on the EG unit at the same hydration degree is caused by water molecules simultaneously bound to a positively charged group ($\text{N}^+(\text{CH}_3)_3$) and a negatively charged group (SO_3^-) on one SB unit. However, when the water/polymer ratios are over the point of the fully hydrated layer formed, the $1/T_2$ values of water components in both two polymer–water mixtures quickly decrease to very close ones in Figure 5. This indicates that water molecules beyond the hydration layer of two polymers act more and more closely to free water. It is worth pointing out that the water molecules adsorbed through electrostatic force are less direction sensitive on zwitterionic

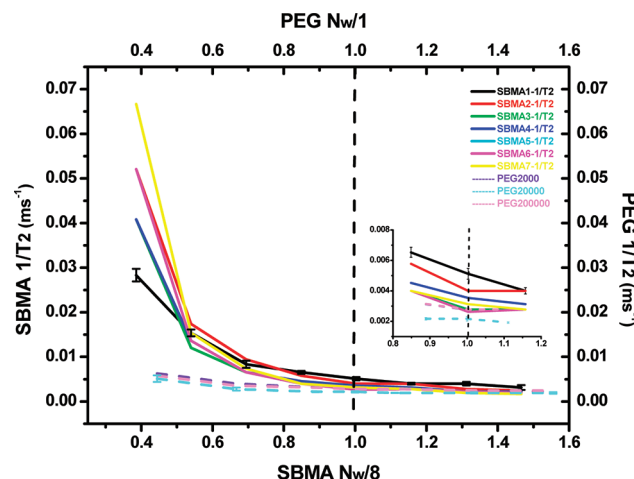


Figure 5. The reciprocal of T_2 of the water component in the inversion spectra, $1/T_2$ (ms^{-1}), versus the hydration degree, which is the ratio of total water amount compared to the water amount for one hydration layer on polymers. According to the results obtained by the NMR method, 1 or 8 water molecules could form a fully hydrated layer on one EG or SB unit, respectively. The inset figure clearly shows lower mobility of water molecules on polySBMA than on PEG, indicating tighter bound water molecules on polySBMA when both polymers are saturated.

groups than through H-bonds on EG groups. It is reasonable to believe that the water molecules on zwitterionic groups should show higher mobility than on EG groups if both binding strengths are similar. Thus, the shorter T_2 of the water molecules on zwitterionic groups indicates even lower mobility of water molecules than those on PEGs at the fully hydrated layer formed on both polymers.

Furthermore, the decreasing rates of $1/T_2$'s of polySBMA/ H_2O mixtures are much faster than those of poly(ethylene oxide) (PEO)/ H_2O mixtures after forming hydration layer. Almost all $1/T_2$'s occur at the same value when there are 40% more water molecules than one hydration layer or when we defined the hydration degrees at 1.4. Since a two-layer model of bound and unbound water on polymers could be used to express different components of water as in the eq 1, this faster decreasing indicates that the unbound water molecules in polySBMA solutions are more mobile than those in PEG solutions. It is believed that such a faster mobility increase is mainly caused by the very high dielectric constant of water, and the charge interaction between SB and water molecules could decrease dramatically after forming the first hydration layer.

In addition, the number of bound water molecules (N_b) per EG-unit and SB-unit obtained by Ishihara's direct enthalpy calculation¹² and through our titration methods are listed in Table 2. It clearly shows the rather close estimation in the number of bound water molecules by all three methods. However, the results obtained by NMR measurement could provide more information on the mobility of water molecules, especially the water molecules after forming a fully hydrated layer. Also interestingly, the T_c 's, the peak values of the ice-to-water-like transition temperature, of the polySBMA solutions are larger and also closer to 0 °C than the PEG ones (Table 2) after the hydration layer is formed. This indicates that the unbound water molecules in the polySBMA solutions behave more like free water than in the PEG ones, which agrees well with the observation in NMR. Thus, all this information

Table 2. Peaks of the Ice-to-Water-like Transition Temperatures and Enthalpy Changes of Water as Measured by DSC at Different Water Concentration of Polymer/Water Mixtures

polymer–water	T_c (°C)	ΔH (J/g)	N_b^a	N_b^b	N_b^c
PEG _{20000-1:1}	−12.57	27.95	0.71	0.5–1	~1
PEG _{20000-2:1}	−11.04	85.28	0.75		
SBMA _{35411-8:1}	−6.18	39.55	6.79	6–8	~8
SBMA _{35411-10:1}	−4.59	63.24	5.85		

^aThe values of the number (N_b) of bound water molecules per EG-unit or SB-unit are calculated from enthalpy changes of freezable water molecules compared with bulk water enthalpy (333.5 J/g) by DSC.

^bThe values of N_b are presented through the turning point of the different phase transition behaviors of water/polymer mixtures from DSC. ^cThe values of N_b are presented through the first derivative of $1/T_2$ by NMR.

provides more insight into the mechanism of the nonfouling property formed by water molecules around polymers.

Finally, after comparing the number of water molecules and the tightness of the hydration layer between PEG polymers and polySBMA polymers, we propose the whole process of water molecules interacting with polymers and the structure of the fully hydrated layer around the two kinds of nonfouling materials shown in Figure 6. In Figure 6, phase I shows that little water is added to the polymers, and the water molecules are very tightly bound to the nonfouling materials, leading to very sharp $1/T_2$ changes versus the amount of water and no observation of an endothermic peak. Phase II shows that the added water is close to the maximum available sites on polymer chains, and the fully hydrated layer is formed, leading to the turning point of the first derivative of $1/T_2$ and the appearance of the ice-to-water-like phase transition peaks in DSC. Phase III shows that the polymer–water solution is formed, and each polymer molecule isolates each other by their structured hydration shell, leading to the slow linearly decrease of $1/T_2$ as the additional water acts just like free/bulk water. Moreover, based on the results by both NMR and DSC, the fully hydrated

layer on both PEG and polySBMA polymers, expressed in Figure 6, are 1 H₂O to 1 EG-unit and 7–8 H₂O to 1 SB-unit, respectively.

CONCLUSIONS

The strong surface hydration layer of nonfouling materials can be determined through measuring the T_2 relaxation time of water molecules in water/polymer mixtures by LF-NMR. About eight water molecules are tightly bound with one SB unit. Comparing with nonfouling PEG hydrated through a H bond, zwitterionic SB could bind with water molecules in higher quantity and quality, and also could maintain more freedom for water molecules except for the first hydration layer. Both might be the reasons for the excellent resistance of SB to nonspecific protein adsorption. After all, it is necessary to further investigate the water molecules around other nonfouling materials, such as poly (2-methacryloyloxyethyl phosphorylcholine), to fully understand the origin of nonfouling property.

However, it should be mentioned that the investigation of polymer hydration in bulk solution mainly focuses on the intrinsic property of polymer hydration. The resistance of surface coatings could be affected by other factors, such as surface packing (i.e., film thickness, packing density, and chain conformation) and chain flexibility, which decides the overall surface hydration and the steric repulsion to resist protein adsorption, respectively. However, the intrinsic property of polymer hydration is the key factor for surface resistance to nonspecific protein adsorption.

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Notes

The authors declare no competing financial interest.

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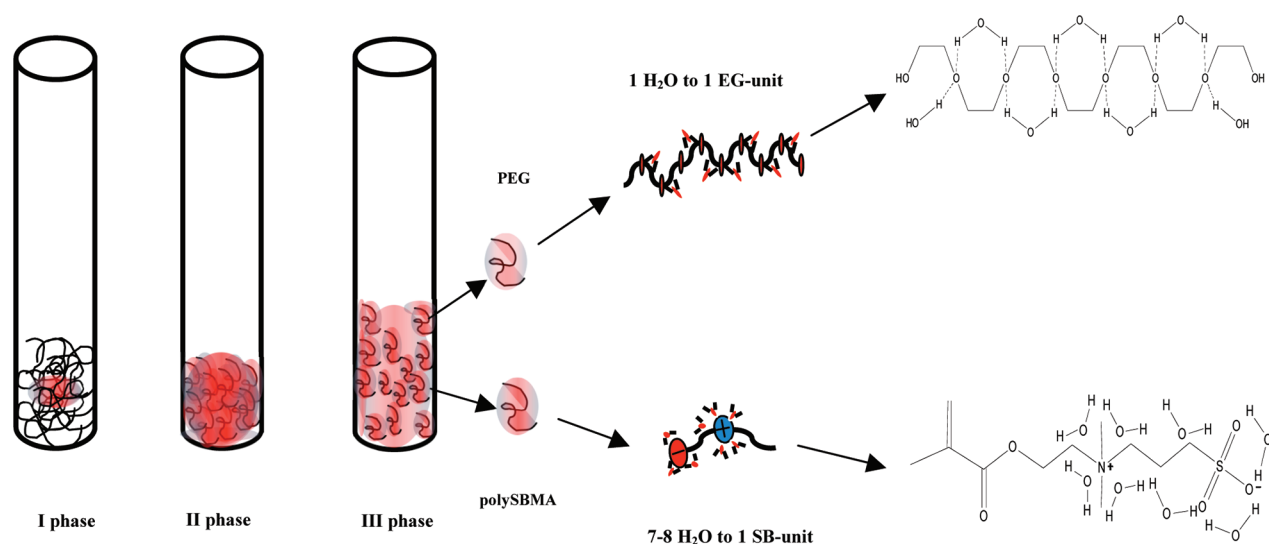


Figure 6. A proposed model of the hydration process of both PEG and polySBMA polymers. The red dots with two black sticks represent one water molecule, while the black lines represent linear polymer chains. The hydration of polymers might go through three stages with increasing water content: water molecules tightly bind to polymers, saturate binding sites of polymers, and finally swell and dissolve polymers. One water molecule could bind with one EG unit through two H bonds, while about eight water molecules could fully hydrate a SB group through electrostatic force.

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