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CMC and dynamic properties of poly(VA-*b*-St) copolymer micelles for drug delivery

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Abstract−The polymeric micelles from amphiphilic block copolymer poly(vinyl alcohol-*b*-styrene) (poly(VA-*b*-St)) with different syndiotacticity of poly(vinyl alcohol) (PVA) block were prepared by dialysis against water. Critical micelle concentration (CMC) and dynamic properties of poly(VA-*b*-St) copolymeric micelles were investigated by fluorescence techniques. From the fluorescence emission spectrum measurements using pyrene as a fluorescence probe, the observed CMC value was in the range of 0.125-4.47 mg/L. The CMC value increased with decreasing the weight ratio of PS to PVA block and with increasing the syndiotacticity of PVA block. The rate of pyrene release was very slow for block copolymers containing PVA block with higher syndiotacticity, which indicates that their micelles have increased kinetic stability.

Key words: Poly(VA-*b*-St), Syndiotacticity, Micelle, Critical Micelle Concentration, Kinetic Stability

INTRODUCTION

The increasing importance and interest in block copolymers arises mainly from their unique properties in solution and in the solid state, which are a consequence of their molecular structure [1,2]. Amphiphilic block copolymers composed of hydrophilic and hydrophobic block in an aqueous phase tend to self-assemble and form microphases, i.e., micelles. These polymeric micelles have nanoscale, high thermodynamic and kinetic stability, and can solubilize hydrophobic substances; therefore, they may be applied to separation systems, drug delivery systems, pharmaceuticals, or emulsion stabilization [2-9].

Poly(ethylene oxide-*b*-styrene) (poly(EO-*b*-St)) block copolymers have been investigated intensively as a typical model copolymer for the study of self-assembling and drug delivery systems [2,10-17]. PEO is often used as a hydrophilic block, because PEO is biocompatible, and can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core [18]. In addition, hydrophobic PS core remains glassy up to temperatures approaching the boiling point of water, which enhances the stability of micelles and reveals a potential application for solubilizing hydrophobic substances [19]. Poly(vinyl alcohol) (PVA) is not only water-soluble, non-toxic, biocompatible, but also possible to form hydrogen bonds between molecular chains. Therefore, poly(VA-*b*-St) copolymers are expected to show higher kinetic stability and slower drug release. Our previous paper reported that poly(VA-*b*-St) copolymers form micelles in an aqueous phase [20].

In this paper, the critical micelle concentration (CMC) and dynamic properties of poly(VA-*b*-St) copolymer micelles were further studied and explained by fluorescence techniques.

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Table 1. The molecular characteristics of poly(VA-*b*-St) copolymers

Sample	PVA	PS		Syndio-tacticity (diad%)	Average micelle size (nm)
	$M_{n,\,NMR}$	$M_{n,\,th}$	$M_{n,NMR}$		
PVA_1-PS_{500}	1540	500	620	53.0	40, 115
PVA_1-PS_{970}		970	-		47
PVA_1-PS_{1520}		1520	-		-
PVA_1-PS_{2260}		2260	-		68
PVA_2-PS_{1040}	1670	1040	1480	56.1	77
PVA_2-PS_{1520}		1520	-		94
PVA_3-PS_{1030}	1580	1030	-	59.1	49
PVA_3-PS_{1470}		1470	1700	59.6	57

$M_{n,\,th}=[St]_0/[Macroinitiator]_0\times 104\times Conversion\ (\%)$
PVA_3: PVA derived from PVPi; PVA_2: PVA derived from Poly(VPi-*co*-VAc); PVA_1: PVA derived from PVAc.

EXPERIMENTAL

1. Materials

Poly(VA-*b*-St) block copolymers containing PVA with different tacticity were prepared as described in our previous papers [20,21]. The molecular characteristics of block copolymer are shown in Table 1. Acetone (Samchun Pure Chemical Co., Ltd, 99%), pyrene (Aldich Chemical Co., Inc, 98%), *N*,*N*′-dimethylformamide (DMF, Junsei Chemical Co., Ltd, 99%), *N*,*N*′-dimethylacetamide (DMAc, Shinyo Pure Chemicals Co., Ltd, 99%), and 1-methyl-2-pyrrolidone (NMP, Samchun Pure Chemical Co., Ltd, 99%) were used as received.

2. Sample Preparation

The micellar solutions of poly(VA-*b*-St) block copolymers were prepared in accordance with a dialysis method. Briefly, 10 mg of the poly(VA-*b*-St) block copolymer was dissolved in 40 ml of DMF, DMAc, or NMP, and stirred several hours for equilibration. This solution was dialyzed against distilled water (Sigma, benzoylated

cellulose tubing, molecular weight cut off 1200) for three days to form micelles. The water was exchanged at regular intervals. The obtained micellar solution was centrifuged to remove aggregated particles and impurities, and then diluted to prepare a solution varying in polymer concentration.

For the measurement of CMC and rate of pyrene release, the micellar solutions loaded with pyrene were prepared as follows. A known amount of pyrene in acetone was added to each of a series of 10 ml vial, and the acetone was evaporated in an oven at 65 °C. Prepared micellar solution from the above was then added to each vial, to give a pyrene concentration in the final solution of 6.0×10^{-7} M, 1.15×10^{-5} M, 2.3×10^{-5} M, 4.6×10^{-5} M. The stoppered vials were heated for 3 h (concentration of pyrene: 6.0×10^{-7} M) or 6 h (other concentrations of pyrene) at 65 °C to equilibrate the pyrene and the micelles, and subsequently allowed to cool overnight to room temperature.

3. Measurements

To determine the CMC of poly(VA-*b*-St) block copolymers in an aqueous phase, and the rate of release and exchange of pyrene in the micellar solution of block copolymers, the fluorescence emission spectra of pyrene were measured at an excitation wavelength of 339 nm with an RF-5301PC spectrofluorophotometer (Shimadzu Co., Japan) at 25 °C.

RESULTS AND DISCUSSION

1. CMC of Poly(VA-*b*-St) Block Copolymers

The amphiphilic block copolymers, poly(VA-*b*-St)s form micelles in an aqueous phase. CMC, which is a measure describing the physical properties of the micelle, refers to the thermodynamic stability of the micelles [22]. The CMC of the block copolymers was determined by a fluorescence technique with pyrene as a probe. Pyrene is probably the most widely used fluorescence probe, because its vibrational fine structure is sensitive to polarity [2,11,23-25] and because it produces distinct excimer fluorescence under conditions of sufficiently high concentration and mobility [25]. In Fig. 1, the fluorescence emission spectra of pyrene are shown at various concentrations of PVA_1-PS_{970} containing 6×10^{-7} M of pyrene. The two noteworthy features of these spectra are that the intensity decreases with decreasing polymer concentration and that there are obvious changes in the intensity ratio of the (0,0) band (I_1, 375 nm) to the (0,2) band (I_3, 385 nm) of pyrene monomer, I_1/I_3. The I_1/I_3 ratio depends on the polarity of the pyrene surroundings, which can be used to determine the CMC values [11,24]. Figs. 2 and 3 show the intensity ratios (I_1/I_3) of pyrene monomer emission spectra versus the logarithm of concentrations of PVA_1 based block copolymers and PVA_1-PS_{970}, PVA_2-PS_{1040}, PVA_3-PS_{1030} block copolymers, respectively. A negligible change of intensity ratios was observed at a low concentration range, but above a certain concentration the intensity ratios show a sharp decrease, which indicates the incorporation of pyrene into the hydrophobic core region of the micelles. Therefore, the CMC was determined from the graphical intersecting point at the low concentration range in Figs. 2 and 3. Fig. 4 shows the change of CMC values of the poly(VA-*b*-St) copolymers along with the weight ratio

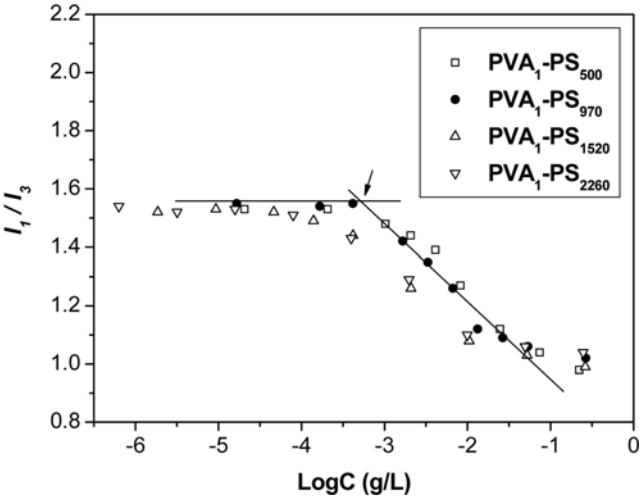

Fig. 2. Plot of the fluorescence intensity ratio I_1/I_3 (from pyrene emission spectra) vs. log C for PVA_1 based block copolymers.

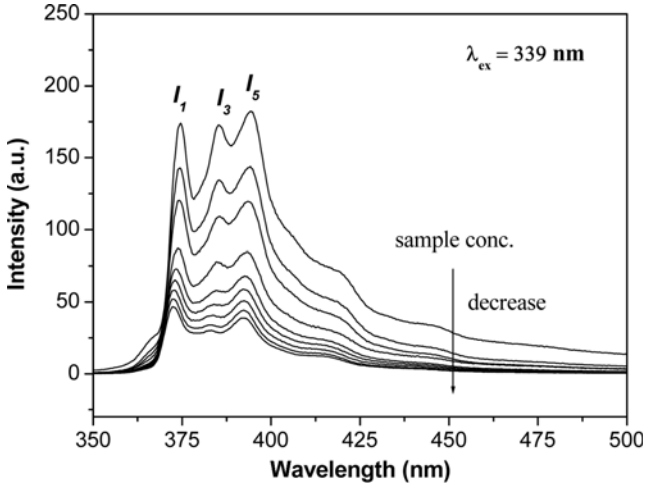

Fig. 1. Fluorescence emission spectra of pyrene (6×10^{-7} M) in the presence of decreasing concentrations of PVA_1-PS_{970} copolymer.

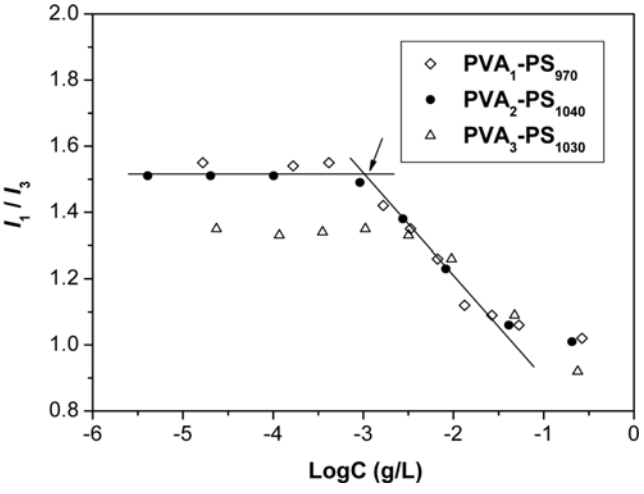

Fig. 3. Plot of the fluorescence intensity ratio I_1/I_3 (from pyrene emission spectra) vs. log C for PVA_1-PS_{970}, PVA_2-PS_{1040}, and PVA_3-PS_{1030} copolymers.

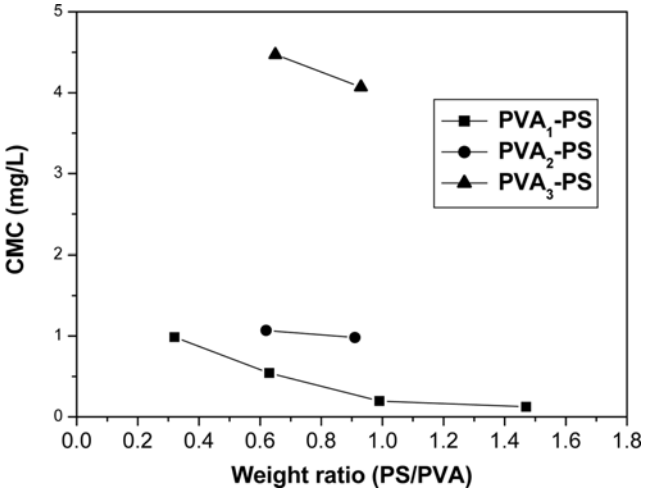

Fig. 4. Relationship between the CMC of poly(VA-*b*-St) micelles and the weight ratio of PS to PVA block in the block copolymers.

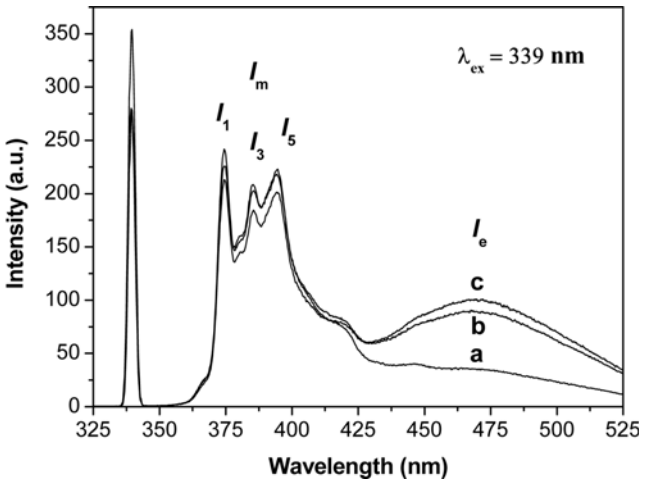

Fig. 5. Fluorescence spectra of pyrene in PVA_1-PS_{970} micelles as a function of pyrene loading level (concentration of pyrene= 1.15×10^{-5} M (a), 2.3×10^{-5} M (b), and 4.6×10^{-5} M (c); concentration of polymer=0.16 g/L).

of PS to PVA block. As can be seen in Fig. 4, the CMC values of the block copolymers increased with the decrease of weight ratio of PS to PVA block and with the increase of the syndiotacticity of PVA block. The former is ascribed to the decreased solubility as the molecular weight of PS block increased, while the latter may be ascribed to more dense arrangement or the formation of multilayer at the interface as PVA blocks have higher syndiotacticity [26]. It is known that PVA homopolymer with high syndiotacticity has stronger intermolecular forces (hydrogen bonding) and poor solubility in water [27, 28]. In addition, the CMC values are much lower than those of common low molecular weight surfactants. This result indicates that the block copolymeric system can retain a micelle structure even in a very diluted condition, featuring stable micelle polymeric nanospheres, which may be useful as drug vehicles.

2. Dynamic Properties of Micelles

Polymeric micelles are in a dynamic equilibrium state with polymer molecules in a selective solvent above CMC. Namely, micelles are dissociated into polymer molecules, and polymer molecules are associated into micelles continuously. Micelles are formed in the aqueous solution due to the existence of a hydrophobic block in the amphiphilic block copolymers and van der Waal's attraction force between hydrophobic chains; they are dissociated by the thermal motion of polymer molecules. Moreover, the dynamics of block copolymer micelles may stretch over a very wide range of times, depending on the copolymer molecular weight, structure and quality of the solvent. The temperature at which the measurements are performed may also have an enormous effect, depending on whether it is above or below the glass transition temperature of the polymer constituting the micelle core [2]. In addition, the attraction force between hydrophilic blocks influences the dynamic properties of micelles.

Fluorescence probing methods are capable of obtaining information on the dynamics of block copolymer micelles through the exchange of molecules solubilized in block copolymer micelles between micelles and intermicellar solution. Cao et al. [25] have investigated the solubilization of pyrene in PMMA-*b*-PS-*b*-PMMA triblock copolymers in water. Micelles with pyrene were mixed with micelles without pyrene, and the time dependence of the ratio of excimer intensity, I_e (at 469 nm) to monomer fluorescence intensity, I_m (in the fluorescence intensity I_1((0, 0) bend), I_3, I_5 of pyrene monomer, express I_m in terms of I_1 at 374.5 nm) was measured. Fig. 5 shows the change of fluorescence intensity of pyrene along with the concentration of pyrene in micelle solution. As can be seen in Fig. 5, when the loading of pyrene increased, the magnitude of the excimer fluorescence (I_e) increased, which indicates the formation of excimer.

In this study, micellar solution containing 4.6×10^{-5} M (c) of pyrene was selected to carry out an exchange experiment of pyrene solubilized in block copolymer micelles. When copolymer micelles containing pyrene are mixed with micelles without pyrene, the pyrene molecules are exchanged between micelles and I_e decreases leading to the I_e/I_m ratio decrease with time as shown in Fig. 6. The time scale of this ratio change reflects the rate at which this exchange occurs, because the rate-determining step is not the rate of micelle-

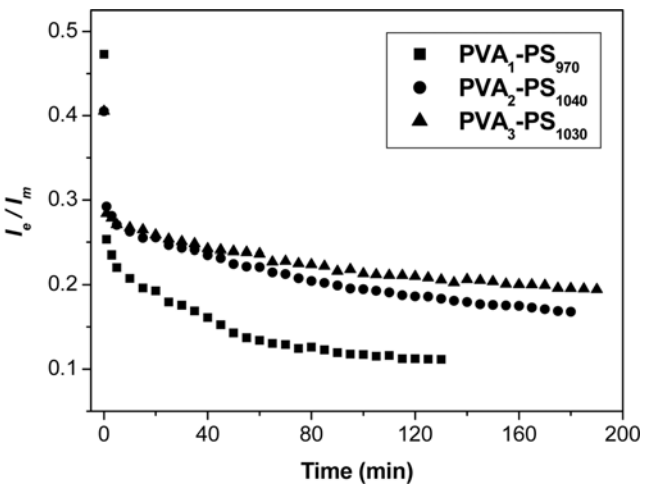

Fig. 6. I_e/I_m ratio as a function of time after mixing pyrene-loaded micelle with pyrene-free micelles.

micelle collision, but pyrene diffusion within the PS core [25]. There is a relatively rapid change in I_e/I_m at the beginning, especially in the case of low syndiotacticity, followed by a very slow equilibration as PVA block has higher syndiotacticity. These indicate that the rate of release and exchange decreases and the equilibration time increases with the syndiotacticity of PVA block after mixing, namely, the kinetic stability of the micelles is enhanced by the higher syndiotacticity. The reason may be related to the fact that the higher syndiotacticity of PVA block forms a stronger intermolecular hydrogen bonding [27,28], so that the hydrophilic PVA block forms a tighter outshell around the micellar core, and so the diffusion of the pyrene from the PS micelle core towards the surface is retarded. Therefore, the polymeric micelles can be applied to the control release of hydrophobic drugs.

CONCLUSIONS

Critical micelle concentration (CMC) and dynamic properties of poly(VA-*b*-St) copolymeric micelles were investigated by fluorescence techniques. The block copolymers in the water showed critical micelle concentrations (CMC) in the range of 0.125-4.47 mg/L. The CMC value increased with decreasing the molecular weight of PS block and with increasing the syndiotacticity of the PVA block. In addition, as the block copolymers contain higher syndiotacticity of PVA block, the rate of release and exchange of pyrene molecules become very slow at long times, that is, the kinetic stability of the micelles was obviously enhanced and pyrene release was slower. Therefore, the poly(VA-*b*-St) copolymeric micelles with higher syndiotactic PVA block have good potential for applications such as drug delivery systems.

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