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Notes

Amphiphilic Copolymer Micelles Containing PEG with Sulfonate End-Group

Young Pil Jung, Young-Kyo Son, and Ji-Heung Kim*

Department of Chemical Engineering, Polymer Technology Institute, Sungkyunkwan University, Gyeonggi 440-746, Korea

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Introduction

Amphiphilic graft copolymers have attracted considerable interest on account of their many industrial applications and ability to be synthesized more easily and affordably than block copolymers. In addition, the micellization of amphiphilic block and graft copolymers in selective solvents is a well known phenomenon. Due to their amphiphilic characteristics, block and graft copolymers containing hydrophobic and hydrophilic components can be used to stabilize dispersions, emulsions and polymer blends, as well as for surface modification, drug delivery, nanoreactors, etc.[1,2]

Poly(ethylene glycol) (PEG)-based amphiphilic block copolymers have gained enormous popularity thus far. All variations in amphiphilic copolymers consisting of ethylene oxide with a hydrophobic component such as styrene, methacrylate, or propylene oxide are now available, and are used in specific applications.[2,3] In addition, amphiphilic copolymer micelles composed of hydrophilic PEG and various hydrophobic blocks, such as polylactide, poly(tetramethylene carbonate) or polyaspartate as carriers for novel drug delivery systems have attracted considerable interest.[4] These amphiphilic copolymers are obtained by the sequential polymerization of the corresponding monomers or by the chain end modification of PEG. PEG has a wide range of beneficial properties for biomedical applications, including low toxicity and non-thrombogenic characteristics.[5-7] Various PEGs have been used to provide a non-fouling surface in different molecular forms for various biomedical applications in contact with the blood or tissue. Many strategies for tailoring the surfaces of materials with PEG-grafts have been developed.[8,9]

*Corresponding Authors. E-mail: kimjh@skku.edu

Moreover, it was reported that a material with a negatively charged surface is more compatible with the blood than a neutral one.[10,11] Han and Kim *et al.* showed that PU grafted with PEG-SO_3 showed superior thrombo-resistance, as determined by the decreased level of platelet adhesion or protein adsorption, and less calcification than on the surface grafted with PEG only.[12-14]

The preparation of telechelic PEG with a sulfonic acid group and a polymerizable methacryloyl group at each end of the PEG chain was able to provide a macromer that could be used in vinyl copolymerization, hydrogel system and surface modification. Previously, we have reported the synthesis, polymerization, and the crosslinked hydrogel of the methacryloyl PEG sulfonate macromer.[15,16] In this short communication, novel amphiphilic graft copolymers containing PEG sulfonate were prepared from the radical copolymerization of this PEG macromer with butyl methacrylate or poly(propylene glycol) methacrylate comonomer, and their micellization behavior in an aqueous solution was confirmed by dynamic light scattering.

Experimental

Chemicals and Measurements. α,ω–Diamino poly(ethylene glycol) (PEG-DA, M_w 1,000) was kindly provided by NOF Co. (Japan). Tetrahydrofuran (Aldrich, 99%) was distilled over $LiAlH_4$. The triethylamine and toluene were dried over CaH_2, and freshly distilled prior to use. The chloroform (99.8%, A.C.S. reagent), 1,3-propane sultone (PST, 98%), and methacrylic anhydride (94%) were purchased from Aldrich and used as received. As radical initiators, ammonium persulfate (APS, Aldrich, 98+%) was used without purification, and 2,2′-azoisobutyronitrile (AIBN) was recrystallized from methanol. Butyl methacrylate (BMA, 00%) and poly (propylene glycol) methacrylate (PPG-MA, M_n ca. 430) were purchased from Aldrich Chem. Co. and passed through an alumina column to remove the polymerization inhibitor prior to use.

The infrared spectra were obtained on a Perkin Elmer Fourier-transform IR spectrometer (FTIR, Model SPECTRUM 2000). The ^{1}H NMR spectra were obtained on a Varian Unity Inova 500 MHz Spectrometer. A dynamic light-scattering instrument (DLS, Brookhaven, BI-200SM) with a Ne-He laser was used to measure the size distribution of the polymeric spheres in distilled water. The polymerization product was dispersed magnetically in distilled water and filtered using a 0.45 μm pore sized filter membrane to remove the oversized material. The light intensity scattered from the polymeric spheres were measured at an angle of 90°.

Preparation and Radical Copolymerization of PEG Macromer (MA-PEG-SO_3H). A PEG macromer with a

Scheme I

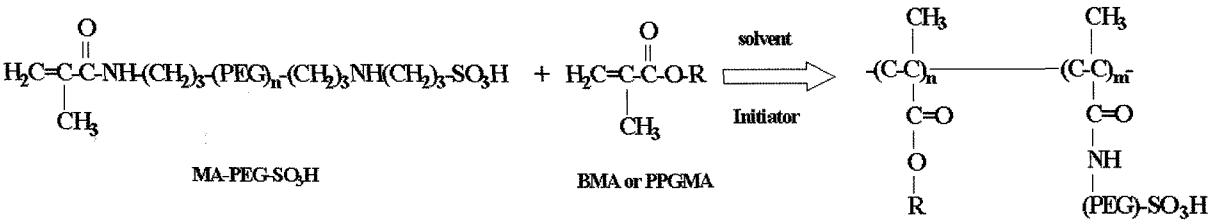

Table I. Conditions and Results of Copolymerization

Run	SPEG-BMA Ratio (mol)	Initiator[a]	Solvent (mL)	Temp. (°C)	Yield (%)	Solution State	Monomer Composition in Copolymer[b]	d_m (nm)[c]
1	1:1	APS	EtOH+water (4/1)	45	65	turbid	1:1.3	157
2	1:2	APS	EtOH+water (4/1)	45	73	turbid	1:1.79	143
Run	SPEG-PPGMA Ratio (mol)	Initiator[a]	Solvent (mL)	Temp. (°C)	Yield (%)	Solution State	Monomer Composition in Copolymer[b]	d_m (nm)[c]
3	1:0.3	AIBN	Toluene (5)	60	67	clear	1:0.25	172
4	1:0.5	AIBN	Toluene (5)	60	72	clear	1:0.47	182
5	1:1	AIBN	Toluene (5)	60	70	clear	1:0.96	195

[a]Initiator 1.0 wt% to monomer. [b]Determined by ^{1}H NMR. [c]d_m=Particle diameter in water by DLS.

sulfonate end, MA-PEG-SO_3H, was prepared using the procedure previously reported.[15,16] Copolymerization of this macromer with BMA or PPG-MA in different solvent systems was carried out using an azo- or redox-type radical initiator (Scheme I). The polymerization procedure was carried out with magnetic stirring in a 50 mL, 3-necked flask fitted with a condenser, a nitrogen inlet and outlet. Table I summarizes the reaction conditions and the polymerization results. The polymerization product was dialyzed in distilled water for 5 days using a cellulose dialysis tube (MWCO 12,000-14,000 Da) to extract the unreacted monomer and oligomers, and lipophilized by freeze-drying. An off-white powdery product was obtained with a yield of ca. 65%.

Results and Discussion

The PEG macromer with methacryloyl and sulfonate groups at each chain end, MA-PEG-SO_3H, was prepared from PEG-diamine via zwitterionic H_2N-PEG-SO_3H (PEG-AS). The IR spectrum of MA-PEG-SO_3H macromer showed weak amide absorption bands at 1650 and 1535 cm^{-1} in addition to a strong ethylene ether(C-O-C) absorption band at 1115 cm^{-1} and a band at 1038 cm^{-1} that was assigned to a sulfonic acid group. The ^{1}H-NMR spectrum of MA-PEG-SO_3H, revealed the vinylic protons at 5.29, 5.78 ppm and a methyl proton at 1.95 ppm, which confirmed the introduction of a methacryloyl group on the PEG. A previous communication reported the free radical polymerization of MA-PEG-SO_3H in different media to provide comb-shaped, PEG graft polymers with a relatively high molecular weight.[16] The resulting polymers were freely soluble in water and methanol, and thermally stable up to 300 °C. In this study, the free-radical copolymerization of the MA-PEG-SO_3H macromer was carried out using two different hydrophobic comonomers, i.e. butyl methacrylate (BMA) and poly(propylene glycol) methacrylate (PPG-MA). Table I shows the results of polymerization. AIBN and ammonium persulfate were used as initiators in the toluene and ethanol/water mixture, respectively. The polymer yields were approximately 65-70%. In the EtOH/water solvent system, the reaction mixture became slightly turbid, which might be caused partly by the micelle-like association of the preformed polymer. On the other hand, in toluene, the reaction mixture remained clear throughout the reaction.

The ^{1}H NMR spectra of both copolymers (Figure 1) showed that the vinyl peaks, which were originally observed at 5~6 ppm, had disappeared. The methyl and methylene proton peaks (1~2 ppm) of the butyl or PPG units could be clearly seen. The prepared polymer was freely soluble in water and methanol, while it showed poor solubility in chloroform and THF.

The DLS measurements confirmed the formation of

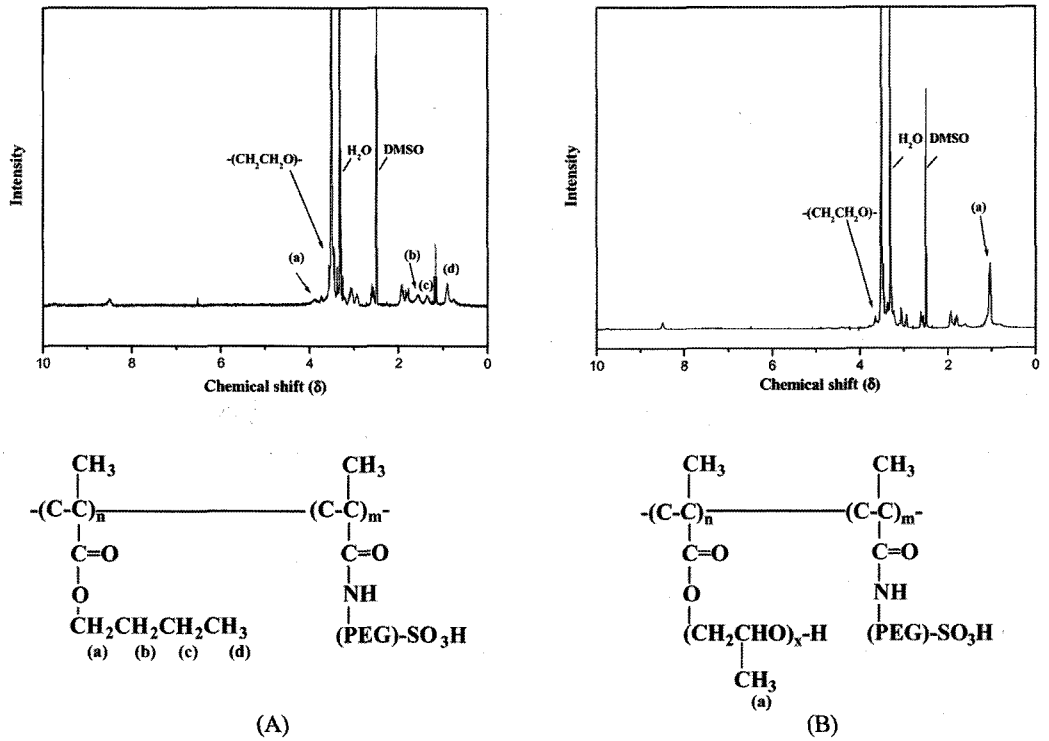

Figure 1. ^{1}H-NMR spectrum of (A) SPEG-BMA and (B) SPEG-PPGMA.

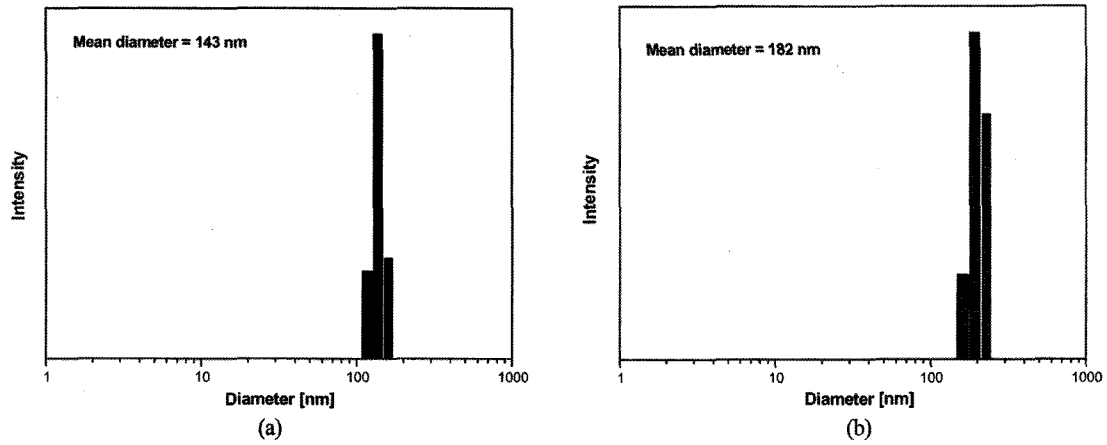

Figure 2. Particle size distribution of (a) SPEG-BMA (1:2) and (b) SPEG-PPGMA (1:0.5) in PBS 7.4.

micelles in the aqueous solution (Figure 2). The mean diameter ranged from 150~190 nm with some variation in the particle size distribution, which confirm an association of the molecules in the aqueous medium. In the case of the SPEG-PPG copolymers, the mean particle size tended to increase linearly with increasing the hydrophobic PPG content. The SPEG-BMA copolymers, which were obtained from the EtOH/water medium, contained relatively smaller sized particles.

In general, the photoelectron autocorrelation function provides hydrodynamic information on a micelle in solution. For spherical particles, the translational diffusion coefficient (D) is independent of the detection angles. Figure 3 shows that relaxation rates (Γ) are proportional to the square of the scattering vector, K ($K=4\pi n_0 \sin(\theta/2)/\lambda_0$, where n_0 is the solvent refractive index, λ_0 is the wave length, and θ is the scattering angle). According to the equation, $\Gamma=DK^2$, there was no angular dependency of D observed, which suggest that the micelles formed a spherical shape. Figure 4 shows the average hydrodynamic micelle diameter as a function of the time. The value of diameter for a particular copolymer remained relatively constant over a long period of time. This

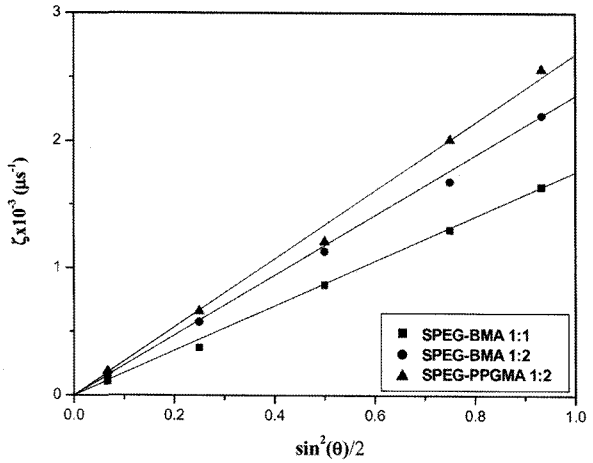

Figure 3. Plot of the relaxation rate (Γ) of SPEG-BMA as function of $\sin^2(\theta/2)$ at room temperature.

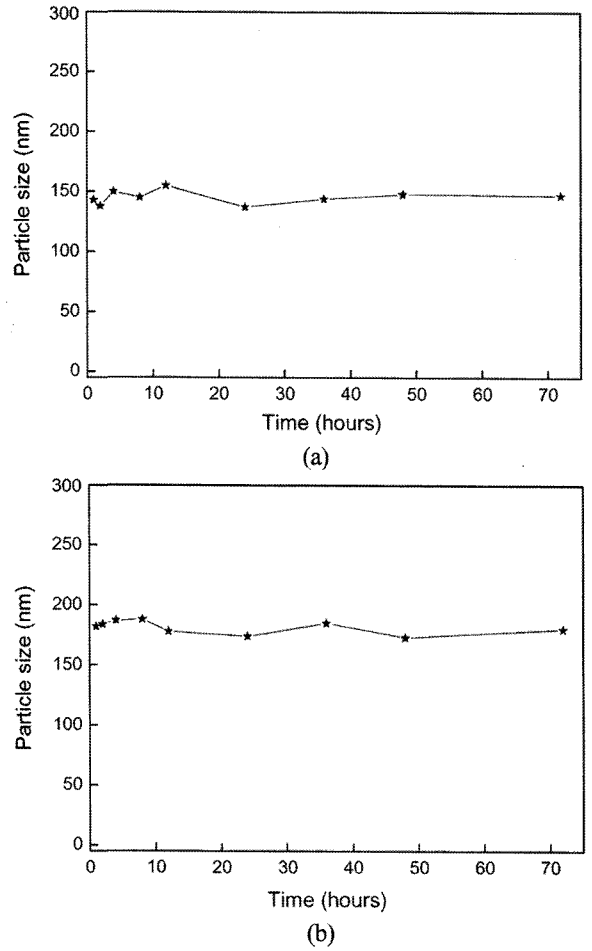

Figure 4. The stability of nanoparticles of (a) SPEG-BMA (Run #2) and (b) SPEG-PPGMA (Run #4) in PBS 7.4 at 25 °C.

observation indicates that satisfactory colloidal stability in aqueous solution was achieved via steric stabilization by imparting a surface layer of SPEG onto the polymeric micelles.

Overall, amphiphilic comb-shaped copolymers consisting of hydrophilic PEG sulfonate and hydrophobic butyl or PPG grafts were prepared, and their micellization behavior in aqueous solution was examined. These polymers might have applications in specific drug delivery systems and surface modification of biomaterials.

Conclusions

A PEG macromer with methacryloyl and sulfonate group at the end of each chain was prepared and used for the radical copolymerization with butyl or PPG methacrylate. The resulting amphiphilic graft polymers were soluble in water and methanol, and dynamic light scattering measurements suggested the formation of nano-sized micelles in the aqueous medium.

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References

(1) A. Horgan, B. Saunderd, B. Vincent, and R. K. Heenan, *J. Colloid Interf. Sci.*, **262,** 548 (2003).
(2) G. Zhu, *Eur. Polym. J.*, **41,** 2671 (2005).
(3) H.-Q. Xie, D. Xie, X.-Y. Chen, and J.-S. Guo, *J. Appl. Polym. Sci.*, **95**, 1295 (2005).
(4) T. Kushibiki, H. Matsuoka, and Y. Tabata, *Biomacromolecules*, **5**, 202 (2004).
(5) N. A. Peppas, Ed., *Hydrogels in Medicine and Pharmacy*, CRC Press, Boca Raton, FL, 1986.
(6) M. J. Harris, *Poly(ethylene glycol) Biotechnical and Biomedical Applications*, Prenum Press, New York, 1992.
(7) B. D. Ratner, in *Biocompatibility of Clinical Implant Materials*, D. F. Williams, Ed., CRC Press, Cleveland, Ohio, 1981, Chapter 7.
(8) N. P. Desai and J. A. Hubblell, *J. Biomed. Mater. Res.*, **25**, 829 (1991).
(9) J. A. Hubblell, *Curr. Opin. Biotech.*, **10**, 123 (1999).
(10) S. Srinivasan and P. N. Saeyer, in *Biomedical Polymer*, A. Rembaum and M. Shen, Eds., Marcel Dekker, New York, 1971, p. 51.
(11) K. Inshihara, H. Fujita, T. Yoneyama, and Y. Iwasaki, *J. Biomater. Sci., Polym. Edn.*, **11**, 1183 (2000).
(12) D. K. Han, G. H. Ryu, K. D. Park, U. Y. Kim, B. G. Min, and Y. H. Kim, *J. Biomed. Mat. Res.*, **30**, 23 (1996).
(13) D. K. Han, G. H. Ryu, K. D. Park, U. Y. Kim, B. G. Min, and Y. H. Kim, *J. Biomed. Mat. Res.*, **24**, 2213 (2003).
(14) K. D. Park, H. D. Park, H. J. Lee, Y. H. Kim, T. Ooya, and N. Yui, *Macromol. Res.*, **12**, 342 (2004).
(15) J.-G. Kim, S. J. Shim, J.-H. Kim, S. H. Kim, and Y. H. Kim, *Macromol. Res.*, **12,** 379 (2004).
(16) J.-H. Kim, J.-G. Kim, D. Kim, and Y. H. Kim, *J. Appl. Polym. Sci.*, **96**, 56 (2005).