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Synthesis and Polymerization of Methacryloyl-PEG-Sulfonic Acid as a Functional Macromer for Biocompatible Polymeric Surfaces

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Abstract: Poly(ethylene glycol)s (PEGs) are unique in their material properties, such as biocompatibility, non-toxicity, and water-solublizing ability, which are extremely useful for a variety of biomedical applications. In addition, a variety of functional PEGs with specific functionality at one or both chain ends have been synthesized for many specialized applications. Surface modifications using PEG have been demonstrated to decrease protein adsorption and platelet or cell adhesion on biomaterials. Furthermore, PEGs having anionic sulfonate terminal units have been proven to enhance the blood compatibility of materials, which has been demonstrated by the *negative cilia* concept. The preparation of telechelic PEGs having a sulfonic acid group at one end and a polymerizable methacryloyl group at the other is an interesting undertaking for providing macromers that can be used in various vinyl copolymerization and gel systems. In this paper, preliminary results on the synthesis and polymerization behavior of a novel PEG macromer is described with the aim of identifying a biocompatible material for applications in various blood-contacting devices.

Keywords: biomaterials, blood-compatibiltity, surface modification, PEG macromer, methacryloyl group.

Introduction

Polymeric materials have contributed significantly to the development and improvement of biomedical devices and systems in medicine. However, there are still several complications impeding wide applications including blood coagulation, calcification, and microbial infection. Surface properties of the polymers have become progressively important in the field of biomaterials, since polymers can contact with physiological components such as blood and living tissue.[1]

Surface modification with various macromolecules, such as albumin, heparin and poly(ethylene glycol) (PEG) have been shown to improve blood compatibility.[2-4] PEG is a well-known and widely used as a component of useful biomaterial. Under aqueous physiological conditions, hydrophilic PEG has kinetic chain mobility and large thermodynamic steric volume, leading to the repulsion of almost all kinds of foreign adherence and adsorption. Meanwhile, a negatively charged surface was found to be more blood compatible than a positive one.[5] Especially many polymers containing sulfonate groups including heparin showed more or less enhanced blood compatibility.[6] Negatively charged sulfonate group expels blood components further by electrical repulsion and also provides anticoagulant activity.[7] Accordingly, the polymeric surface with hydrophilic PEG containing sulfonate terminals is expected to provide much better blood-compatibility with reduced protein adsorption and platelet adhesion due to their synergistic effect. Kim et al. recently reported a series of works on these subjects from several different polymer systems, and the related surface characteristics of the materials and results of physiological experiments have been discussed.[8,9]

To expand the potential usefulness of this approach and also to be used in developing new biomaterial, PEG macromer (MA-PEG-SO_3H) as a hetero-telechelic PEG with an anionic sulfonate group and a polymerizable methacryloyl group at each end of PEG chain was prepared in this work. The preparation and preliminary results on the polymerization reaction thereof are discussed. Copolymerization with other vinyl-type monomers and also crosslinking polymerization with hydrophilic monomers are interesting, which might be able to provide novel biocompatible polymers for coating, grafting, or water-swollen gel form.

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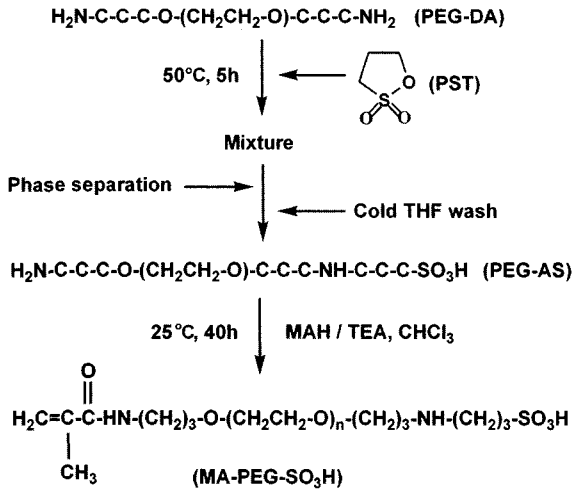
Experimental

Chemicals and Measurements. Diamino poly(ethylene glycol) (PEG-DA, av. M_w 1,000 g/mol) was cordially provided by NOF (Japan). MALDI-MS (Matrix-assisted laser desorption ionization mass spectrometry) of this sample showed narrow distribution with peak molar mass of 1,232 m/z. PEG methyl ether methacrylate (average M_n 1,100 g/mol) was purchased from Aldrich Chemical Co. Tetrahydrofuran (Aldrich, 99%) was distilled over $LiAlH_4$. Triethylamine and toluene was dried over CaH_2, and freshly distilled before use. 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, 2,2-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044, Wako Pure Chemical Ind. Ltd) and ammonium persulfate (APS, Aldrich, 98+%) were used without purification. 2,2-Azobisisobutyronitrile (AIBN) was recrystallized from methanol.

The FT-IR spectra were obtained on a Perkin Elmer FT-IR spectrometer (Model SPECTRUM 2000). ^1H NMR spectra were taken on a Varian Unity Inova 500 MHz Spectrometer. The thermal analysis was carried out on a Perkin Elmer DSC/TGA7 Series thermal analysis system. The molecular weight data were obtained by gel permeation chromatography (GPC; Waters, USA) using water (contains sodium nitrite) as eluent at a flow rate of 0.1 mL/min. PEO standards were used to calibrate the molecular weight. A dynamic light-scattering instrument (DLS, Brookhaven, BI-200SM, USA) with a Ne-He laser was used to measure the size distribution of polymeric spheres in distilled water (concentration, 1 wt/v%). The polymerization product was magnetically dispersed in distilled water and then filtrated using 0.45 μm pore sized filter paper to remove oversized materials. The light intensities scattered from the polymeric spheres were measured at the angle of 90°.

Preparation of PEG Macromer (MA-PEG-SO_3H). MA-PEG-SO_3H was prepared by the following procedure: 1) PST (2.45 g) in THF was added dropwise to 10% solution of PEG-diamine (20 g) in THF, and reacted at 50 °C for 5 h. The reaction mixture was placed still at room temperature to obtain a phase separation, and then the upper layer was decanted. The remaining oily product was washed with cold THF once, and then dried in desiccator under vacuum for several days to get the zwitterionic amino-PEG sulfonic acid (PEG-AS) with 50~55% yield. Elemental analysis showed C, 50.8; H, 9.09; N, 2.05; S, 2.7 wt%, respectively. 2) Above-prepared PEG-AS (3 g) in 30 mL $CHCl_3$ was reacted with molar excess amounts of methacrylic anhydride (MAH, 0.55 g) at 25 °C for 40 h in the presence of triethylamine (TEA, 0.09 g). The resulting mixture was poured into a large amount of diethyl ether to give a sticky precipitate on the bottom, which was separated, washed with flash ether, and then dissolved in deionized water to be freeze-dried for about 3 days. The yield of PEG macromer (MA-PEG-SO_3H) was 75~80%. Elemental analysis showed C, 47.53; H, 9.37; N, 3.08; S, 3.22 wt%, respectively.

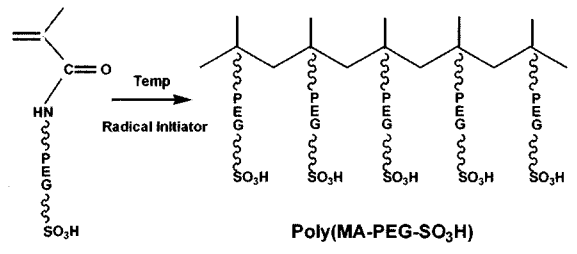


Scheme I. Synthesis of MA-PEG-SO_3H Macromer.

Radical Polymerization of MA-PEG-SO_3H Macromer. Polymerization of the macromer, MA-PEG-SO_3H, in several different solvent systems was carried out using azo- or redox-type radical initiator. The polymerization was conducted with magnetic stirring in 50 mL 3-necked flask fitted with a condenser, nitrogen inlet and outlet. The reaction condition and the polymerization result are presented in Table I. The polymerization product was dialyzed in distilled water for 5 days using a cellulose dialysis tube (MWCO 12,000-14,000 Da) to extract unreacted monomer and oligomers, and then lipophilized by freeze-drying. Off-white powdery products were obtained with yield of ca. 55% for higher molecular weight. Elemental analysis showed average values C, 48.01; H, 9.14; N, 2.28; S, 2.61 wt%, respectively.

Results and Discussion

Synthesis and Characterization of MA-PEG-SO_3H Macromer. MA-PEG-SO_3H, the PEG macromer with methacryloyl and sulfonate groups at each chain end was



Scheme II. Radical Polymerization of PEG Macromer.

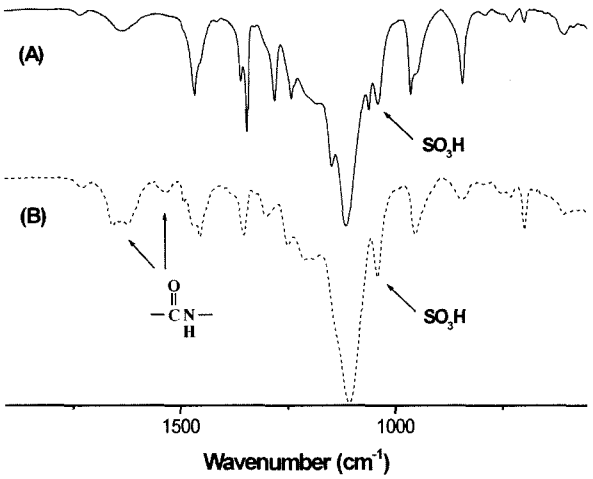


Figure 1. FT-IR Spectra of (A) PEG-AS and (B) MA-PEG-SO_3H.

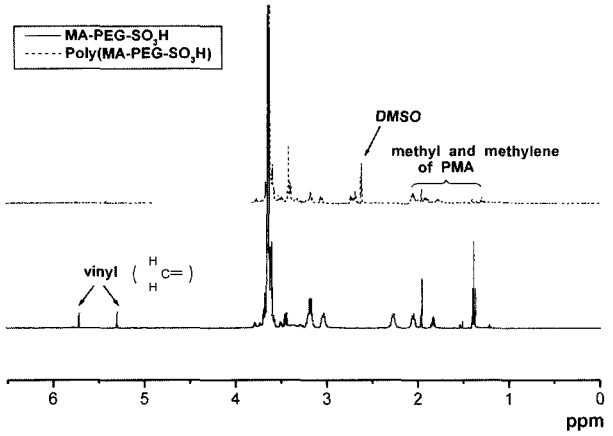


Figure 2. ^{1}H-NMR spectra of MA-PEG-SO_3H and poly(MA-PEG-SO_3H).

prepared from PEG-diamine (M_w of ca. 1,200 g/mol) via zwitterionic H_2N-PEG-SO_3H (PEG-AS) by the modified method previously reported.[9] The choice of the starting PEG molecular weight is based on the prior study investigating the effect of PEG-SO_3H with different size on the platelet adhesion, where PEG molecular weight of about 1,000 g/mol was high enough to exhibit a considerable anti-fouling property of the modified surface therewith.[7] The general preparation of PEG-AS was shortly described in the experimental part. PEG-AS was recovered in separated layer within the reaction mixture, due to the limited solubility of zwitterionic salt form in THF. The followed washing with cold THF provided PEG-AS in rather pure form. The derivatization reaction through amine end-group of PEG using methacrylic anhydride seemed to proceed smooth at room temperature in the presence of triethylamine catalyst. Introduction of methacryloyl groups up to 70%, as calculated based on oxyethylene PEG backbone in ^{1}H-NMR data, could be obtained. The product should contain appreciable amount of unmodified byproducts, though, no extensive purification work was employed here. It is believed that only PEG macromer with methacryloyl end participate in the next polymerization reaction and the oligomeric unmodified macromer or impurities remained can be removed by the polymer precipitation and dialysis separation. The structure of MA-PEG-SO_3H was characterized by FT-IR and ^{1}H-NMR (Figure 2, bottom). IR spectrum of PEG-AS (Figure 1A) showed strong ethylene ether(C-O-C) absorption band at 1115 cm^{-1} with a characteristic band at 1038 cm^{-1} assignable to sulfonic acid group. IR spectrum of MA-PEG-SO_3H macromer showed amide absorption bands at 1650 and 1535 cm^{-1}. From the ^{1}H-NMR spectrum of MA-PEG-SO_3H, the vinylic protons at 5.29, 5.78 ppm and methyl proton at 1.95 ppm were observed, respectively, to confirm the introduction of methacryloyl group on the PEG. DSC measurement of MA-PEG-SO_3H showed a melting transition at around 40 °C.

Radical Polymerization of MA-PEG-SO_3H. Free-radical polymerization reaction of MA-PEG-SO_3H macromer was conducted in different media using several different initiators. The results of polymerization are shown in Table I. polymerization in water using VA-044 or ammonium persulfate provided higher molecular weight polymer. Polymerization in organic toluene using AIBN gave also relatively high molecular weight polymer, but the yield was low, probably

Table I. Free Radical Polymerization of MA-PEG-SO_3H

Run	Initiator[a]	Solvent (mL)	Temp. (°C)	Time (hr)	Yield (%)	GPC		dm (nm)[b]
						M_n	M_w	
1	AIBN	Toluene (5)	65	20	23	43,900	125,100	170
2	AIBN	EtOH+water (4/1)	65	20	30	3,220	5,560	143
3	VA-044[c]	Water (5)	44	20	52	57,900	278,200	172
4	APS[d]	Water (5)	40	20	53	55,700	249,000	190

[a]Initiator 1.5 wt% to monomer. [b]dm = Particle diameter in water determined by DLS.
[c]2,2'-Azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride. [d]Ammonium peroxydisulfate.

caused by poor solubility of polymer in the same solvent. On the contrary, the polymerization in EtOH/water mixture resulted in only oligomeric polymer, suggesting that the polymerization did not proceed well in this particular solvent system probably due to the chain transfer to ethanol solvent as known. This result is in contrast with those in pure water system. The possible micelle formation during the polymerization process might be responsible for this solvent effect, where methanol solvent can prevent micelle forming and retard the polymerization of the rather big-sized PEG macromer.

Typical GPC traces of high polymer and macromer are shown in Figure 3. The molecular size distribution of polymers was a little broad. ^{1}H NMR spectra (Figure 2, top) showed that the vinyl peak of macromer, originally at 5~6 ppm, disappeared, and methyl and methylene proton peaks (1~2 ppm) of poly(methacryl amide) backbone was newly discernible. The prepared polymer was soluble in water and methanol freely, while it showed poor solubility in chloroform and THF. DSC and TGA thermograms of a representative polymer are shown in Figure 4. The polymer did not show weight loss up to about 300 °C in both air and nitrogen atmosphere, which suggest fairly good thermal stability of this PEG graft polymer. DSC of quenched polymer sample showed glass transition at around -43 °C and crystallization exotherm at the temperature -15~10 °C, which was followed by endothermic melting transition with the peak at 28 °C. Evidence of micelle formation in aqueous solution was obtained by DLS measurement (Figure 5). The particle size distributions came out with some variation, though, the mean diameter was in the range of 170~190 nm, which suggest the association of the molecule during the course of polymerization and the possible influence on the polymerization kinetics.[10] Additional supporting analyses are needed for the detailed polymerization behavior, which are cur-

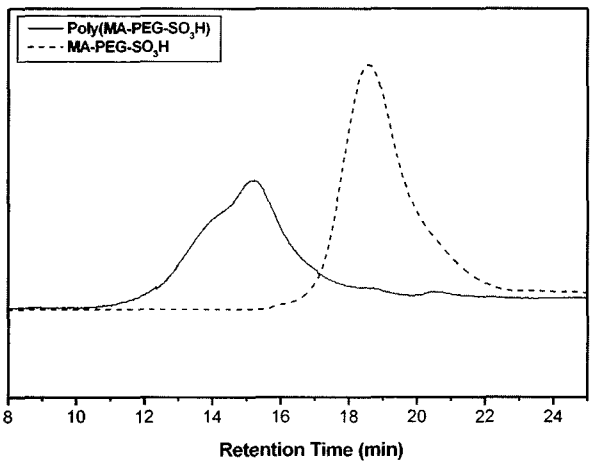


Figure 3. Typical GPC chromatograms of MA-PEG-SO_3H and poly(MA-PEG-SO_3H).

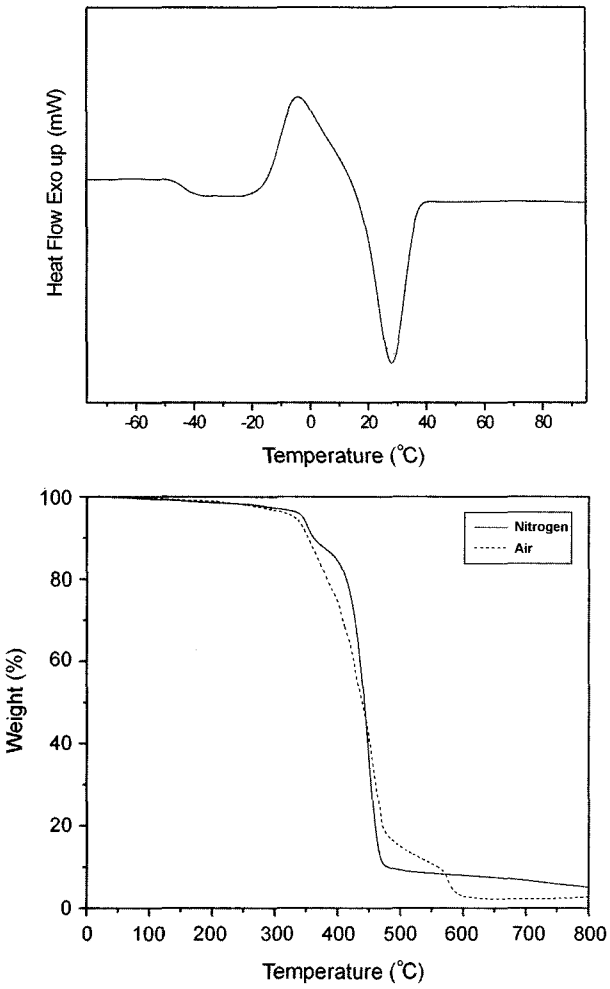


Figure 4. DSC and TGA thermograms of poly(MA-PEG-SO_3H).

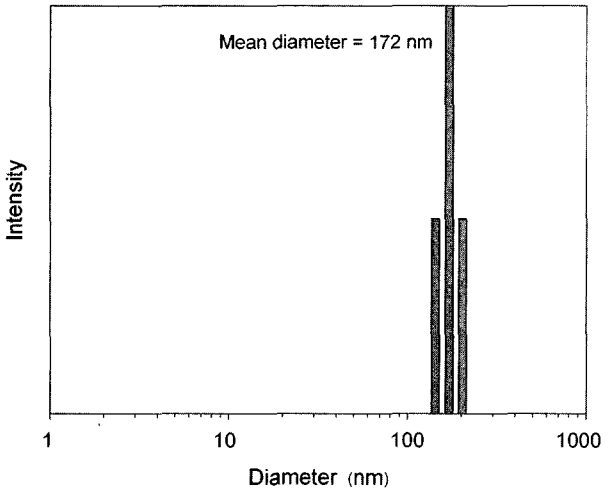


Figure 5. Particle size distribution by dynamic light scattering measurement.

rently under investigation. Copolymerzation of MA-PEG-SO_3H with another vinyl monomer such as hydrophobic alkyl methacrylate, and also crosslinking (co)polymerization to prepare novel hydrogels containing PEG-sulfonate will be the topics to be studied, and their various properties are to be reported in next communication.

Conclusions

Functional PEG macromonomer with methacryloyl and sulfonate groups at each chain end were prepared from PEG-diamine via zwitterionic amino-PEG sulfonate.

Free radical polymerization of the PEG macromonomer in different media was investigated to synthesize comb-shaped, PEG graft polymers with relatively high molecular weight. The resulting polymers was freely soluble in water and methanol, and thermally stable up to 300 °C. Possible micelle formation in aqueous medium was evidenced by dynamic light scattering measurements.

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