Preparation and Properties of PEG Hydrogel from PEG Macromonomer with Sulfonate End Group

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ABSTRACT: A novel PEG macromonomer with methacryloyl and sulfonate group at each chain end was prepared, and new PEG-based hydrogels were prepared by crosslinking polymerization of this PEG macromonomer in the presence of PEG dimethacrylate. Their swelling properties are measured and compared with those of reference hydrogel from methoxy PEG methacrylate to elucidate the effect of the sulfonate end group. The prepared sulfonated PEG hydrogels exhibited water absorbency in the range of 19 ~ 42 g water/g dry-gel depending on the composition. These hydrogels with anionic sulfonate group showed swelling behavior varying with salt type, concentration, and also with pH of aqueous solution. The morphology of the sulfonated PEG gels by SEM showed irregular porous network structure varying with the composition. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 96: 56–61, 2005

Key words: PEG; macromonomers; hydrogels; swelling; sulfonate group

INTRODUCTION

Hydrogels are highly biocompatible because of their low surface tension, their hydrodynamic properties being similar to those of natural biological gels and tissues, and their minimal mechanical irritation due to their soft and rubbery state. Increasing interest has been devoted over the years to the synthesis of polymeric hydrogels based on poly(ethylene glycol) (PEG) elastic chains.[1–4] PEG · possesses a wide range of beneficial properties for biomedical applications, including having low toxicity and being nonthrombogenic.[4–6] Nevertheless, PEG is water soluble and cannot be used directly in contact with blood or tissue. PEG chains aimed for use in biomedical applications have to be either grafted onto surfaces or crosslinked. To identify the efficient "nonfouling" surfaces, a variety of strategies for tailoring the surfaces of materials with PEG grafts have been developed.[2,4,7]

On the other hand, it was reported that material with a negatively charged surface exhibited improved blood compatibility compared to a neutral one.[8] Kim et al.[9] reported that PU grafted with PEG–SO_3 exhibited a superior effect on thromboresistance as determined by decreased platelet adhesion or protein adsorption, and suppressed calcification, which was compared with the surface grafted with PEG only. Accordingly, it is highly probable that PEG containing sulfonate end groups, i.e., sulfonated PEG (PEG–SO_3H), or substrate with modified surface containing PEG–SO_3H brush enhance biocompatibility of materials significantly by means of a synergistic effect of the dynamic mobility of PEG chains and the negatively charged sulfonate groups.

The objective of this study was to prepare a novel PEG-based hydrogel from methacryloyl PEG macromonomer containing a sulfonate end group to identify a novel biocompatible hydrogel and possible biomedical applications, including coatings or matrices for drug delivery and tissue engineering.

EXPERIMENTAL PROCEDURES

Chemicals and measurements

MA–PEG–SO_3H, which was prepared in this work, and poly(ethylene glycol) methyl ether methacrylate (MA–PEG–OMe, M_w = 1,100, Aldrich) were vacuum dried for 1 week before use. Ammonium peroxodisulfate (APS, Aldrich, 99%) and poly(ethylene glycol) dimethacrylate (PEGDMA, M_w = 400, Polysciences Inc.) were used without further purification. Deionized water was used as the reaction medium.

The IR spectra were obtained on a Unicam 1000 FTIR spectrometer. Surface morphology of the dry-gel scaffold was measured by SEM (Model XL30 ESEM-FEC, FEI Co.) to observe the porous structure. Powder samples were mounted on a metal stub with double-

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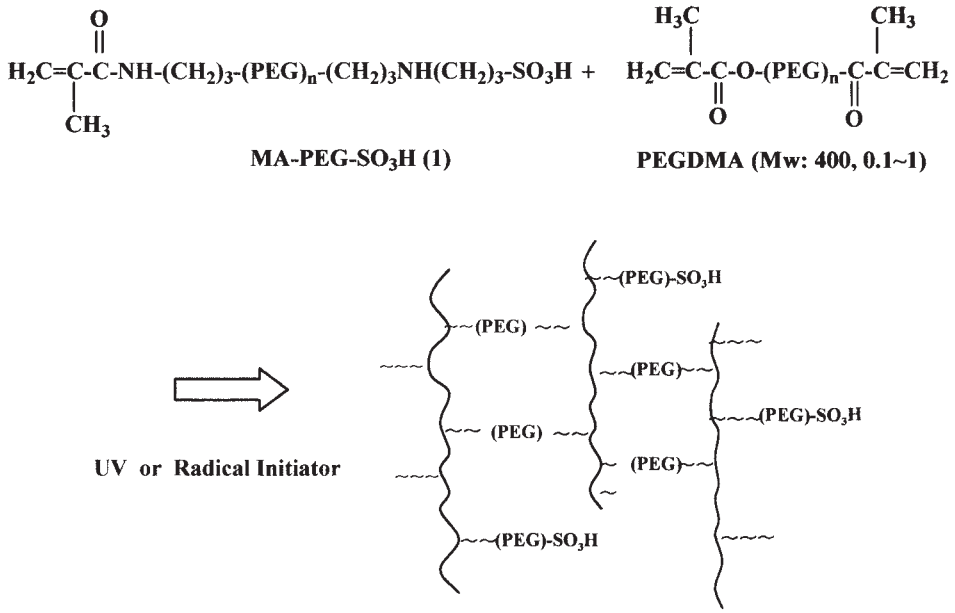


Scheme 1 Preparation of sulfonated PEG hydrogels.

sided tape and coated with platinum for 30 s under argon atmosphere using plasma sputter.

Preparation of PEG macromonomer

MA–PEG–SO_3H macromonomer was prepared using the following procedure: briefly, 10% PST (2.45 g) in THF was added dropwise to 10% PEG–diamine (M_w = 1,100; 20 g) solution in THF and reacted at 50°C for 5 h. The reaction mixture then was placed at room temperature until phase separation was obtained, and the upper layer was decanted. The remaining oily product was washed with cold THF and then dried at room temperature for several days to obtain the zwitterionic sulfonated PEG–amine (PEG–AS). Consecutively, 10% PEG–AS (3 g) in $CHCl_3$ was reacted with excess amounts of methacrylic anhydride (MAH, 0.55g) at 25°C for 40 h in the presence of triethylamine (TEA, 0.09 g). The reaction mixture was precipitated into a large amount of diethyl ether. The resulting sticky product was separated and dissolved in deionized water and then freeze-dried to yield a white powdery PEG macromonomer (MA–PEG–SO_3H) in about 80% yield. Elemental analysis showed average values C, 48.01; H, 9.14; N, 2.28; and S, 2.61 wt %, respectively.

Radical crosslinking polymerization of PEG macromonomers

The PEG macromonomer containing a sulfonate end group, MA–PEG–SO_3H, was prepared according to the modified method previously reported[9–11] and used for the preparation of hydrogel with commercially available PEG–dimethacrylate (M_w = 400) as the difunctional crosslinker with a PEG backbone. The chemical structure of MA–PEG–SO_3H and a schematic representation of the networks are shown in Scheme 1. A small-sized glass ampule was used for the reaction. Typically, to the flame-dried ampule, MA–PEG–SO_3H 0.5 g (0.357 mmol) and various molar amount of PEG-DMA were added and dissolved in 2 mL of deionized water. The reaction ampule was capped with a rubber septum and the system was purified by repeated vacuum application and nitrogen purge through a three-way stopcock. The initiator (APS) solution was added by microsyringe to the above solution and then it was placed in a water bath, controlled at 40°C, to react for 10 h. The prepared gel product, after washing in distilled water for 24 h to remove any remaining soluble fraction, was freeze-dried to obtain white, porous dry-gel with the yields in the range of 65 to 70%. As reference materials, the same procedure was used to prepare a series of PEG hydrogel from PEG methacrylate with a methoxy end group, MA–PEG–OMe, with yields of 85 ~ 90%.

Water absorbency and swelling measurement

The swelling degree and rate in different media were measured by using a simple tea bag method or direct weighing of the swelled gel sample. A certain amount of dry-gel powder or pressed disc (W_{dry}) was weighed (in an empty bag) and placed in an aqueous medium until equilibrium swelling was obtained. The weight of the swollen gel (W_{swell}) was measured directly or was obtained by subtracting the predetermined empty

TABLE I
Preparation of Sulfonated PEG and Methoxy PEG Gel[a]

Code	MA–PEG–SO_3H, (g)	PEGDMA[b] (g)	Yield (%)	State	Code	MeO–PEG–MA, g	PEGDMA[b] (g)	Yield (%)	State
SPEG-1	0.5	0.143 (28.6)	67	Hetero	MPEG-1	0.5	0.163 (32.6)	94	Homo
SPEG-2	0.5	0.100 (20.0)	68	Hetero	MPEG-2	0.5	0.127 (25.4)	90	Homo
SPEG-3	0.5	0.071 (14.2)	63	Homo	MPEG-3	0.5	0.091 (18.2)	88	Homo
SPEG-4	0.5	0.043 (8.6)	65	Homo	MPEG-4	0.5	0.054 (10.8)	87	Homo
SPEG-5	0.5	0.014 (2.8)	64	Homo	MPEG-5	0.5	0.018 (3.6)	86	Homo

[a] Initiator:ammonium peroxodisulfate, (1 wt % of total monomer), Solvent; deionized water (2 ml).
[b] Values in parentheses are wt % based on macromonomer.

wet tea bag weight from the total weight of the bag including gel sample. The swelling ratio (or water absorbency) was simply calculated using the equation below:

$$\text{Swelling Ratio} = W_{swell}/W_{dry} \times 100$$

RESULTS AND DISCUSSION

Preparation of sulfonated PEG macromonomer and the hydrogel

Macromonomers, both MA–PEG–SO_3H and MA–PEG–OMe, were used to prepare PEG-based hydrogels with difunctional PEGDMA as the crosslinker in deionized water. MA–PEG–SO_3H was synthesized according to the procedure described previously, and the introduction level of the methacryloyl group was calculated to be about 70% from the ^1H NMR analysis. The composition and yields of the prepared gels are shown in Table I. When PEGDMA content was 20 wt % and higher for sulfonated PEG (SPEG) gel, a heterogeneous and elastic solid gel was finally obtained. In the lower contents below 20 wt %, transparent and homogeneous gel products were formed. As the PEGDMA content decreases, the gel exhibited a less elastic, but more viscous nature, which will be ascribed to the loosely crosslinked structure formed at lower PEGDMA content. In the case of the methoxy–PEG (MPEG) gel, clear and transparent gels were obtained throughout the entire composition range. The yields of the recovered gels in the SPEG gel series (63–68%) were lower than those of the MPEG gel (86 ~ 94%), which resulted from the lower purity level of MA–PEG–SO_3H macromonomer.

Figure 1 shows a typical FT-IR spectrum of a SPEG gel sample (SPEG-3). The characteristic absorption band of PEG backbone (C–O–C) appeared at 1115 cm^{-1}, along with band at 1033 cm^{-1} corresponding to –SO_3H and those at 1643 and 1730 cm^{-1} of the amide group.

Swelling properties of sulfonated PEG hydrogel

Figure 2 shows the swelling ratio as a function of PEGDMA content for both SPEG and MPEG gels. SPEG gel showed swelling ratios in the range of 19

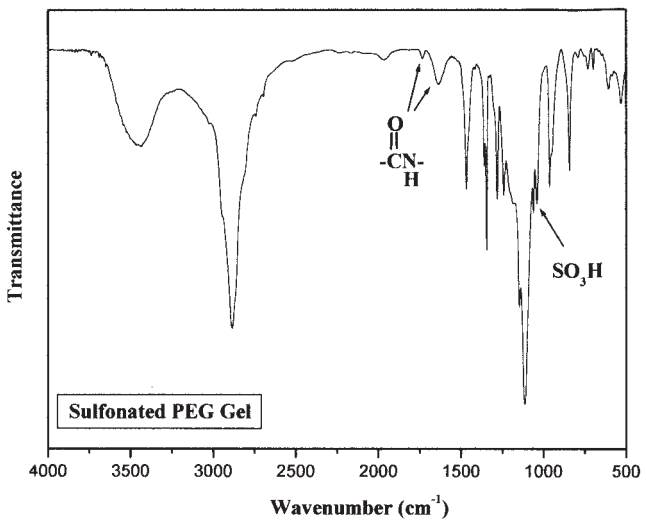


Figure 1 FT-IR spectrum of SPEG gel sample (SPEG-3).

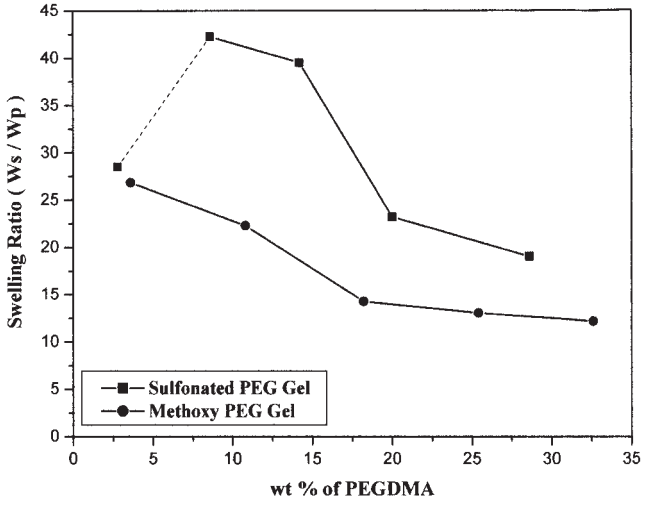


Figure 2 Swelling ratios of both SPEG and MPEG gels as a function of PEGDMA content.

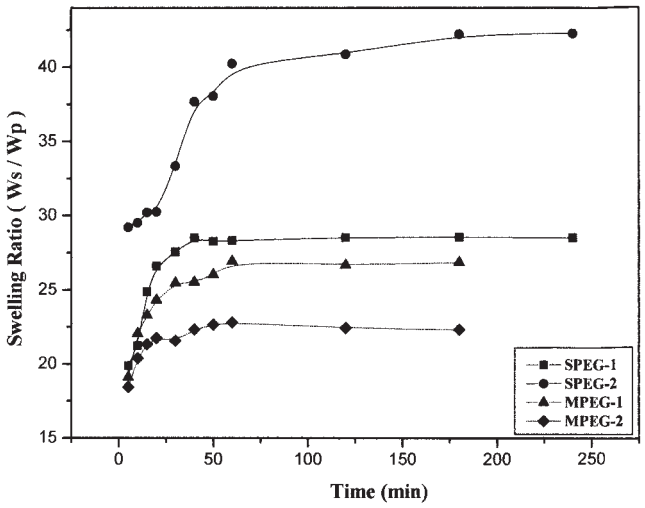


Figure 3 Swelling curves of the different PEG gel samples.

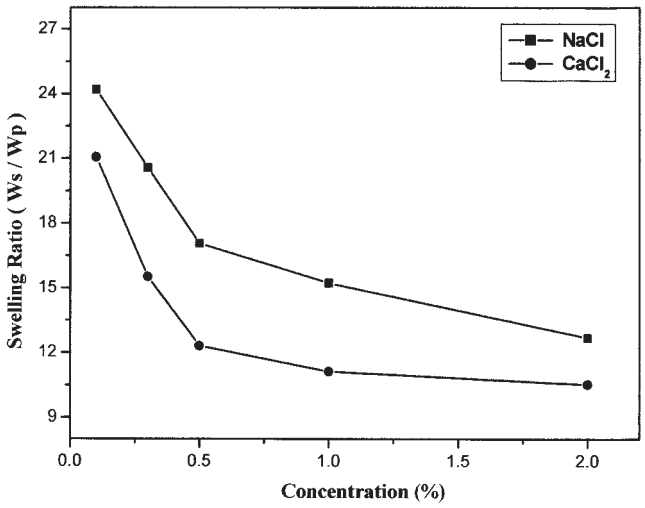


Figure 5 Change of swelling in aqueous solution containing different amount of salt additives (gel sample SPEG-4, soaking time: 3 h).

~ 42 g water/g dry-gel, which were higher compared to those of MPEG gels with 12 ~ 27g water/g dry-gel. More hydrophilic sulfonate groups attached in SPEG gel should contribute to increase affinity toward water, resulting in higher swelling at a similar level of crosslinking degree. The swelling ratio tends to decrease as the PEGDMA content increases, due to the increased crosslinking density. As can be noticed in Figure 2, however, the swelling ratio of the SPEG-5 sample was observed to be lower than that of SPEG-4. This deviation from the increasing tendency seems to result from the relatively loose and underdeveloped network structure that might be formed at this relatively low level of crosslinking. Both types of gel samples exhibited fast swelling initially, then leveled off to equilibrium values in about 1 h as the curve shown in Figure 3.

For both SPEG gel and MPEG gel, the changes in water absorbency value in phosphate-buffered saline (PBS, pH 7.4) as a function of PEGDMA content are plotted (Fig. 4). First of all, SPEG gels showed a much lower swelling degree (~ 15 g water/g dry-gel) compared to those in pure water, which could be explained from the fact that high ionic strength of the medium acted adversely to the equilibrium swelling capacity of this PEG gel with the ionic sulfonate group. Also they exhibited very small differences in swelling as a function of PEGDMA content except for the SPEG-5 sample. The same explanation will be applicable to the observation of lower absorption for SPEG-5 as above. Comparatively, the swelling degrees

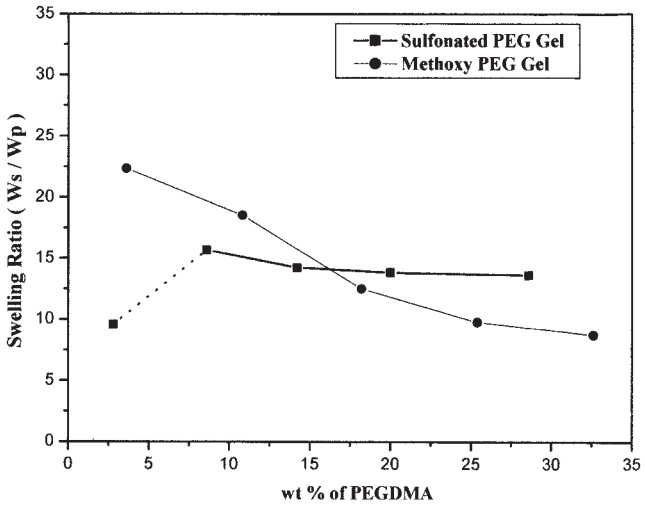


Figure 4 Change of water absorbency in phosphate-buffered saline (PBS, pH 7.4) as a function of PEGDMA content.

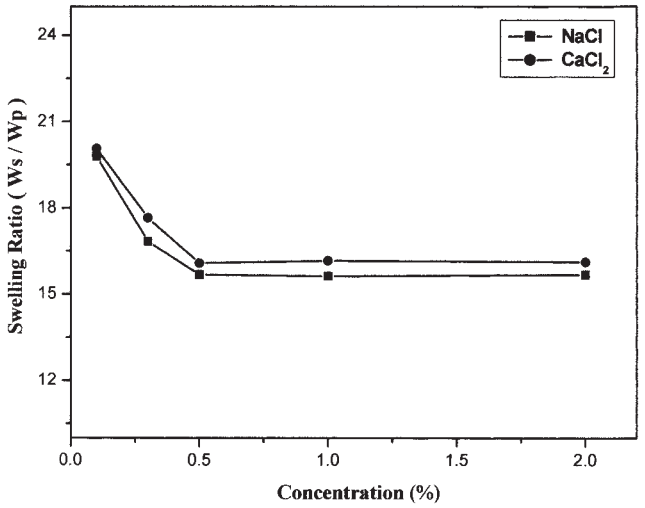


Figure 6 Change of swelling in aqueous solution containing different amount of salt additives (gel sample MPEG-4, soaking time: 3 h).

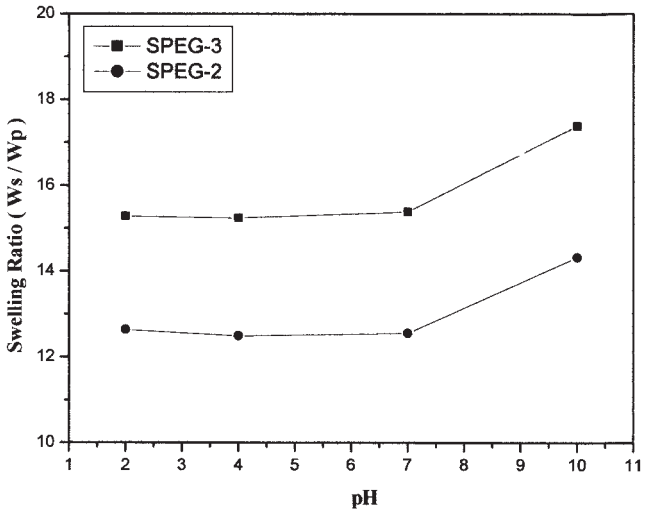


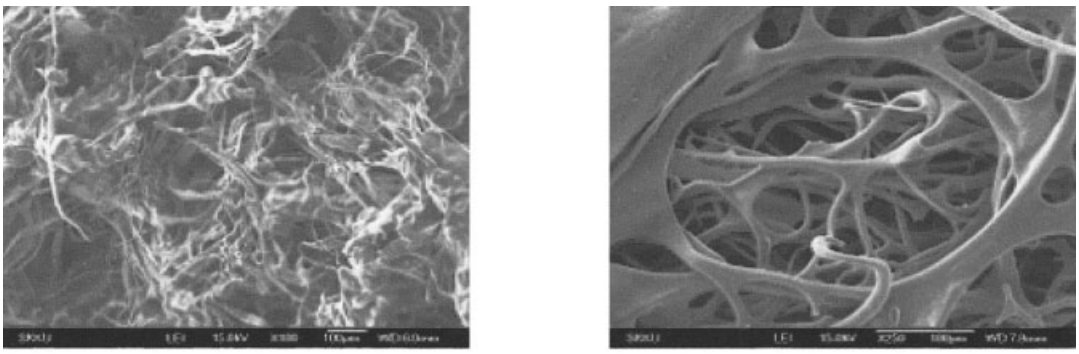
Figure 7 Swelling ratios at different pH of buffer solution (gel sample: SPEG-2 and SPEG-3, soaking time: 3 h).

of MPEG gels in PBS solution were not much different from those in pure water, which would be due to the neutral and nonionic nature of the unmodified PEG gel. The water absorbency, however, decreased gradually as function of PEGDMA content as usual.

The basic swelling behavior of the SPEG hydrogel suggests that the ionic sulfonate groups at the end of PEG chains influence significantly not only the overall gel property but the gel surface nature. Figure 5 shows swelling in ion-containing aqueous solution of two different salt compounds for SPEG gel. As the salt concentration increases, the water absorbency decreases gradually and seems to level off. Compared to the NaCl solution, the absorbency in the divalent $CaCl_2$ solution appeared at a lower level, decreasing more rapidly as the salt concentration was increased. The difference can be ascribed to both high ionic strength and effect of counter-ion association in aqueous $CaCl_2$ solution. On the contrary, nonionic MPEG gels exhibited almost the same level of water absorbency in both solutions (Fig. 6). Except for the very low concentration range below 0.5 wt %, the swelling degree did not change as a function of salt concentration. These results are also compared to those of the SPEG gel.

Figure 7 shows the swelling dependency on the pH of aqueous buffer solution. SPEG-2 and SPEG-3 gel samples were used for the test at room temperature, and the water absorbency value after the immersion time of 3 h was taken. The swelling degrees at alkaline pH were higher, even though the differences were not large. The terminal sulfonate groups on the PEG chains, although the molecular fraction is small, will be responsible for this increased absorption at higher pH. The fully ionized form existing at higher pH can provide increased water absorption compared to the acidic form. So, it is reasonably expected that the influence of the terminal sulfonate groups will come out more significantly at the elevated content of acidic sulfonate group within the gel system. The temperature dependency on the gel swelling behavior was also evaluated. From the measurement at different temperatures (20 $\sim$ 50°C), the initial swelling degree was higher at higher temperatures, probably caused by the thermal expansion effect. However, the equilibrium swelling degrees were almost same with marginal differences, i.e., the temperature dependency on swelling degree was negligibly small.

Figure 8 shows typical SEM micrographs of a freeze-dried SPEG hydrogel. An irregular, entangled fibrous morphology is seen in the SPEG-3 sample. The morphology of SPEG-4 appeared somewhat different, where relatively regular pores of tens to hundreds micrometers in size are formed through well-connected gel matrices. The porous network structure of this hydrogel with its biodegradability and relatively strong gel strength might be useful as a biocompatible biomaterial. Further studies on the gel surface prop-



(a) (b)

Figure 8 SEM images of freeze-dried, sulfonated PEG gel. (a) SPEG-3, ×100 (b) SPEG-4, ×250.

erties and introduction of sulfonated PEG to other hydrogel systems are currently under investigation.

CONCLUSION

New PEG-based hydrogels were prepared by crosslinking polymerization of a novel PEG macromonomer containing a sulfonate end group in the presence of PEG dimethacrylate, and their swelling properties were measured and compared with those of a reference hydrogel from methoxy PEG methacrylate. The prepared sulfonated PEG hydrogels exhibited water absorbency in the range of 19 $\sim$ 42g water/g dry-gel depending on the composition. These hydrogels with anionic sulfonate groups showed swelling behavior varying with salt type and concentration, where the swelling degrees decreased as the salt concentration increased and the effect was much greater in divalent $CaCl_2$ compared to NaCl aqueous solution. In addition, the swelling degree was high at an alkaline pH of aqueous solution. The morphology of the sulfonated PEG gels by SEM showed a porous network structure desirable for current biomedical applications.

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