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Preparation and Properties of Modified PHEMA Hydrogels Containing Thermo-responsive Pluronic Component

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Abstract: To modify and strengthen the properties of PHEMA hydrogel, composite hydrogels containing varying amounts of a Pluronic (PEO-PPO-PEO) component were synthesized by bulk polymerization of HEMA in the presence of Pluronic dimethacrylate under mild photoinitiating conditions. The effects of the Pluronic component on gel properties were investigated by measuring the degree of swelling with its temperature responsive behavior, the mechanical properties, and the morphology of the composite hydrogels. With increased Pluronic content, the modified PHEMA hydrogels exhibited an increase in the degree of swelling, and the swelling showed an enhanced thermo-responsive behavior that was completely reversible. In addition, improved mechanical strength and the development of a microporous gel morphology were observed in hydrogels containing Pluronic.

Keywords: PHEMA, Pluronic F127, thermo-responsive swelling, photo-polymerization.

Itroduction

Hydrogels have been broadly used for a variety of biomedical applications including contact lenses, wound-healing bioadhesives, artificial kidney membranes, articular cartilage, maxillofacial and sexual organ reconstruction materials, and artificial skin.[1] Among the different types of hydrogels, stimuli-responsive polymers and hydrogels, which undergo a phase transition in response to external stimuli like temperature,[2-6] pH,[7,8] and light,[9] have received much attention during the last several years. In particular, temperature-responsive hydrogels like poly(*N*-isopropylacrylacrylamide) (PNIPAAm) or poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (Pluronic®) have been widely studied for use in diverse applications such as drug delivery,[10,11] tissue engineering,[12] and cell culture.[13] A reverse thermoresponsive event is usually called a reverse thermal gelation (RTG) and this quality constitutes one of the most likely strategies for the development of injectable systems. An aqueous solution of Pluronic, PF-127, at 20% or higher concentrations exhibits the phenomena of reverse gel when the temperature increases from 4 to 37 °C (body temperature); this gelation is reversible upon a decrease in temperature. The hydrogel formed by PF-127 has been studied extensively in biomedical applications and has been used for protein and peptide drug delivery.[14]

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Poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels are highly biocompatible, transparent, soft materials with a high thermal stability, resistance to acid and alkaline hydrolysis, and tunable mechanical properties.[1] These properties make PHEMA hydrogels particularly useful for application in biomedical devices such as catheters, intrauterine inserts, prosthesis, or intraocular and soft contact lenses, as well as a basis for drug delivery systems. Bulk polymerization of 2-hydroxyethyl methacrylate (HEMA) results in a glassy and crystalline polymer which has similar hardness to poly (methyl methacrylate); however, this HEMA polymer becomes soft and flexible when wetted with water. Although bulk-polymerized PHEMA allows the transfer of swelling agents and some low molecular weight solutes, it is considered non-porous. To enhance the potential of PHEMA hydrogels for use in drug delivery systems, its chemical bonding with drugs or copolymerization with monomers containing ionic or hydrophobic groups has been widely studied.[15,16] Ayhan *et al.* prepared PHEMA-based hydrogels containing PEG-diacrylate and studied the drug release behavior.[17] And also, in our previous studies, we investigated PHEMA gels modified with PEG or SPEG (PEG with sulfonate end-group) macromers to elucidate the effects of a PEG tether on the swelling behavior, morphology, and biocompatibility of the gels.[18-20]

In this study, we attempted to synthesize PHEMA hydrogels containing the Pluronic, PEO-PPO-PEO triblock copolymer, which is well known as a thermo-responsive biocompatible

polymer. A Pluronic dimethacrylate macromer was prepared and used during photo-polymerization of HEMA under a nitrogen atmosphere. It is predicted that the resulting PHEMA-*co*-Pluronic composite hydrogels would possess a thermally responsive swelling-deswelling behavior caused by the temperature-induced molecular rearrangement of Pluronic component within the hydrogel matrix.

Experimental

Chemicals and Measurements. 2-Hydroxyethyl methacrylate (HEMA, 97%) was purchased from Aldrich (St. Louis, MO) and, before use, was passed through an alumina column to remove any polymerization inhibitors. Pluronic F127 ($(PEO)_{99}(PPO)_{67}(PEO)_{99}$) was obtained from Aldrich and vacuum dried for 48 h before use. Methacrylic anhydride (MA, 94%) and 2,2-dimethoxy-2-phenylacetophenone (DMPAP, 99%) were purchased from Aldrich Chemical Co.

IR spectra were obtained using a Perkin Elmer FT-IR spectrometer (Model SPECTRUM 2000). The morphology of the dried gel was observed using a scanning electron microscope (HITACHI S-4100, Japan). A porous gel sample was mounted on a metal stub with double-sided carbon tape and coated with Pt for 20 min under vacuum (10^{-3} Torr) using plasma sputtering (Ion sputter coater HC-21). ^{1}H-NMR spectra were recorded on a Bruker AMX-500 spectrometer using $CDCl_3$ as the solvent. Mechanical strength was measured using a Universal Testing Machine (Lloyd, England) at a crosshead speed of 1.0 mm/min. For each test, five measurements were obtained and the average value was taken.

Swelling Degree and Optical Transmittance Measurement. The degree of swelling of the gel sample was determined by conventional gravimetric analysis. A pre-weighed piece of dry gel (W_{dry}) was immersed into a swelling medium and allowed to swell. The swollen piece was then removed, pressed gently between two pieces of filter paper to remove any excess water, and weighed. This procedure was continued until equilibrium swelling was obtained. At this point, the weight of the swollen gel (W_{swell}) was measured. The swelling ratio (%) was expressed as follows:

$$\text{Swelling Ratio (\%)} = (W_{swell} - W_{dry}) / W_{dry} \times 100$$

To examine the temperature-responsive behaviors of P(HEMA-*co*-Pluronic) hydrogels, swelling ratios at different temperatures were measured. Equilibration was carried out for 12 h before measuring the wet weight. For the cyclic swelling measurements, gel samples were incubated in distilled water and the temperature was varied between 20 and 40 °C in a step-wise manner.

The degree of transmittance of the prepared hydrogel at different temperatures was measured by a UV-visible spectrophotometer (Libra S22, Biochrom, UK) using 500 nm of UV light, after an initial equilibrium swelling at 20 °C in distilled water. A homo PHEMA hydrogel was used as the reference, and transmittance values were measured by raising the temperature at 1 °C/min from 20 to 60 °C.

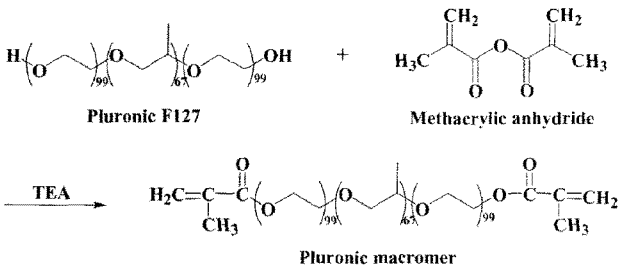
Synthesis of Pluronic-Dimethacrylate (Pluronic-DMA) Macromer. Ten grams (1.0 eq) of Pluronic F127 was poured into a three-neck flask and dried as described above. The polymer was then dissolved in 20 mL of chloroform and the solution cooled to 0 °C in an ice bath. After cooling, 880 μL of TEA (8.0 eq) was added to the solution. Next, 1,140 μL (8.0 eq) of methacrylic anhydride was diluted in 5 mL of chloroform and then added dropwise to the cooled mixture for 1 h under a dry nitrogen flow and with magnetic stirring. The reaction was allowed to proceed for 24 h at 50 °C. The crude product was filtered and the filtrate was poured into 500 mL diethyl ether under vigorous stirring. The precipitate was filtered on a glass funnel and washed twice with pure ether solvent. The white, solid product was dried in a vacuum at room temperature for 48 h (yield ~82%). The structure of Pluronic with methacrylate end-groups was confirmed by ^{1}H-NMR.

Synthesis of P(HEMA-*co*-Pluronic) Hydrogels Using a Photo-Polymerization Method. Different amounts (1, 3, 5, 10% (w/w)) of Pluronic macromer and HEMA were weighed, placed into vials, and stirred for 1 h. Then, DMPAP at 1% (w/w) of the polymer was added to the mixture solution as the photo-initiator. Eight hundred μL of each of the above solutions was transferred into a silicone mold (3 cm×3 cm ×1 mm) and a polymerization reaction carried out to form a crosslinked gel. Gels were exposed to low intensity UV light with a wavelength of 365 nm (UVP model UVGL-58, Upland, CA) for 20 min under a nitrogen atmosphere. Cured gels were washed in distilled water for 3 days to remove unreacted monomers. The prepared gel plates were approximately 1 mm thick.

Results and Discussion

Preparation of Pluronic-Containing PHEMA Hydrogels. Pluronic dimethacrylate (Pluronic-DMA) macromer was synthesized as the reaction of OH-terminated Pluronic according to the previously described procedure,[21] which was shown in Scheme 1. The structure was confirmed by ^{1}H-NMR analysis, which showed incorporation of methacrylic groups at both ends of the Pluronic polymer. The vinyl protons of the methacrylate group (=CH_2) appeared at 5.58 ppm and 6.13 ppm, and the three protons of the methyl substituent (=CCH_3) are shown at 1.95 ppm.

Pluronic-DMA was introduced to the HEMA gel preparation by photo-polymerization. The mixed solution of HEMA and a predetermined amount of Pluronic-DMA was placed in a mold and was irradiated by UV light resulting in gel blocks with ca. 1 mm thickness. Figure 1 shows the FT-IR spectra of the Pluronic, PHEMA and the composite gels. The characteristic absorption band corresponding to the



Scheme I. Synthesis of Pluronic dimethacrylate.

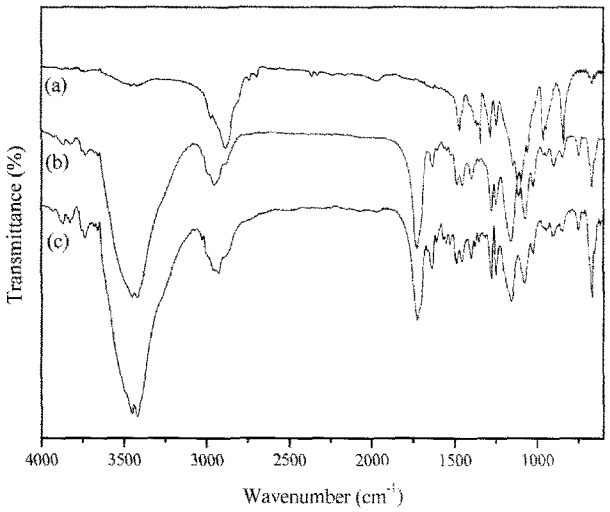


Figure 1. FT-IR spectra of (a) Pluronic macromer, (b) PHEMA, and (c) P(HEMA-*co*-Pluronic-10%).

C-O-C bond of the Pluronic backbone and methylene (C-H) appeared at 1161 cm^{-1} and 2925 cm^{-1}, respectively, with enhanced intensity in addition to those of neat PHEMA.

Swelling Properties and Transmittance of P(HEMA-*co*-Plurnoic) Hydrogels. The swelling curves in Figure 2 show that gel samples reached equilibrium swelling in approximately 6 h and remained constant thereafter. The swelling ratio increased linearly as the Pluronic content was increased from 0 to 10%. A more hydrophilic PEO group of the Pluronic would probably result in a higher swelling capacity of the composite gel. Figure 3 shows the swelling ratio of P(HEMA-*co*-Pluronic) hydrogels as a function of temperature. Swelling ratios were determined after incubating the hydrogels in distilled water for 12 h at each different temperature. Note that in all samples the swelling ratios decreased monotonously with increasing temperature. The dependence on the temperature, however, was more pronounced in gels with higher Pluronic content. This result suggests that the well-known reverse thermo-responsive behavior of the Pluronic component occurs and plays an important role in the deswelling of the composite hydrogels at elevated temperatures. This phenomenon can be attributed to molecular reorganization of PEO-PPOPEO segments

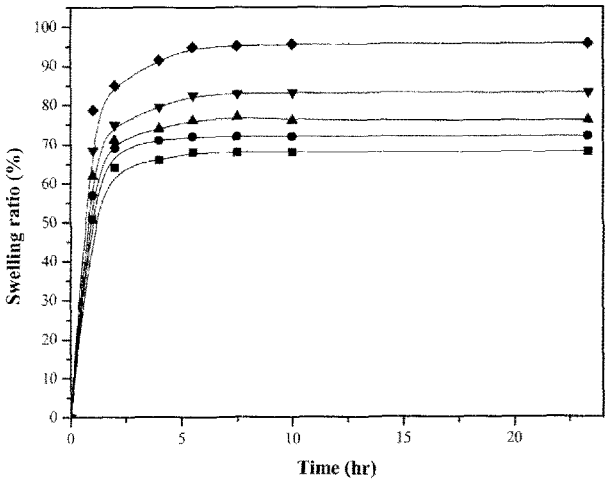


Figure 2. Swelling curves of the hydrogels: (■) pure PHEMA, (●) P(HEMA-*co*-Pluronic-1%), (▲) P(HEMA-*co*-Pluronic-3%), (▼) P(HEMA-*co*-Pluronic-5%), (◆)P(HEMA-*co*-Pluronic-10%).

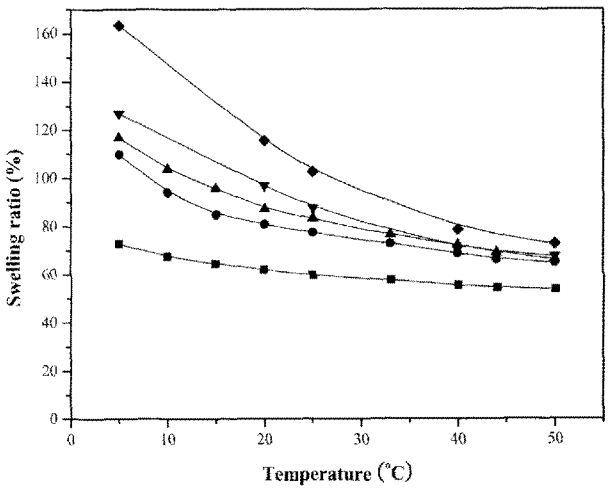


Figure 3. The swelling ratio-temperature curves of the hydrogels: (■) pure PHEMA, (●) P(HEMA-*co*-Pluronic-1%), (▲) P(HEMA-*co*-Pluronic-3%), (▼) P(HEMA-*co*-Pluronic-5%), (◆) P(HEMA-*co*-Pluronic-10%).

between crosslinkages, resulting in shrinkage of the mesh size within the gel at a higher temperature (see Figure 4).

Changes in the transmittance (or turbidity) of hydrogel samples as a function of temperature were monitored to further investigate their thermo-responsive behavior, and the trends are shown in Figure 5. Transmittance of the hydrogels at each temperature was measured on UV (500 nm) by slowly raising the cell temperature (the gel sample was mounted on the cell wall) from 20 to 60 °C at a rate of about 1 °C/min. Neat PHEMA hydrogel was used as the reference. Composite hydrogels showed increasing turbidity as the Pluronic component was added (Figure 5). Also, gels exhibited a decrease in transmittance at a certain temperature range, which broadened and shifted to a lower tempera-

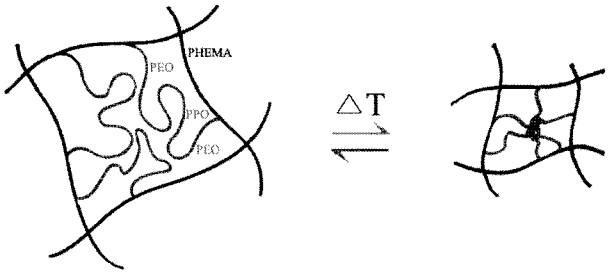


Figure 4. Schematic diagram of P(HEMA-*co*-Pluronic) hydrogels indicating cohesion of Pluronic hydrophobic groups as a function of temperature.

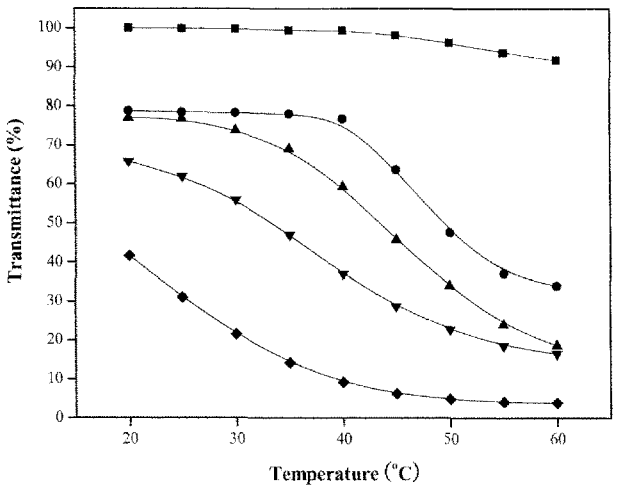


Figure 5. The transmittance-temperature curves of the hydrogels: (■) pure PHEMA, (●) P(HEMA-*co*-Pluronic-1%), (▲) P(HEMA-*co*-Pluronic-2%), (▼) P(HEMA-*co*-Pluronic-3%), (◆) P(HEMA-*co*-Pluronic-4%).

ture as the Pluronic content increased. Again, these results are thought to be caused by the reverse thermal transition of the Pluronic component, generating a phase-segregated domain of Pluronic segment within the swollen gel matrix. When the sample was cooled, the transparency of the gel returned to the original level with complete reversibility.

To investigate the dynamics of reversible swelling behavior of P(HEMA-*co*-Pluronic) hydrogels as a function of temperature change, the swelling and deswelling of hydrogels were induced by cycling temperatures between 20 and 40 °C in a step-wise function. As the results show in Figure 6, the P(HEMA-*co*-Pluronic (5, 10%)) hydrogels responded to temperature cycles repeatedly with exact reproducibility. The differences in the degree of swelling between two temperatures, i.e. the depth of swelling, are more pronounced proportional to the Pluronic content.

Mechanical Properties of Hydrogels. The biocompatible hydrogels need to be rigid enough to resist structural collapse upon implantation, yet sufficiently compliant so as

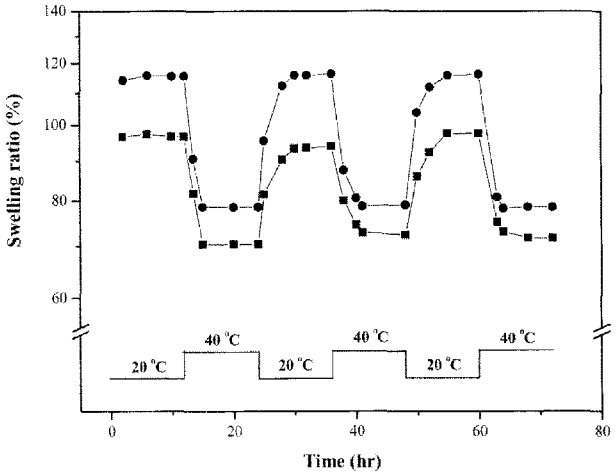


Figure 6. The swelling-deswelling curves of hydrogels in distilled water: (■) P(HEMA-*co*-Pluronic-5%), (◆) P(HEMA-*co*-Pluronic-10%).

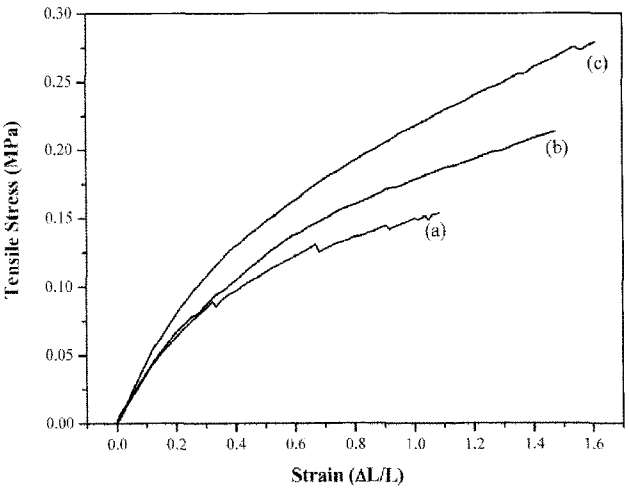


Figure 7. The stress-strain dependence of the hydrogels: (a) pure PHEMA, (b) P(HEMA-*co*-Pluronic-5%), and (c) P(HEMA-*co*-Pluronic-10%).

not to damage the surrounding tissue, which can cause necrosis and inflammation *in vivo* applications. Figure 7 shows the stress-strain curves of the different hydrogels. The stress values in hydrogels with a maximum load of P(HEMA-*co*-Pluronic) were 0.203 and 0.286 MPa for the 5 and 10% Pluronic containing hydrogels, respectively. These results were significantly higher than the stress values for homo PHEMA hydrogels (0.155 MPa). In addition, the strain at the break was also increased. The improvement in mechanical strength of the hydrogel by adding a Pluronic component is probably caused by the reinforcing effect of molecularly organized Pluronic segments between crosslinks that are better able to withstand tensile stress, along with the introduction of flexible PEG chains to the interpenetrating network structure.[22]

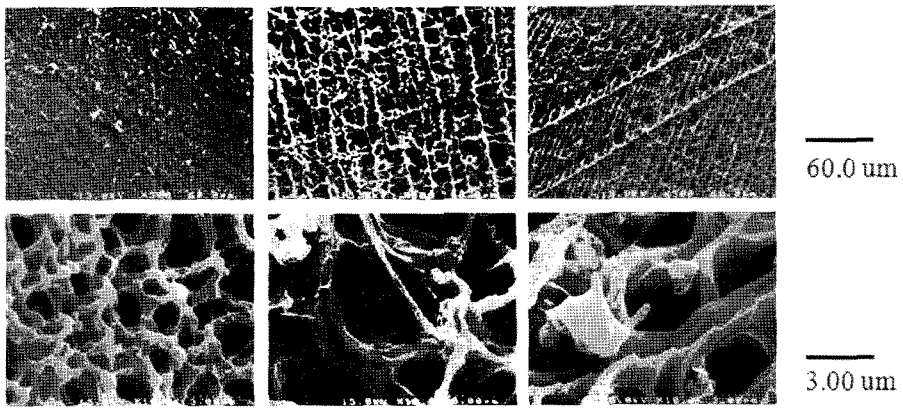


Figure 8. SEM images of freeze-dried hydrogels: (a) P(HEMA-*co*-Pluronic-2%), (b) P(HEMA-*co*-Pluronic-3%), and (c) P(HEMA-*co*-Pluronic-4%).

Morphology of Freeze-dried Hydrogels. Freeze-dried samples of water-swollen hydrogels had a characteristic morphology that changed according to the Pluronic content (Figure 8). Hydrogels with low Pluronic content was more transparent and possessed a very dense structure with small pores. As the amount of Pluronic increased, the network became more porous and the pore-size appeared to gradually increase. Essentially nonporous, pure PHEMA turned into a microporous structure when the Pluronic component was added. This structural change might result from phase separation caused by ternary interactions among polymers and water molecules. The controlled porosity along with the temperature responsive swelling of the hydrogels may be utilized beneficially for current drug delivery systems. Related studies on the drug loading and release behavior (temperature-responsive) of these Pluronic containing hydrogels are currently underway.

Conclusions

2-Hydroxyethyl methacrylate (HEMA)-based hydrogels modified by PEO-PPO-PEO triblock copolymer (Pluronic F-127) were prepared by photo-polymerization. The degree of swelling of P(HEMA-*co*-Pluronic) hydrogels increased with increasing Pluronic content. The hydrogels had a porous microstructure and the mechanical strength was increased by the introduction of the Pluronic component. In addition, composite hydrogels exhibited temperature-dependent swelling and deswelling behavior, which was probably caused by the increased hydrophobic interaction of Pluronic polymer within the gel matrix. This thermo-responsive P(HEMA-*co*-Pluronic) hydrogel can potentially be used for novel, controlled drug delivery.

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