Control of the Swelling Rate of Superporous Hydrogels

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ABSTRACT: Superporous hydrogels (SPHs) have a fast swelling property because of the presence of interconnected pores. While the fast swelling property is an advantage, sometimes it is necessary to control the swelling rate. A method of coating the SPH surface with a polymer layer was studied to control the swelling kinetics of SPHs in aqueous solutions. Poly(ethylene glycol-*b*-tetramethylene oxide) (PEGTMO), an amphiphilic block copolymer, dissolved in ethanol was used. The coating was done by dipping and equilibrium soaking in PEGTMO solutions. The delay in swelling of PEGTMO-coated SPHs was dependent on the PEGTMO concentration used. Poly(acrylamide-*co*-acrylic acid)-SPHs coated with a PEGTMO film showed lower hydrophilicity as measured by contact angle. SEM analysis revealed that the number of surface pores of SPHs was decreased by coating with PEGTMO. It appears that the PEGTMO coating reduced the surface hydrophilicity as well as the porosity, leading to slower swelling in aqueous solution.

INTRODUCTION

Superporous hydrogels (SPHs) developed in our laboratory showed extremely fast swelling characteristics [1,2]. The possible

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applications of SPHs include development of a gastric retention device for oral drug delivery [3–6] and a chemoembolizing agent for cancer treatment [7]. While this fast swelling property is quite useful in many applications, the complete swelling of SPHs needs to be delayed until they reach the target site. For example, in chemoembolization applications, premature swelling of SPHs has to be prevented until they reach the intended site of action in the blood vessel [7]. In addition, SPHs designed for gastric retention devices should not swell until they reach the stomach. Premature swelling of SPHs may prevent them from reaching the target site. For this reason, we investigated a method of altering the swelling kinetics.

The swelling kinetics of SPHs can be affected by various factors, such as monomer composition, porosity, degree of cross-linking, and ionic strength or pH of the swelling medium. Although monomer composition, porosity, and degree of cross-linking can be changed to control the swelling kinetics, it can also affect other important properties of SPHs, such as the equilibrium swelling ratio and mechanical strength. Thus, control of swelling kinetics of SPHs needs to be done without altering the fundamental properties of SPHs. In this study, we examined the effect of coating SPHs with poly(ethylene glycol-*b*-tetramethylene oxide) (PEGTMO) on the swelling kinetics of SPHs. PEGTMO is a hydrogel that swells slowly in aqueous solution.

EXPERIMENTAL METHODS

Preparation of Poly(acrylamide-*co*-acrylic acid) SPHs

SPHs were produced using acrylic acid (AA) and acrylamide (AM) with *N*,*N*′-methylenebisacrylamide (BIS) as the cross-linker. Monomer solution was prepared containing 15% (w/v) AM, 10% (v/v) AA, 0.25% (w/v) BIS, 0.4% (v/v) *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), and 0.5% (w/v) Pluronic® F127. After the pH of the solution was adjusted to 5.1, 0.6% (w/v) ammonium persulfate (APS) was added. After 3.5 min, 50 mg of sodium bicarbonate was added to a 1 mL aliquot of the monomer solution. After 4 h, the SPHs were transferred to ethanol to dehydrate the superporous hydrogels. The dehydrated SPHs were dried in a food dehydrator at 80°C for 6 h.

Synthesis of Poly(ethylene glycol-*b*-tetramethylene oxide) (PEGTMO)

Poly(ethylene oxide) (PEG, Mn 2000) was dissolved in

tetrahydrofuran (THF) with equivalent molar amount of poly(tetramethylene oxide) (PTMO, Mn 2000) and a few drops of dibutyltin dilaurate as a catalyst. The mixture was then stirred in the presence of hexane diisocyanate (2× equivalent of PTMO) for 1 day at room temperature. The synthesized block copolymer was precipitated in n-hexane. After filtration, it was further washed three times in distilled water.

Determination of PEGTMO Molecular Weight

The molecular weight of PEGTMO was determined by gel permeation chromatography (Waters 410, Waters Corporation, Milford, MA, USA). PEGTMO solution of 0.2% (w/v) in THF was injected into a Styragel column containing various pore sizes. THF was used as a mobile phase and the flow rate was 1.0 mL/min. The polymer molecular weight was determined from a calibration curve obtained using polystyrene standard samples.

Coating of SPHs with PEGTMO

PEGTMO was dissolved in ethanol, and dried SPHs were immersed in the PEGTMO solution (various concentrations were used) for a few seconds. The PEGTMO-coated SPHs were dried in a food dehydrator for 3 h. In another method, synthesized SPHs were allowed to equilibrate overnight in PEGTMO solutions to produce a semi-interpenetrating network (sIPN).

Swelling of Dried SPHs

Dried SPHs were allowed to swell in phosphate buffered saline (PBS, pH 7.2). The weight of the swelling SPHs was measured at timed intervals. Weight swelling ratio (q) was determined using the equation:

$$q = (w_s - w_d)/w_d$$

where w_s and w_d are the weights of swollen and dried gels, respectively. Since maximum swelling of SPHs was observed in less than 10 min, the swelling ratio at 20 min was chosen as the equilibrium swelling ratio.

Mechanical Strength of Swollen SPHs

After the SPHs were swollen to equilibrium in PBS, the compression strength was measured in triplicate using a comparator (Ames,

Waltham, MA, USA). The weight at fracture was converted to pressure by dividing mass by area of weight loading.

Scanning Electron Microscopy (SEM)

SEM was used to determine the morphology of the dried samples' surfaces. Samples were cut using a scalpel to expose an appropriate portion of the sample for SEM analysis. JSM-840 scanning electron microscope (JEOL USA, Inc., Peabody, MA, USA) was used after coating the samples with gold using a Hummer I Sputter Coater (Technics, Ltd., Alexandria, VA, USA). SEM images were captured using a digital capture card and Digital Scan Generator 1.

Contact Angle Measurement

It is inherently difficult to measure the contact angles of SPHs due to their tendency to absorb water extremely fast through the pores. The liquid penetrated into SPHs before the contact angle could be measured. Thus, instead of SPHs, polymer films were used to indirectly measure the contact angle of the polymers with water.

A polymer solution, that had the same copolymer ratio with SPHs, was prepared by incubating monomer solution containing 5% (w/v) AM, 3.7% (v/v) AA, 0.13% (v/v) TEMED, and 0.13% (w/v) APS at 60°C overnight. One milliliter of the polymer solution was spread onto a clean glass slide. It was air-dried for 8 h and further vacuum dried for 10 h at room temperature. Polymer films were coated with various concentrations of PEGTMO in ethanol, and then the solvent was evaporated completely. Advancing contact angles of water droplets were measured using a goniometer (Rame-Hart, Inc., Mountain Lakes, NJ, USA).

RESULTS AND DISCUSSION

Characterization of Poly(ethylene glycol-*b*-tetramethylene oxide) (PEGTMO)

Poly(ethylene glycol-*b*-tetramethylene oxide) (PEGTMO) is an amphiphilic block copolymer prepared by equivalent moles of poly(ethylene glycol) and poly(tetramethylene oxide) (Figure 1). Number and average molecular weights of PEGTMO were 52,000 and 66,000, respectively, as determined by gel permeation chromatography; the polydispersity index was 1.28. PEGTMO was soluble in many organic solvents, including ethanol and tetrahydrofuran but was insoluble in

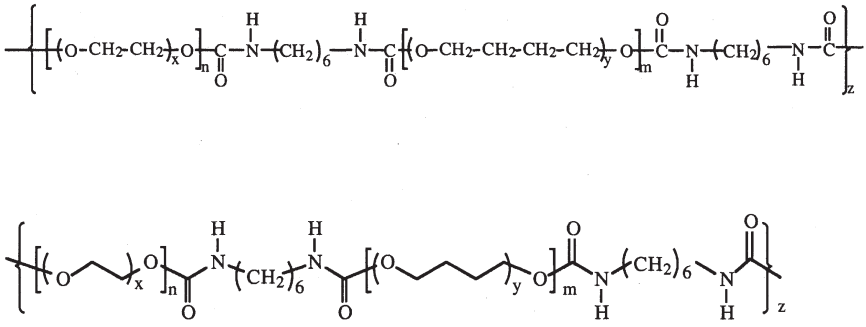

Figure 1. Structure of poly(ethylene glycon-*b*-tetramethylene oxide) (PEGTMO).

water and *n*-hexane. Since SPHs did not swell in ethanol it was used as the solvent during the coating process. In addition, ethanol could be removed easily by evaporation.

Swelling Property of Coated SPHs

In order to decrease the swelling rate of SPHs, the outer surface of SPHs was coated with PEGTMO by immersing dried SPHs for a few seconds in a PEGTMO solution (various PEGTMO concentrations were evaluated). When the SPHs were swollen in phosphate-buffered saline (PBS, pH 7.2), the time for maximum swelling was 1 min for untreated SPH, but SPHs dip-coated in 0.5%–4% (w/v) PEGTMO solutions showed a concentration-dependent increase in the swelling time from 3–10 min. Furthermore, the initial swelling rate, which is represented by the initial slope of the swelling curve in Figure 2, decreased as the PEGTMO coating concentration increased. There were large variations in the swelling ratios of SPHs coated with PEGTMO before equilibrium swelling was reached. This is understandable, because the surface coating of PEGTMO was not expected to be perfectly homogeneous. Although the swelling rate was affected by PEGTMO concentrations, the equilibrium swelling ratio of the SPHs was around 70 regardless of the PEGTMO concentrations (Table 1). In addition, there was little difference in the mechanical strength among the swollen SPHs coated with different PEGTMO concentrations. The results in Table 1 clearly indicate that the PEGTMO coating decreased the swelling rate of SPHs, but it did not significantly influence other properties, such as the equilibrium swelling ratio and mechanical strength. The thickness of PEGTMO coating on the surface of SPHs is expected to be very small. Although a thin PEGTMO coating can delay SPH swelling, once SPHs are swollen to a

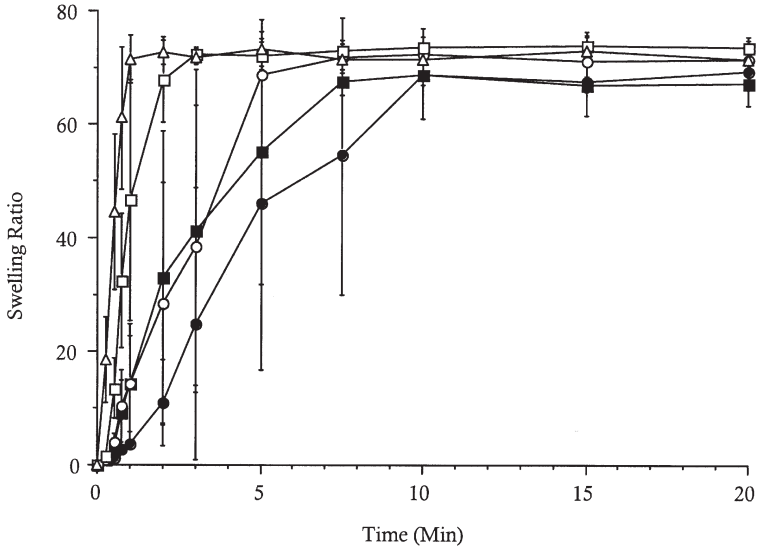

Figure 2. Swelling kinetics of dried SPHs dip-coated in the PEGTMO concentration of 0% (△), 0.125% (□), 0.25% (○), 0.5% (■), or 1.0% (●).

certain size, the coating is not able to prevent SPHs from fully swelling. Thus, dip-coated SPHs showed similar equilibrium swelling ratio and mechanical strength values regardless of PEGTMO concentration.

The effect of extensive PEGTMO coating was also studied by using semi-interpenetrating network (SIPN) of SPHs with PEGTMO. SIPN was prepared by equilibrating SPHs in PEGTMO solutions. The swelling kinetics of SIPN was similar to those of dip-coated SPHs. Higher concentrations of PEGTMO resulted in longer delays in the maximum swelling time and greater decrease in the initial swelling rate of SIPN as

Table 1. Effect of PEGTMO concentration during dip-coating on equilibrium swelling ratio in PBS and mechanical strength of dip-coated superporous hydrogels (SPHs).

PEGTMO Concentration (%, w/v)	Equilibrium Swelling Ratio	UCP* (kPa)
0	71.4 ± 1.3	1.09 ± 0.24
0.5	73.5 ± 1.5	1.15 ± 0.12
1.0	71.4 ± 2.0	1.15 ± 0.31
2.0	67.4 ± 0.8	1.36 ± 0.31
4.0	69.4 ± 6.2	1.15 ± 0.31

*Ultimate compression pressure. $n = 3$.

shown in Figure 3. As shown in Figure 2 for dip-coated SPHs, large deviations in the swelling ratio were observed before the gels reached equilibrium swelling. This also indicates that the SIPN formation was not homogeneous and not reproducible from sample to sample. The concentrations of PEGTMO necessary to achieve the same effects were much smaller with SIPN. The equilibrium swelling ratio and mechanical strength of SIPN were not significantly affected, although there was a slight trend toward a decreasing in the equilibrium swelling ratio and an increasing mechanical strength (Table 2). Equilibrating SPHs in PEGTMO solutions will result in the larger surface area being covered by the coating material, either the outer surface of the SPHs or the inner surface of the porous structure in SPHs. Thus, SPH/SIPN resulted in a greater delay in maximum swelling time than the dip-coated SPHs at the same concentration of PEGTMO for coating. These results suggest that coating SPHs with PEGTMO can control the swelling kinetics of SPHs, which would be useful in preventing SPH from premature swelling. Since PEGTMO is also a hydrogel and is applied only in a small quantity, the overall swelling property of PEGTMO-coated SPHs did not change by coating except for the swelling kinetics.

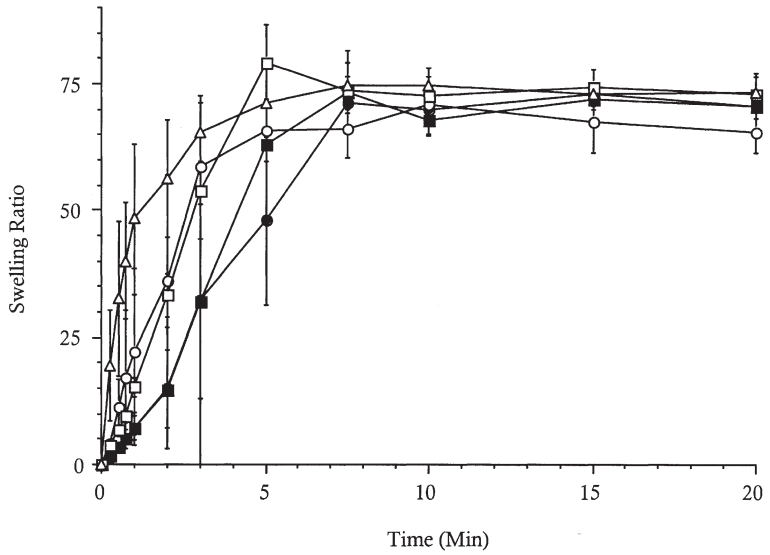

Figure 3. Swelling kinetics of dried semi-interpenetrating network (SIPN), SPHs were placed in ethanol with the PEGTMO concentration of 0% (△), 0.5% (□), 1% (○), 2% (■), or 4% (●).

Table 2. Effect of PEGTMO coating by equilibrium soaking on equilibrium swelling ratio in PBS, and mechanical strength of superporous hydrogels (SPHs).

PEGTMO Concentration (w/v %)	Equilibrium Swelling Ratio	UCP* (kPa)
0	73.3 ± 3.8	0.88 ± 0.12
0.125	72.9 ± 3.4	1.22 ± 0.20
0.25	65.6 ± 4.1	1.22 ± 0.00
0.5	70.6 ± 2.3	1.43 ± 0.20
1.0	70.7 ± 0.3	1.29 ± 0.31

*Ultimate compression pressure. $n = 3$.

Surface Property of Coated SPHs

Effect of coating on the surface property of SPHs was studied using scanning electron microscopy (SEM) and contact angle measurement. PEGTMO is more hydrophobic than the polymer used to make SPH, which is mostly composed of highly hydrophilic acrylamide (AM) and acrylic acid (AA). Contact angle measurements were used to find changes in the surface properties of coated SPHs. Direct application of water droplets onto the SPH surface resulted in fast absorption of water through porous channels and obscured the advancing contact angle measurement for the SPH samples. To circumvent this problem, poly(AM-*co*-AA) films with the same AM:AA ratio used in SPHs were prepared to indirectly measure the contact angles. The contact angle of uncoated polymer film was 41°. However, the advancing contact angles of PEGTMO-coated polymer films ranged from 84° to 93° when coated with PEGTMO at concentrations of 0.125%–4% (Table 3). This means that a thin layer of PEGTMO was formed on the poly(AM-*co*-AA) film surface, even at the lowest PEGTMO concentration of 0.125%, and the

Table 3. Effect of PEGTMO coating on the contact angle of poly(AM-co-AA) films.

PEGTMO Concentration (%, w/v)	Contact Angle
0.0	41 ± 1
0.125	87 ± 4
0.25	88 ± 3
0.5	84 ± 4
1.0	88 ± 3
2.0	93 ± 3
4.0	90 ± 0

$n = 3$.

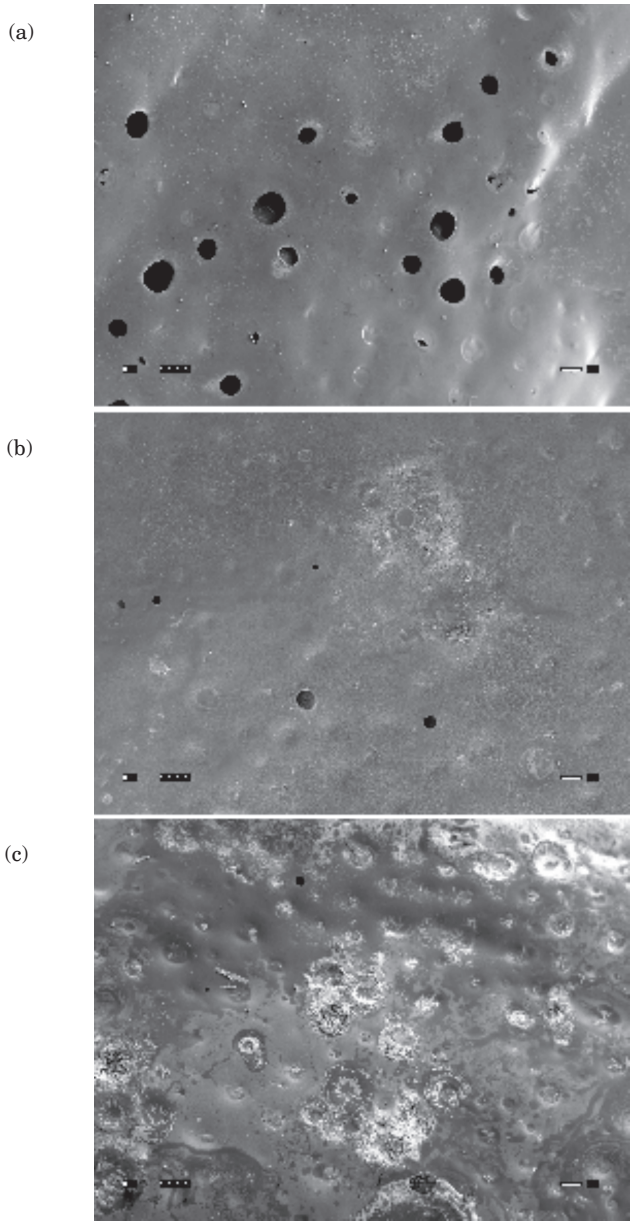

Figure 4. Scanning electron micrographs of the surface of the superporous hydrogels dip-coated with PEGTMO solutions: (a) 0%, (b) 1%, and (c) 4%. The length of the scale bar is 100 μm.

PEGTMO layer increased the surface hydrophobicity of poly(AM-*co*-AA) film. Although there was little difference in the contact angles between concentrations of PEGTMO, a higher concentration of PEGTMO might form thicker PEGTMO films. The results support the concept that a PEGTMO layer decreases the wettability of SPH surfaces, thereby increasing the swelling time. Greater delays in the swelling of SPHs coated with higher PEGTMO concentrations might have increased the PEGTMO film thickness, which would have increased the diffusion time of water molecules through the PEGTMO layer.

SEM images were obtained for SPHs coated with PEGTMO. The number of surface pores decreased depending upon the concentration of PEGTMO solution used in the dip-coating process. As shown in Figure 4, untreated SPH had a large number of surface pores, but for the SPHs coated with 1% PEGTMO solution, the number of surface pores decreased drastically. When a 4% PEGTMO solution was used, surface pores can barely be seen by SEM. These results suggest that the PEGTMO polymer blocked some of the surface pores and work as a physical barrier for the penetration of water. Fast water absorption through surface pores into inner capillary channels is responsible for the fast swelling property of SPHs. A decrease in the number and size of the surface pores would decrease the swelling rate by delaying the capillary absorption of the swelling medium.

CONCLUSIONS

SPHs coated with a block copolymer of PEG and PTMO were used to control the swelling kinetics of SPHs. High concentrations of PEGTMO resulted in greater delays in the swelling. A decrease in both the surface hydrophilicity and the number of surface pores on SPH was apparent in the SPHs coated with PEGTMO. The coating of SPHs with polymer was shown to be a promising way to control the swelling kinetics without any detrimental effect on the properties of SPH such as equilibrium swelling ratio and mechanical properties.

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