

pH-sensitivity of fast responsive superporous hydrogels

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Received 1 June 2000; accepted 1 August 2000

Abstract—Stimuli-sensitive hydrogels (or smart hydrogels) are hydrogels that swell or shrink in response to small changes in environmental conditions in which they are placed. While the extent of swelling or shrinking may be large, the kinetics of such changes is slow, since the diffusion of water into and out of the hydrogel is a slow process. To obtain fast responses, we have prepared superporous hydrogels (SPHs) that can swell or shrink extremely fast regardless of their dimensions. The swelling and shrinking are orders of magnitude faster than expected for a nonporous hydrogel of the same dimensions. Water molecules are taken up into the SPHs by capillary forces, and this makes water uptake much faster than diffusion. The swelling ratio of the poly(acrylamide-*co*-acrylic acid) (p(AM-*co*-AA)) SPHs was dependent on the pH and ionic strength of the medium. The effect of pH was most pronounced and the effect of ionic strength was observed at all pH values. SPHs made at pH around 5 showed transient maximum swelling when exposed to pH 1.2 medium due to the transient low hydrogen ion concentration inside the swelling SPHs. The p(AM-*co*-AA) SPHs showed repeated swelling and shrinking by alternating the medium pH between 1.2 and 7.5, and the changes in swelling ratio was quite fast occurring in a matter of a minute. This fast sensitivity may make the stimuli sensitive hydrogels useful in many applications not previously possible. These materials can be used for applications where a single-piece hydrogel is more advantageous than hydrogel microparticulates.

Key words: Hydrogel; superporous hydrogel; smart hydrogel; fast response; superabsorbent.

INTRODUCTION

Hydrogels are cross-linked networks of water-soluble polymers. As individual polymer chains try to dissolve in water, the three-dimensional network absorbs water and swell in the presence of abundant water. Stimuli-sensitive hydrogels (or smart hydrogels) are hydrogels that undergo large changes in the swelling ratio (i.e.

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either swell more or shrink) by only a small variation in environmental conditions, such as temperature [1–4], pH [5–9], light [10], electric field [11–15], pressure [16, 17], carbohydrates [18, 19], and antigens [20]. Although the swelling ratio changes greatly by a small change in an environmental factor, the kinetics of such changes has been slow. These hydrogels respond to the conditions on the order of hours to days, depending on their sizes. The response time has been shortened by reducing the dimensions of the hydrogels. Quite frequently, the diameter of particles or rods, and the thickness of sheets or membranes are brought to very small values to minimize the diffusion length of absorbed water. Dependence on the shape and size of these systems, however, limits their applications, especially when large structures are needed.

An alternative approach of making fast-responsive hydrogel systems has been preparing comb-type polymers. Comb-type polymers having hydrophobic pendant chains are known to collapse much quicker than conventional hydrogels [21, 22]. The increase in shrinking rate was, however, not associated with an increase in swelling rate. Porous hydrogels have also been prepared. Porous hydrogels have been made by methods, such as porogen leaching [23–27], phase separation [22, 28–30], particulate cross-linking [31–33], microemulsions [34], and freeze-drying [35]. Hydrogels prepared by some methods, such as freeze-drying, do not retain their pore structure after swelling, while others contain a significant number of closed pore structures. For these reasons, we were interested in preparation of porous hydrogels that can be made reproducibly with open pore structures. Since the pore size of the prepared hydrogels is in the range of 100 μm which is substantially larger than others reported in the literature, we called such them superporous hydrogels (SPHs) [36]. In this study, pH-dependent changes of the swelling ratio have been examined using poly(acrylamide-*co*-acrylic acid) (p(AM-*co*-AA)) SPHs.

MATERIALS AND METHODS

Synthesis of p(AM-co-AA) SPHs

All chemicals were obtained from Aldrich Chemical Company (Milwaukee, WI, USA) and used as-received unless otherwise stated. Superporous hydrogels were produced using acrylic acid (AA) and acrylamide (AM) with *N,N'*-methylene-bis-acrylamide (BIS) as the cross-linker in concentrations of 15 (v/v)%, 10 (w/v)%, and 0.25 (w/v)%, respectively. Pluronic[®] F127 (BASF Corporation, Parsippany, NJ, USA) was added at a concentration of 0.5 (w/v)%. The redox initiator pair, *N,N,N',N'*-tetramethylene diamine (TEMED) and ammonium persulfate (APS), was added at a concentration of 2% to the weight of monomer with TEMED being added to the stock monomer solution, and APS being added to the solution at the time of polymerization. Once the stock monomer solution was made, the pH of the solution was adjusted to 5.1 using 50 (w/v)% sodium hydroxide. This

solution was added to a 16 mm diameter \times 100 mm length borosilicate culture tube (Fisher Scientific, Pittsburgh, PA, USA) along with the appropriate amount of APS. Sodium bicarbonate (50 mg, Mallinkrodt Specialty Chemical Co., Paris, KY, USA) was added 210 s after adding the initiators. The tube was then mixed thoroughly using a spatula to distribute sodium bicarbonate evenly throughout the tube. Polymerization was allowed to proceed for the next 4 h. The synthesized superporous hydrogels were removed from the tubes by adding a small quantity of absolute ethanol (McCormick Distilling Co., Brookfield, CT, USA). Finally, the SPHs were dried in a food dehydrator (Mr. Coffee, Inc., Bedford Heights, OH, USA) at a temperature of 80°C for 6 h.

Swelling studies

Cylindrical SPHs were weighed and placed in solutions of the appropriate type and allowed to swell for specific times. All data was obtained in triplicate at the least. At the desired time, the SPH was removed from the solution and blotted dry using a Kimwipe[®] (Kimberly-Clark Corp., Roswell, GA, USA) to remove excess water from the surface. Water that is still present in the pore structure is considered to be a part of the swollen network. The swelling was characterized by using the swelling ratio, Q , which was defined as the ratio of the weight of the swollen hydrogel (w_s) to the weight of the dried hydrogel (w_d):

$$Q = w_s/w_d. \quad (1)$$

To determine the pH profile for equilibrium swelling, SPHs were immersed in buffer solutions of different pH values. Each buffer was made according to published formulas and adjusted to the physiologic ionic strength using sodium chloride. The pH of the solution was adjusted using 0.1 M sodium hydroxide or hydrochloric acid. For equilibrium swelling data, the SPH was weighed daily until the weight did not vary with changes in the solution every other day.

Scanning electron microscopic examination

Dried SPHs were examined using scanning electron microscopy (SEM) and hydrated SPHs were examined using cryo-SEM. Dried samples were first dehydrated in ethanol (100%) for at least 10 h followed by placement in a 60°C oven for at least 5 h. The samples were cut with a scalpel and placed on a specimen holder using aluminum tape and silver paint. After the silver paint dried sufficiently, the samples were coated with 10 Å of gold using a Hummer I Sputter Coater (Technics Inc., Alexandria, VA, USA) immediately prior to examination. Freeze-dried samples were examined using the same procedures as dried samples after the samples were immersed in liquid nitrogen and freeze-dried.

Cryo preparation of samples does not use any fixative or preparation of the sample other than flash freezing the sample in a nitrogen slurry. Reduced pressure caused the liquid nitrogen to solidify at successively higher temperatures until it changed

into a solid phase. At this point, the pressure was returned to atmospheric in the chamber and the sample was immersed in the nitrogen slurry. This process allowed for immediate freezing of the sample without disruption of delicate structures in the sample. Some surface changes at the point of contact between the sample and the nitrogen slurry can be noted during freezing, but the sample can be fractured after freezing, exposing an undisturbed surface for examination.

A Hexland Ltd (Oxon, UK) CT 1000 Cryotrans System attached to a JEOL JSM-840 scanning electron microscope (Jeol USA, Peabody, MA, USA) was used after coating the samples with gold using an internal sputter coater. Images were captured using a digital capture card and Digital Scan Generator 1 (Jeol). Samples were cut using a scalpel to allow for the appropriate portion of the sample to be visible to the SEM. Dried samples were blown clean using compressed air to remove any particles of the broken SPH examined using the same instrument, without the use of the cryo-stage.

Mercury porosimetry of dried superporous hydrogels

Size of pores in the SPHs were determined using an Autopore II 9220 (Micromeritics, Norcross, GA, USA) mercury porosimeter after adjustment for compressibility of mercury and sample. A 6-ml penetrometer was used for all experiments. For uncompressed SPHs, samples were taken from a 60°C oven and cut into 1 cm sections. Three samples from one SPH were considered a single data point. Since a pore volume of 0.39 ml was the maximum intrusion volume that could be measured, it was necessary to reduce the size of each piece for uncompressed SPHs. At least four samples were used to take into account any error introduced by cutting the samples. The bulk and solid densities of samples were also calculated using mercury porosimetry. The bulk density is the density of SPH that include pores, and the solid density is the density of polymer solid without pores. The SPH sample with predetermined mass (M) was surrounded by a non-wetting fluid, mercury. At pressure of 0.5 psi, mercury does not penetrate into SPH pores due to its non-wetting property. So, the total volume at 0.5 psi includes the volumes of mercury and the sample. Since the volume of mercury was known from the weight and density of mercury before intrusion, the sample volume at 0.5 psi ($V_{0.5 \text{ psi}}$), which is the bulk volume, could be calculated. At pressure high enough to cause the filling of all pores with mercury (i.e. at 60 000 psi), the total volume decreased. Thus, the volume of the sample at 60 000 psi ($V_{60 \text{ 000 psi}}$) representing the SPH solid could be obtained. The bulk density and the solid density of the SPH sample were calculated using Eqs 2 and 3.

$$\rho_{\text{bulk}} = M / V_{0.5 \text{ psi}}, \quad (2)$$

$$\rho_{\text{solid}} = M / V_{60 \text{ 000 psi}}. \quad (3)$$

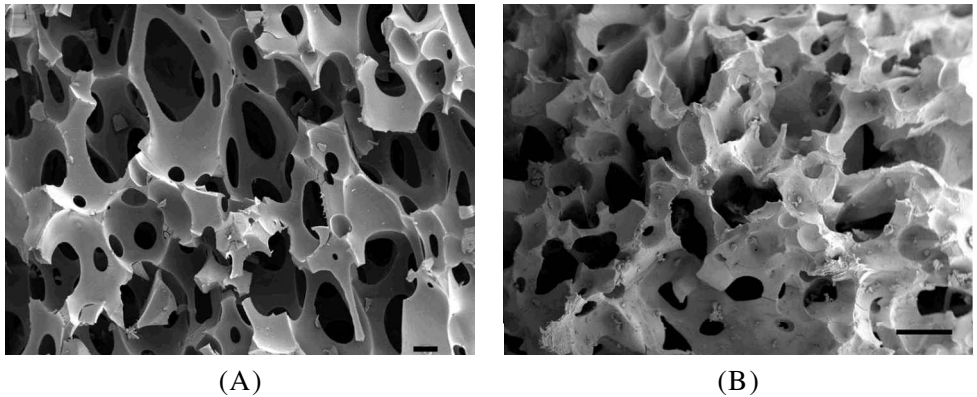


Figure 1. Scanning electron micrograph (A) of a dried poly(acrylamide-*co*-acrylic acid) and cryo-scanning electron micrograph (B) of a poly(acrylamide-*co*-acrylic acid) superporous hydrogel swollen in phosphate buffered saline (pH \approx 7.4). The scale bars are 0.1 and 1 mm, respectively.

RESULTS

SPHs were produced with excess sodium bicarbonate so that a maximum swelling in fluids would occur [37]. Starting with 1 ml of monomer mixture, SPHs that had a final polymerized volume of 3.5 ± 0.2 ml were produced. After dehydration, the volume of the SPHs decreased to 2.65 ± 0.24 ml. This volume was determined by mercury porosimetry. Also from mercury porosimetry, the density of the bulk SPH was found to be 0.30 ± 0.03 g ml $^{-1}$ while the solid density was 1.43 ± 0.15 g ml $^{-1}$. The solid density of a nonporous hydrogel (1.33 ± 0.02 g ml $^{-1}$) was not significantly different than that of the SPH. This should be true since the solid structure of the SPH is nonporous whether dried or swollen. Figure 1 shows SEM and cryo-SEM pictures of a poly(acrylamide-*co*-acrylic acid) SPH. The hydrogel struts were nonporous whether they were dried (Fig. 1A) or swollen in aqueous solution (Fig. 1B).

Swelling of the SPH in ionic media

Swelling of p(AM-*co*-AA) SPHs in deionized water resulted in high swelling ratios, reaching 250. Increasing the ionic strength of the media resulted in substantial decreases ($p < 0.05$) in the swelling capacity of the SPH for all of the samples (Fig. 2). For the hydrogels with ionic groups, such as p(AM-*co*-AA) hydrogels, swelling was dependent on the ionic strength regardless of pH of the media. The effect of ionic strength, however, decreases as the pH becomes lowered. At pH 1.2, the swelling of the dried SPHs showed a transient maximum which was significantly greater than the equilibrium value (Fig. 3). Increasing ionic strength decreased the time to the transient maximum as well as the value of the weight swelling ratio. The transient maximum in swelling was eliminated by swelling SPHs in acidic media followed by dehydration. Thus, the transient maximum swelling is expected to be related to the transient changes in hydrogen ion concentration inside the swelling

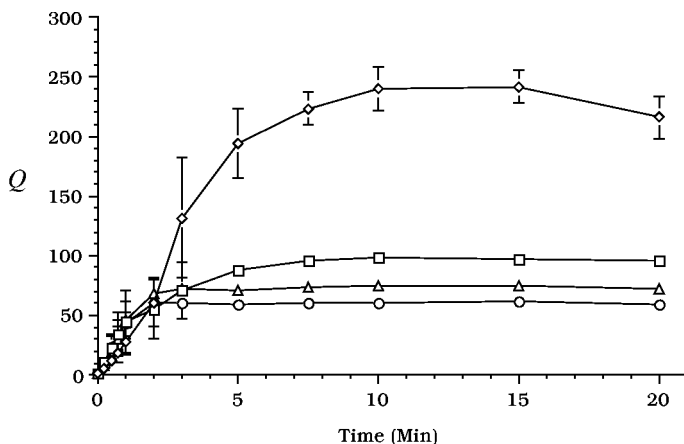


Figure 2. Dynamic weight swelling ratio (Q) of poly(acrylamide-*co*-acrylic acid) superporous hydrogels in distilled deionized water (\diamond) and phosphate buffer at pH 5 with ionic strength of 0.09 M (\square), 0.18 M (\triangle), and 0.36 M (\circ). Each hydrogel was dehydrated in ethanol followed by drying to constant weight. Each dried SPH was a cylinder of approximately 15 mm \times 30 mm. The conventional hydrogels without the superporous structure did not show any appreciable swelling ($n = 3$, mean \pm S.E.M.).

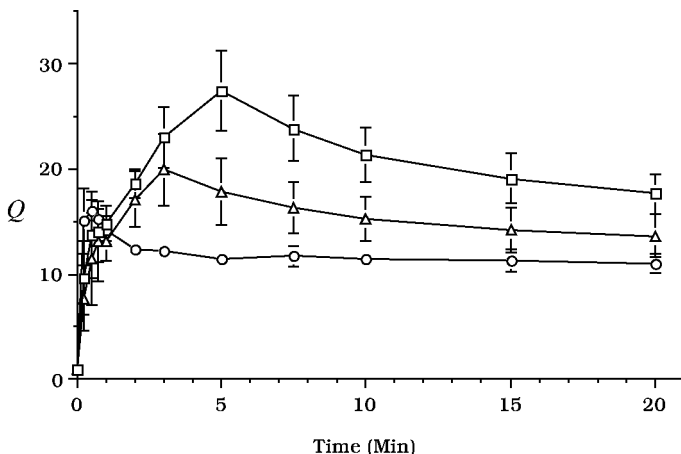


Figure 3. Dynamic weight swelling ratio (Q) of poly(acrylamide-*co*-acrylic acid) superporous hydrogels in buffered saline with a pH of 1.2 and ionic strength of 0.09 M (\square), 0.18 M (\triangle), and 0.36 M (\circ). Each hydrogel was dehydrated in ethanol followed by drying to constant weight. Each dried SPH was a cylinder of approximately 15 mm \times 30 mm ($n = 3$, mean \pm S.E.M.).

SPHs. The pH effect on equilibrium swelling showed the familiar curve for acrylic acid (Fig. 4), with the pK_a of acrylic acid approximately 4.2 [38]. As the pH was increased, the equilibrium swelling ratio of the SPH increased until a plateau value at a pH of 6. Also, as the pH was decreased below 2, there was no further decrease in the equilibrium swelling ratio.

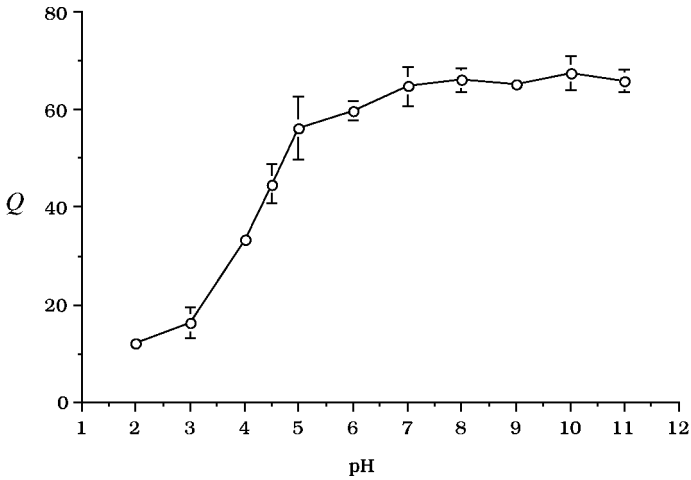


Figure 4. Equilibrium weight swelling ratio (Q) of poly(acrylamide-*co*-acrylic acid) superporous hydrogels in buffered saline at varying pH and an ionic strength of 0.18 M. Each hydrogel was dehydrated in ethanol followed by drying to constant weight. Each dried SPH was a cylinder of approximately 15 mm \times 30 mm ($n = 3$, mean \pm S.E.M.).

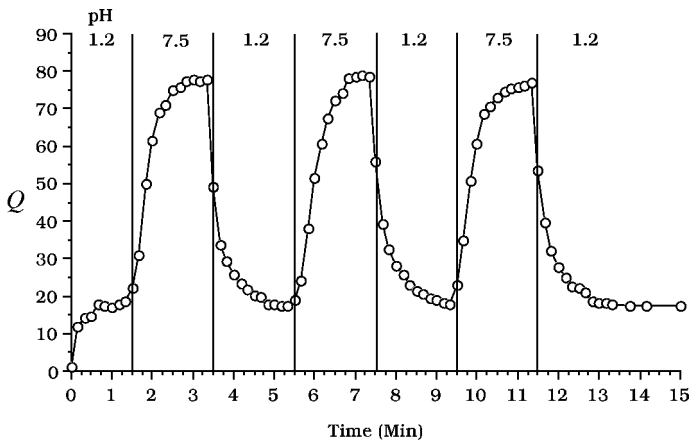


Figure 5. Dynamic weight swelling ratio (Q) of a poly(acrylamide-*co*-acrylic acid) superporous hydrogel (SPH) in buffered saline at varying pH and an ionic strength of 0.18 M. The SPH was first swollen in buffer at a pH of 1.2, then at 1.5 min transferred to buffer at a pH of 7.5. The SPH was transferred to alternating solutions every 2 min for the next 10 min. The dried SPH was a cylinder of approximately 15 mm \times 30 mm.

*Repeated swelling and collapse of the p(AM-*co*-AA) SPH*

One of the unique properties of SPHs is the fast response, i.e. swelling or collapse, upon environmental changes. The presence of carboxyl groups in p(AM-*co*-AA) SPHs makes it ideal to respond fast to changes in environmental pH. When p(AM-*co*-AA) SPHs were placed in pH 1.2 media and then transferred to pH 7.5 media, rapid swelling took place that was similar to the swelling of a dry SPH (Fig. 5). In a

matter of a minute, the SPH swelled to the size that is observed at pH 7.5. When the SPH was returned to the pH 1.2 media, it collapsed also in a matter of a minute. The rates of change of the weight swelling ratio for swelling and collapse of the SPHs were both 55 min^{-1} . A nonporous p(AM-co-AA) hydrogel had a rate of change for collapse on the order of 0.1 min^{-1} . SPHs are useful whenever fast changes in swelling ratios are required.

DISCUSSION

Scanning electron micrographs showed that there is little porosity in the swollen or dried SPHs below $10 \mu\text{m}$. Care must be taken, however, when examining cryo-SEM images of hydrogels. It is possible to freeze-dry the sample in the instrument chamber creating a false porosity on the surface of the swollen hydrogel. Occasionally, this was seen on samples of the SPHs, but further examination showed that the ice on the surface of the SPH had been sublimated and further dehydration had taken place. When these samples were rehydrated and examined a second time under the cryo-SEM, no porous structure was seen.

Some variability in the swelling ratio was observed in samples swollen in deionized water due to loss of hydrogel after swelling. There was also a loss of weight over time in these samples. SPHs swollen in water are quite fragile and particulate loss was observed for most samples. SPHs swollen in other media showed no appreciable loss to breakage. At low pH, the strength of p(AM-co-AA) SPHs was high enough to handle without breakage. Control over the swelling is attained by control over the pH and ionic strength of the media. At low pH, the media has the least effect on the swelling properties. This is due to the ionization state of the acrylic acid moieties on the polymer backbone. At low pH, the acrylic acid is protonated and little or no charged structure exists [39]. Ionic strength comes into play in the swelling due to shielding of the ions on the polymer backbone. At high ionic strength, there are a large number of counterions present close to the ionized moieties on the backbone creating an ionic shield that disguised the ions on the polymer chain. Low ionic strength solutions lack the ions to shield the polymer chains from one another, thus larger swelling is observed. Equilibrium values of the weight swelling ratio of SPHs swollen in acidic media showed little sensitivity to ionic strength since they were unionized. The response of dried p(AM-co-AA) SPHs to acidic media was not typical of the response at other pHs. The SPHs swelled to a value that was higher before reaching the equilibrium value (Fig. 3). The acid swollen and redried SPHs did not show this type of behavior. Thus, the transient maximum swelling is expected to be due to the higher pH values inside the SPHs, i.e. pH 5.1 used in the synthesis. As the hydrogen ions diffuse into the polymer chains, the local pH becomes equilibrated with that of the medium (pH 1.2), and thus lowering the swelling ratio.

The rate of response of the superporous hydrogels is orders of magnitude faster than other stimuli-sensitive hydrogels. Even newly synthesized comb polymers that

have a smaller size than the SPHs respond in the range of 20 min [2, 21]. Comb polymers are thought to have much faster response than typical polymers, yet the SPH responds at a much faster rate than the comb polymers. Incorporation of comb polymers may even increase the sensitivity of the SPHs to environmental cues.

Superporous hydrogels are hydrogels with incredible sensitivity to external stimuli. These materials may be used in various fields, especially biomaterials and drug delivery. Since SPHs are produced using radical polymerization methods, any stimuli sensitive hydrogel that has been produced could be made using this technology. Temperature sensitive hydrogels have been produced and have shown similar sensitivity and swelling rates as the ionic-sensitive SPHs shown [37]. SPHs are retained in the stomach of animals for extended periods, and can be used for local controlled delivery [40]. The stimuli-sensitive SPHs could be used to control delivery even further, by allowing delivery only at specific times based on the stimuli presented during delivery. The porosity of the SPH is key to its sensitivity; however, drug delivery from a porous network is quite rapid. To control drug delivery from an SPH, a secondary means of control must be established. Drug delivery studies are underway that will use the sensitivity of the SPH in combination with the diffusional properties of a nonporous hydrogel to control drug delivery. The SPH is expected to play an important role in drug delivery and biomaterials.

Acknowledgement

This study was supported in part by the National Institutes of Health through grants GM 08298. The authors also wish to thank Debra Sherman and the Microscopy Center in Agriculture for assistance with and use of the scanning electron microscope.

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