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Superporous IPN Hydrogels Having Enhanced Mechanical Properties

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ABSTRACT

The objective of this study was to improve the mechanical properties of superporous hydrogels (SPHs), which were used to develop gastric retention devices for long-term oral drug delivery. The main approach used in this study was to form an interpenetrating polymer network by incorporating a second polymer network inside an SPH structure. Polyacrylonitrile was used as the second network inside an SPH. Mechanical properties including compression strength and elasticity were significantly improved, up to 50 times as compared with the control SPHs. The enhanced mechanical properties were a result of the scaffold-like fiber network structures formed inside the cell walls of SPHs. The fast swelling property of SPHs was not affected by the incorporation of the second polymer network because the interconnected pore structures were maintained. Gastric retention devices based on superporous IPN hydrogels (SPIHs) with the improved mechanical properties are expected to withstand compression pressure and mechanical frictions in the stomach better than the control SPHs.

KEYWORDS: superporous hydrogels, interpenetrating polymer networks, polyacrylonitrile, gastric retention devices, elasticity

INTRODUCTION

A superporous hydrogel (SPH) is a 3-dimensional network of a hydrophilic polymer that absorbs a large amount of water in a very short period of time due to the presence of interconnected microscopic pores.[1] Because of the porous structure, SPHs also possess hundreds of times more surface area and shorter diffusion distance than conventional hydrogels do. These features allow dried SPHs to swell very fast to a very large size on contact with water. Because of these unique properties, SPHs were initially proposed to develop gastric retention devices for extending the gastric residence time of drugs for achieving long-term, oral-controlled drug delivery.[2] Gastric retention devices would be most beneficial for drugs that need to act locally in the stomach, eg antacids and antibiotics for bacteria-based ulcers or drugs that may be absorbed primarily in the stomach.[3] For many drugs that have a narrow absorption window, ie mainly absorbed from the proximal small intestine, such as riboflavin, levodopa, and p-aminobenzoic acid,[4,5] the bioavailability would be increased by gastric retention. For drugs that are absorbed rapidly from the gastrointestinal (GI) tract, eg, amoxicillin,[6] slow release from the stomach is also expected to improve the bioavailability. Gastric retention devices could also be used for drugs that are poorly soluble at an alkaline pH or drugs that degrade in the colon (eg, metoprolol). Several important properties of SPHs, such as fast swelling, large swelling ratio, and surface slipperiness, make them an excellent candidate material to develop gastric retention devices.

Although SPHs have unique properties that make them useful as a platform for gastric retention, the weak mechanical properties of the fully swollen SPHs have been a main hurdle limiting their practical applications. One approach to improve the mechanical properties was making SPH composites.[2,7] Several superdisintegrants, Ac-Di-Sol®, Primojel®, Explotab®, and Crospovidone® were used as model composite materials to promote the swelling speed and to improve the mechanical properties. Ac-Di-Sol was found to be the best composite material among those excipients. The main role of Ac-Di-Sol was to increase the physical crosslinking of polymer chains so that the porous structure was maintained during drying of the SPHs. Al-

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though the SPH composites showed better mechanical properties than the control SPHs, their mechanical strength was still not the ideal condition for the intended applications. Thus, further improvement in mechanical strength while keeping the fast swelling kinetics was necessary for the development of gastric retention devices. The method used in this study was to incorporate the second polymer network into the SPH frame to form the interpenetrating polymer network (IPN) structure. Polyacrylonitrile (PAN) was used to form the second polymer network that penetrates inside the SPH structure. The swelling and mechanical properties of the resulting superporous IPN hydrogels (SPIHs) were characterized, and the microscopic structure of SPIH was examined to explain the improved mechanical properties.

MATERIALS AND METHODS

Materials

Acrylonitrile (AN), acrylic acid (AA), acrylamide (AM), 3-sulfopropyl acrylate potassium salt (SPAK), *N,N′*-methylenebisacrylamide (Bis), N,N,N',N'-tetramethylene diamine (TEMED), potassium metabisulfite (PMBS), and ammonium persulfate (APS) were obtained from Aldrich Chemical Company (Milwaukee, WI). Pluronic® F127 was obtained from BASF Corporation (Parsippany, NJ). Zinc chloride ($ZnCl_2$) and sodium bicarbonate ($NaHCO_3$) were purchased from Mallinkrodt Specialty Chemical Co (Paris, KY).

Synthesis of Various SPIHs

SPHs were synthesized using various vinyl monomers. **Figure 1** shows the structures of vinyl monomers used in this study. SPHs were produced following the methods described in our previous studies.[7,8] The monomers used in this study were AM, SPAK, and neutralized acrylic acid (the mixture of acrylic acid and sodium acrylate, pH 5.1). To make a poly(AM-co-SPAK) SPHs, the following components were added sequentially to a 16 mm × 100 mm glass test tube: 600 µL of 50% AM and 400 µL of 50% SPAK as monomers, 250 µL of 2.5% Bis as crosslinker, 50 µL of 10% Pluronic F127 as foam stabilizer, 20 µL of 50% AA, 30 µL of 20% APS, and 30 µL of 20% TEMED as redox initiator pair. Deionized, distilled water (DDW) was used for making SPHs. The exact amount of each component can be varied to optimize the properties of SPHs. The test tube was shaken to mix the solution after each component was added. Sodium bicarbonate (100 mg) was added 90 seconds after adding the initiators, and the mixture was then stirred vigorously using a spatula to distribute $NaHCO_3$ evenly throughout the tube. Polymerization was accelerated after adding $NaHCO_3$, and was subsequently cured at room temperature for 1 hour. The synthesized SPHs were retrieved from the test tubes by adding 2 mL of absolute ethanol, and dried in an oven at 60°C for 6 hours. AN monomer solution was made by dissolving 30 parts by weight of AN in 70 parts by weight of aqueous 70% $ZnCl_2$ solution. The fully dried SPHs were cut into 1.5-cm discs by a razor blade and immersed in 1.5 mL of the 30% AN monomer solution for 6 hours. After loading AN monomer, the calculated amounts of 5% (wt/vol) PMBS and 5% (wt/vol) APS were added to the SPH samples drop by drop using a pipette. Because the SPH samples were fully soaked with the AN monomer solution, the initiator pair of PMBS and APS solution could easily diffuse into the SPH discs. Heat was applied after adding the initiator pair to accelerate the polymerization. The polymerization was allowed to continue for 12 hours. When polymerization was complete, the SPH discs were then thoroughly washed in DDW to remove the unreacted chemicals. Finally, the resulting superporous IPN hydrogels (SPIHs) were dehydrated using absolute ethanol and dried in an oven at 60°C overnight.

Monomer	Structure
Acrylamide	$H_2C{=}CH{-}C(=O){-}NH_2$
Acrylic acid	$H_2C{=}CH{-}C(=O){-}OH$
Acrylonitrile	$H_2C{=}CH{-}CN$
3-Sulfopropyl acrylate, potassium salt	$H_2C{=}CH{-}C(=O){-}O{-}CH_2CH_2CH_2SO_3K$

Figure 1. Vinyl monomers used in the synthesis of superporous hydrogels and IPN structures.

SPH composites containing PAN were also synthesized according to a method described previously[2,7,9] for comparison with the PAN SPIHs. Poly(AM-co-SPAK) superporous hydrogel composites were made by adding PAN powder (average M_w 15 000) to the formulation

of poly(AM-co-SPAK) SPH. Before adding TEMED, 70 mg of PAN powder was added to the solution and the mixture was stirred using a spatula to evenly distribute the PAN powder. After the initiator pair and $NaHCO_3$ were added, the mixture was vigorously stirred to accelerate foaming and to distribute PAN and gas bubbles. The PAN content was approximately 10% of the SPH formulation, resembling the PAN content in the IPN formulation.

Swelling Studies

Swelling experiments were conducted in DDW. All data were obtained in triplicate unless stated otherwise. Cylindrical shape hydrogel samples were weighed and measured in diameter and length. Samples were immersed into DDW at room temperature. At predetermined time intervals, each sample was taken out of the water to measure the weight, diameter, and length of the swollen sample using a balance (Denver Instrument Co, Denver, CO) and an electronic digital caliper (Control Company, Friendswood, TX). The weight swelling ratio and volume swelling ratio were calculated based on those measured data. The weight swelling ratio (Q_w) is defined as:

$$Qw = \frac{w_s}{w_d} \tag{1}$$

where w_s is the weight of the swollen SPIH sample and w_d is the weight of dried SPIH sample. The volume swelling ratio (Q_v) is defined as:

$$Qv = \frac{V_s}{V_d} \tag{2}$$

where V_s and V_d are the volume of the swollen and dry SPIH samples, respectively. The weight and volume swelling curves were plotted to compare the swelling kinetics of hydrogel samples.

Mechanical Property Studies

Mechanical properties of swollen SPHs and SPIHs were examined using the Stable Micro Systems Texture Analyzers (Texture Technologies Corp Scarsdale, NY). The hydrogel samples were cut into certain lengths of cylindrical shape and swollen in DDW to equilibrium. The swollen hydrogel samples were mounted on the Stable Micro Systems. The initial diameter and length of the hydrogel sample was measured in order to calculate the cross-section area and the percent of strain. Both compression and tensile strength were examined. For compression or tensile tests, the pre-test speed, test speed, and post-test speed were 2.0 mm/sec, 1.0 mm/sec, and 2.0 mm/sec, respectively. The trigger force was set to be 0.02 *N*. All data were obtained in quintuplicate unless stated otherwise.

Scanning Electron Microscopy

Dried hydrogel samples were examined by scanning electron microscopy (SEM). Hydrated hydrogel samples were examined by cryo scanning electron microscopy (cryo SEM), which can maintain the structure of the hydrated materials in the most natural state. Hydrated samples were frozen by plunging them into liquid nitrogen. Samples were fractured and then sublimated at –75°C for 20 seconds prior to sputter-coating for 4 seconds with gold at –160°C. The sample was immediately frozen first, and the liquid nitrogen solidified under reduced pressure at successively higher temperatures. The pressure was changed to normal at this point to allow sublimation, and the sample was immersed in the nitrogen slurry. A CT 1000 Cryotrans System (Hexland Ltd, Oxford, England) attached to a scanning electron microscope was used. Samples were imaged at –140°C in a JEOL JSM-840 SEM (Jeol USA Inc, Peabody, MA) using 5 kV accelerating voltage.

RESULTS AND DISCUSSION

Synthesis of PAN Superporous IPN Hydrogels

PAN is not water soluble due to strong dipole-dipole interactions between nitrile groups of different polymer chains.[10] PAN molecules synthesized in SPH are expected to form a network by physical crosslinks, resulting in IPN. The properties of the synthesized SPIHs were significantly dependent on the amount of the initiator pair. As shown in **Figure 2**, when the loading amounts of APS and PMBS were about 0.5 mol% of the AN monomers, a homogeneous IPN gel was obtained, which swelled to a volume comparable to the control SPH samples. When a larger amount of initiator pair was added, eg, 2 mol% and 1 mol%, the formed SPIHs were heterogeneous. A yellowish core was formed in the center of each hydrogel disc, and the gel disc did not swell as much as the control did. The appearances of swollen SPHs and SPIHs were also different, as shown in **Figure 3**. When the PAN network was formed inside an original superporous hydrogel, the SPIH was opaque as shown in **Figure 3A**. Since the PAN polymer network was distributed inside the

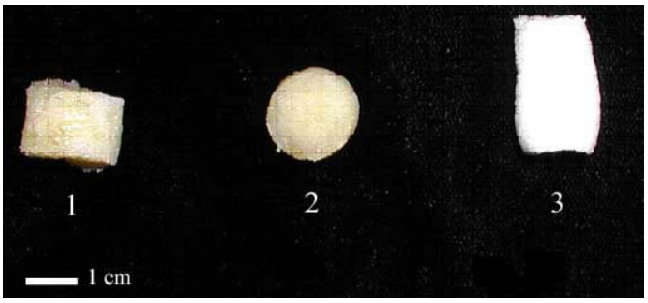

Figure 2. Photographs of PAN SPIHs synthesized using different amounts of initiators, APS and PMBS. (1) 2 mol%; (2) 1 mol%; and (3) 0.5 mol%.

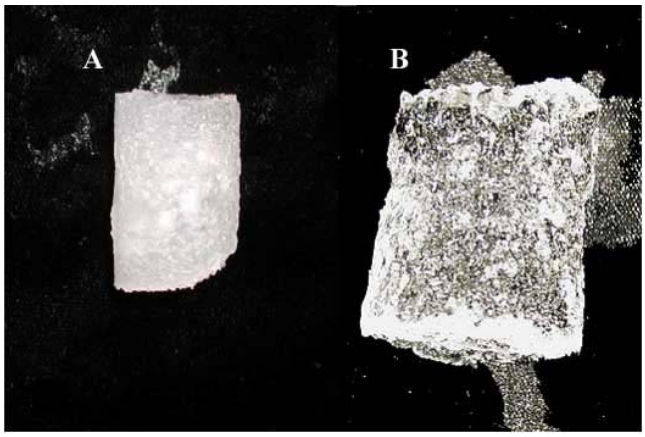

Figure 3. Photographs of a swollen PAN superporous IPN hydrogel (A) and a swollen superporous hydrogel (B).

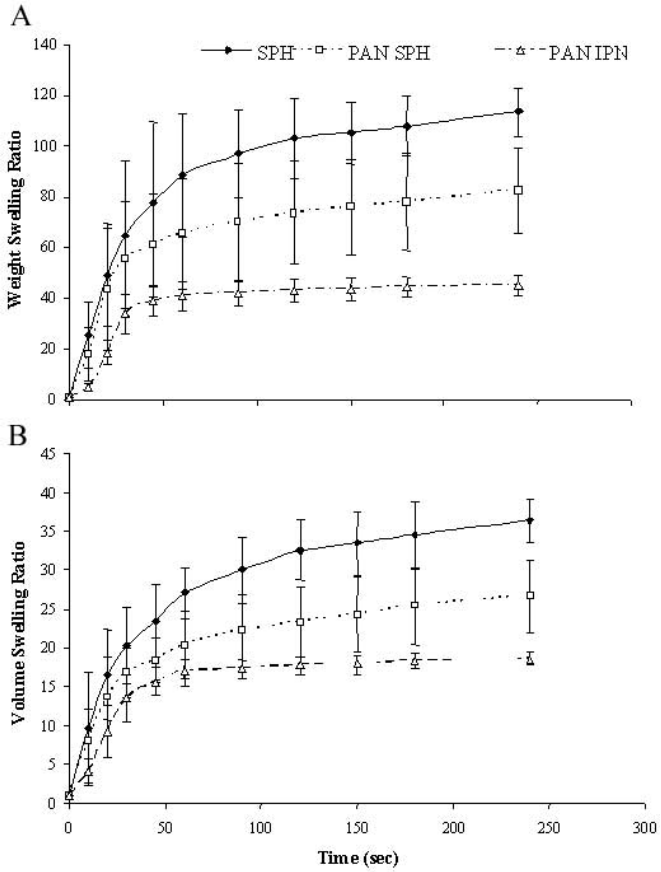

Figure 4. Weight swelling curves (A) and volume swelling curves (B) of 3 types of P(AM-co-SPAK) hydrogels (n =3, mean ± SE).

SPH structure, no visible phase separation was observed. The control SPH, which was composed of hydrophilic polymers, eg, polyacrylamide or poly(acrylic acid), remained clear and transparent after fully swelling as shown in **Figure 3B**.

Swelling Properties of PAN SPIHs

The swelling profiles of P(AM-co-SPAK) SPH, PAN incorporated P(AM-co-SPAK) SPH composite, and PAN/P(AM-co-SPAK) SPIH are shown in **Figure 4**. The weight equilibrium swelling ratio, the volume equilibrium swelling ratio, and the time to reach the equilibrium swelling of those samples are summarized in **Table 1**. As shown in **Figure 4**, although the extent of swelling was decreased when an IPN structure was formed inside an SPH, the swelling of the SPIH was still as fast as the control, reaching equilibrium in about 4 minutes. These results indicated that the interconnected pores (ie, open channels) were not blocked by the PAN network, and the capillary effect to accelerate water absorption was maintained in the SPIH.

Mechanical Properties of PAN SPIHs

For a gastric retention device, the swollen SPH should be strong enough to withstand repeated peristaltic contractions. Thus, it was necessary to improve 2 mechanical properties of SPHs: compression strength and elasticity. As shown in **Figure 5A**, the control SPH is rather weak after equilibrium swelling. The fracture, when it occurred, could be observed in the compression curve. **Figure 5A** shows an example of the fracture, which is labeled as the breaking point. The compression strength curve of PAN/SPIH is shown in **Figure 5B**. No fracture was observed in the compression curves of IPN hydrogel samples. When the compression stress disappeared, the IPN hydrogel samples relaxed to their original states. The compression strength and strain of the control P(AM-co-SPAK) SPH, PAN incorporated P(AM-co-SPAK) SPH composite, and PAN/P(AM-co-SPAK) SPIH are summarized in **Table**

Table 1. Summary of Swelling Properties of 3 Types of P(AM-co-SPAK) Hydrogels*

SPH Type	Equilibrium Swelling Ratio (Weight)	Equilibrium Swelling Ratio (Volume)
SPH	113.4 ± 9.5	36.3 ± 2.8
SPH composite	82.5 ± 17.2	26.7 ± 4.6
SPH IPN	45.2 ± 4.0	18.6 ± 0.8

*SPH indicates the control P(AM-co-SPAK) superporous hydrogel; SPH composite, the PAN incorporated superporous hydrogel composite; SPH IPN, the PAN penetrated superporous IPN hydrogel. The swelling ratio was measured in deionized, distilled water (n = 3, mean ± SE): the time to reach the equilibrium swelling was 240 seconds for all 3 types of P(AM-co-SPAK) hydrogels.

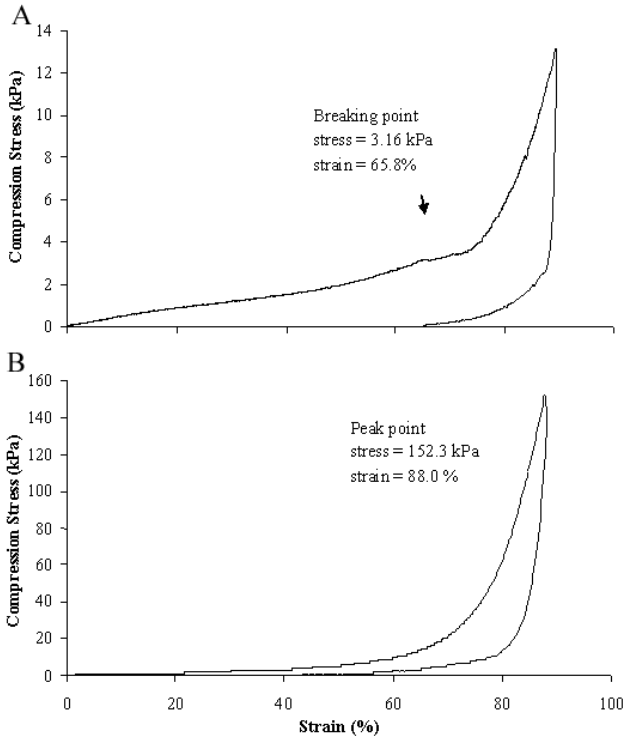

Figure 5. Compression strength curves of a swollen P(AM-co-SPAK) SPH (A) and a swollen PAN/P(AM-co-SPAK) superporous IPN hydrogel (B).

2. It was found that simple blending of PAN polymers in SPH structures did not improve the mechanical strength. On the other hand, when a PAN network was formed inside an SPH, the compression strength was improved approximately 50-fold.

Elasticity was estimated from the tensile strength measurements. Because the control SPHs and SPH composites were too weak, the tensile strength test could not be conducted on those 2 types of SPHs. A tensile strength curve of a PAN SPIH is shown in **Figure 6**. The stress was calculated for the cross-section area of the control sample. Strain is relative elongation in percent from its original length. As shown in **Figure 6**, the PAN/P(AM-co-SPAK) SPIH can be stretched to 173% of its original length before breaking. The mean elongation strain and breaking point tensile stress of 5 samples were summarized. The elongation strain before breaking was found to be 170.0% ± 13.3%, and the tensile stress before breaking was found to be 11.53 ± 3.76 kPa. The elastic modulus, E, was also determined from the slope of linear dependence of the following equation,

$$\sigma = E(\lambda - \lambda^{-2}) \quad (3)$$

where σ is the applied stress and λ is the relative deformation of the specimen, ie, the elongation strain in the tensile test. Based on the slope of the regression line, the elastic modulus, E, for the PAN/P(AM-co-SPAK) SPIHs was estimated to be 8.18 ± 2.57 kPa.

Microscopic Structure of PAN SPIHs

Because the fast swelling kinetics were maintained for the PAN SPIHs, it appears that the incorporated PAN networks did not block the capillary channels that were formed by the interconnected pores. SEM and cryo SEM were used to examine the detailed structures of the inside of SPHs and SPIHs under the dry and hydrated states. **Figure 7** shows the comparison of a P(AM-co-SPAK) SPH sample and a PAN/P(AM-co-SPAK) SPIH sample in the dry state. The images clearly show that the pore sizes and structures are similar for the control SPH and the PAN SPIH samples. The pore size is approximately 100 μm, and the pores are all interconnected. Unlike on the control SPH samples, many collapsed fibrous structures can be observed on the struts of SPIH samples, which make the IPN sample coarser in appearance.

Table 2. Summary of Mechanical Properties of Different Types of P(AM-co-SPAK)/PAN Superporous Hydrogels*

SPH Type	Compression Stress (kPa)	Compression Strain (%)	Fracture under Compression
P(AM-co-SPAK) SPH	3.51 ± 0.93	67.31 ± 4.6	Yes
PAN/P(AM-co-SPAK) SPH composite	3.35 ± 0.28	69.8 ± 2.7	Yes
PAN/P(AM-co-SPAK) SPH IPN (Radial)	68.9 ± 20.5	81.7 ± 0.8	No
PAN/P(AM-co-SPAK) SPH IPN (Axial)	175.4 ± 26.7	88.2 ± 2.3	No

*Compression strength of PAN/P(AM-co-SPAK) superporous IPN samples were examined in the radial and axial directions. SPH indicates the control P(AM-co-SPAK) superporous hydrogel; SPH composite, the PAN incorporated superporous hydrogel composite; SPH IPN, the PAN penetrated superporous IPN hydrogel. All the testing samples were hydrated and fully swollen (n = 5, mean ± SE).

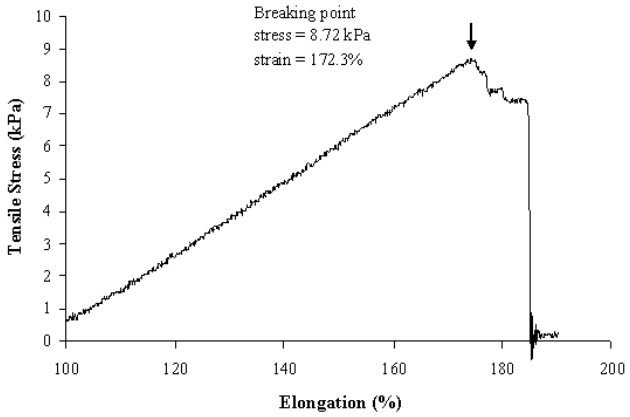

Figure 6. A tension curve of a swollen PAN/P(AM-co-SPAK) superporous IPN hydrogel.

Figure 8 shows the cryo SEM images of a PAN/P(AM-co-SPAK) SPIH sample in the swollen state. An overall appearance was obtained at low magnification (**Figure 8A**) and a detailed structure near the cell walls of the hydrated SPIH pores was obtained at higher magnification (**Figure 8B**). There were many fibrous networks formed along and between the SPIH pore walls. But those fibrous networks did not block the open pore structures, and just formed scaffold-like structures connecting the pore walls together. The micrographic analysis is consistent with the results of the swelling and mechanical studies. Visual observation of the interconnected fibrous networks along and between the SPIH pore walls is consistent with the experimental data showing the same swelling kinetics with significantly improved mechanical properties. The improvement in mechanical property was most likely due to the PAN polymer networks formed inside the pores of an SPIH that prevent the fragile pore structure

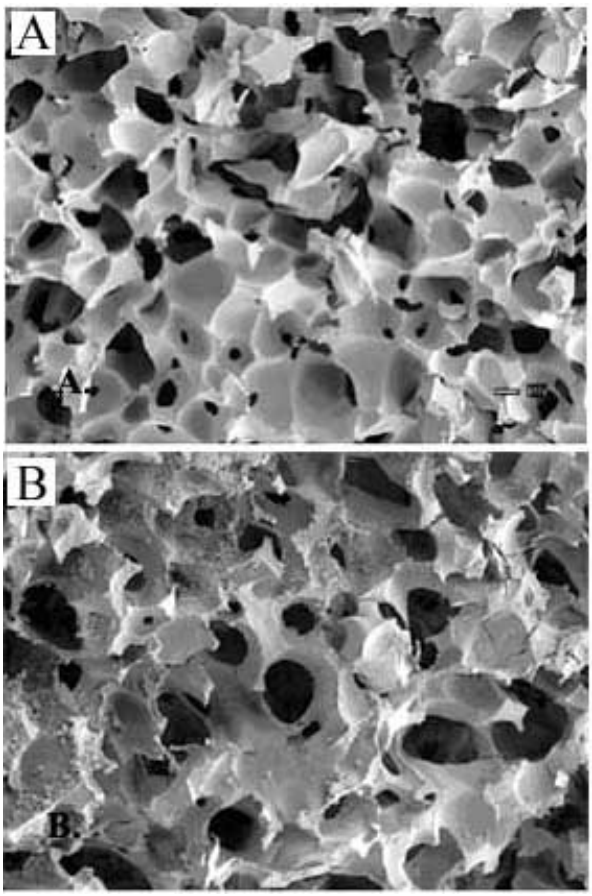

Figure 7. Scanning electron micrographs of P(AM-co-SPAK) SPH (A) and PAN/P(AM-co-SPAK) superporous IPN gel (B) in the dry state. The magnification of the micrographs is ×50, and the scale bar indicates 100 μm.

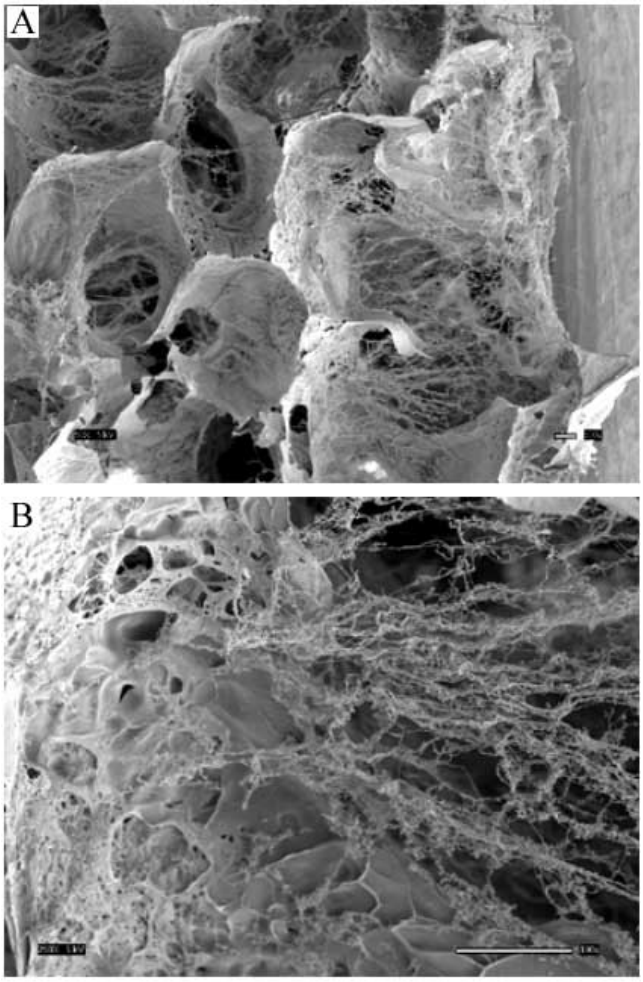

Figure 8. Cryo SEM images of a hydrated PAN/P(AM-co-SPAK) SPIH (A) and an area near the pore walls of the SPIH (B). The magnifications of the micrographs A and B are ×50 and ×250, respectively. The scale bars are both 100 μm.

from collapsing easily under the compression pressure. Improvements in the elastic property with high elastic modulus can be attributed to the network structures as well. Because the polymer network connects the cell walls inside the SPIH pore structure, it restricts a volume change during swelling of an SPIH in water. The volume cannot be increased further once the PAN polymer fibers reach their extension limits. Microscopic structures of the SPIH samples can explain the macroscopic properties, such as swelling behavior, and improvements in the mechanical properties. The fast swelling and strong mechanical properties of SPIHs make them highly useful for various pharmaceutical and biomedical applications.

CONCLUSION

SPHs having enhanced mechanical properties were prepared by introducing the IPN structures. Swelling of the resultant SPIHs was still fast, indicating that the interconnected pore structures were not destroyed by the penetrating polymer networks. The mechanical strength of SPIHs was significantly increased. The compression strength was improved by approximately 50-fold, and elasticity was also improved with 170% elongation of the original length. The improved mechanical properties are due to the highly oriented PAN network structures formed along and between the pore walls of SPIHs. The SPIHs with improved mechanical properties are most suitable for developing gastric retention devices.

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