Preparation and Characterization of a Prolonged and Sustained Drug Delivery System: Linear Polyacrylamide in Poly(*N*-isopropylacrylamide)/Clay Hydrogels

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ABSTRACT: In this contribution, a novel smart drug delivery system based on poly(*N*-isopropylacrylamide) (PNIPAAm), clay, and linear polyacrylamide (PAAm) was developed for prolonged and sustained controlled drug release. Various amounts linear PAAm were incorporated into PNIPAAm/clay hydrogels. Resulting hydrogels were characterized by scanning electron microscopy, differential scanning calorimetry, and compression measurements to investigate the morphological, thermal, and mechanical properties. The swelling ratio and response kinetics on heating or cooling were also investigated to understand the smart properties. Finally, bovine serum albumin (BSA), used as the model drug, was loaded into the hydrogels to examine and compare the effects of controlled release at different temperatures (20°C and 37°C). The result indicated that all the PNIPAAm/clay/linear PAAm gels showed good smart property with a higher swelling ratio and more complicated deswelling behavior. Although the compression properties of the resulting hydrogels decreased by incorporating the linear PAAm into the network of PNIPAAm/clay, they still showed high compression stress and excellent reversibility. BSA release behavior at 20°C and 37°C revealed that a prolonged release of BSA with the auto-adjustable function to external temperature changes. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 125: E148–E156, 2012

Key words: drug delivery system; clay; hydrogels; temperature sensitive; linear PAAm

INTRODUCTION

Stimulus-responsive hydrogels have attracted extensive research interest due to their attractive properties: they undergo a large and abrupt, physical changes in response to external stimuli. Among those external stimuli, temperature is an important triggering signal for phase transitions in hydrogels and poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel is the most typical thermosensitive polymeric network, which exhibits a lower critical solution temperature (LCST) at about 33°C.[1–4] At a temperature above LCST, the hydrogen-bonding interaction becomes weaker for proper solubility of PNIPAAm in water. Consequently, a thermoreversible phase separation occurs and a polymer-enriched phase and an aqueous phase that contains nearly no polymer form. Due to this unique property, PNIPAAm hydrogel has been widely studied for biomedical uses including as drug delivery system (DDS),[5–9] artificial organs[10] and actuators,[11] etc.

DDS is developed by encapsulating drugs into a specific delivery system to provide a predetermined drug amount at a proper time and/or targeted site over the duration from several hours to several years.[12–15] Hence, proper drug delivery rate is very important to improve their therapeutic value by reducing toxic side effects of drugs. A PNIPAAm hydrogel is used as a drug carrier for controlled release, due to its inherent temperature-triggering capability. Many researchers have focused their attention on improving PNIPAAm hydrogel's drug delivery rate.[16] However, quick release of drugs is not always favorable. Zhang et al.[17] fabricated DDS consisting of hydroxyl-functionalized glycerol poly- (ecaprolactone) (PGCL)-based microspheres and PNIPAAm hydrogel. The resulted DDS obtained a prolonged drug release. However, the poor mechanical property prohibits their applications. Too soft and easily broken nature makes it difficult to handle during surgical procedures.

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TABLE I
Compositions of S-P Hydrogels

	Composition					
Hydrogels	Clay (g)	NIPAAm (g)	Linear PAAm (g)	TEMED (uL)	KPS (g)	H_2O (mL)
S3	0.9	3	0	24	0.03	30
S3P1	0.9	3	0.3	24	0.03	30
S3P3	0.9	3	0.9	24	0.03	30
S3P5	0.9	3	1.5	24	0.03	30
S7	2.1	3	0	24	0.03	30
S7P1	2.1	3	0.3	24	0.03	30
S7P3	2.1	3	0.9	24	0.03	30
S7P5	2.1	3	1.5	24	0.03	30

More recently, a new type of nanocomposite hydrogel (NC gel) consists of PNIPAAm and synthetic hectorite clay was invented.[18] Quite distinct from the general purpose that the clay incorporated into the polymer matrix is used as filler to reinforce the nanocomposites,[19,20] the inorganic hectorite clay acts as a multifunctional crosslinker in the NC gels. PNIPAAm chains growing from the surface of the individual clay during gelation may form bridges between the clay platelets and the clay platelets are surrounded by the polymer chains after the state of hydrogel preparation. As a result, the novel NC gels overcome all of these mechanical disadvantages of conventional PNIPAAm hydrogels (abbreviated as OR gels, crosslinked by *N*,*N*′-methylenebisacrylamide) and show very large deformability, better resilience, and amazing toughness-the tensile strength approaches nearly 1 MPa.[21] However, up to date, there is no report about the study of a prolonged drug release using PNIPAAm/clay hydrogels.

In our previous study, a linear polyacrylamide (PAAm) with an average viscosimetric molecular weight 3.97×10^3 kg mol^{-1} was added to the prereaction solution for the preparation of PNIPAAm/clay NC gels. The effects of the linear PAAm on the optical transparency and tensile property of the resulting PNIPAAm/clay/linear PAAm hydrogels were systematically investigated.[22] In this study, the effect of linear PAAm on the morphological, thermal, compression properties, and the drug release behavior of the resulting PNIPAAm/clay/linear PAAm hydrogels were characterized. Bovine serum albumin (BSA) was chosen as delivery model to evaluate delivery capability of PNIPAAm/clay/linear PAAm hydrogels at 20 and 37°C.

EXPERIMENTAL

Materials

Acrylamide (AAm) (98.5%, chemically pure; Shanghai Fine Chemical Material Institute), synthetic hectorite Laponite XLS (Clay-S) (Rockwood Co., 92.32 wt % $Mg_{5.34}Li_{0.66}$ Si_8O_{20} $(OH)_4$ $Na_{0.66}$ and 7.68 wt % $Na_4P_2O_7$], potassium persulfate (KPS), and *N*,*N*,*N*′,*N*′-tetramethyldiamine (TEMED) (analytical reagent; Shanghai Chemical Reagent, Shanghai) were used as-received. All solutions used in the experiments were prepared in deionized water.

Preparation of linear PAAm hydrogels

PAAm homopolymer was prepared by redox polymerization with the same method with the fabrication of linear PNIPAAm.[23] The intrinsic viscosity, [η], of the polymer was 569 cm^3 g^{-1} measured in water at 25°C. From that value, the average viscosimetric weight of the PAAm was calculated as 3.97×10^3 kg mol^{-1} by using Mark-Houwink-Sakurada equation. The values of *a* and *K* used here were 0.97 and 2.26×10^{-4} cm^3 g^{-1}, respectively, according to Chiantore et al.[24]

Preparation of PNIPAAm/clay/linear PAAm hydrogels

The procedure for synthesis of PNIPAAm/clay/linear PAAm hydrogels was identical with the method reported previously for NC hydrogel,[21] except for the addition of the linear PAAm. First, a transparent aqueous solution consisting of water (28 mL), Clay-S (0.9–2.1 g), was prepared. Next, linear PAAm (0–4.7 g), prepared as aforementioned, was added to the former solution by stirring at 25°C for 4–6 h until the mixed solution became homogeneous. Then, NIPAAm (10 wt % to total water content), TEMED (24 mL), and KPS (0.03 g dissolved in 2 mL water) were added to the mixed solution. After bubbling nitrogen for 20 min, free radical polymerization was performed at room temperature for 120 h. All the hydrogels were synthesized in airtight glass tubes (interior size of 5 mm in diameter and 60 mm in length).

In this article, the resulting hydrogels are expressed as SxPy gels (abbreviated as S-P gels), where x, y stand for the clay's and linear PAAm's weight percent to water weight, respectively. The NIPAAm/water ratio was fixed at 10/100 (w/w) in all cases. The hydrogels without loading linear PAAm are named as Sx. The compositions of resultant gels are summarized in Table I.

Differential scanning calorimetry

The thermal behavior of hydrogels was evaluated with a modulated differential scanning calorimeter (MDSC 2910, TA Instruments). The thermal analysis was performed on the as-prepared hydrogels (about 10 mg) from 25°C to 45°C with a heating rate of 1°C min^{-1} under dry nitrogen.

Scanning electron microscopy

The as-prepared S3 and S3P5 gels (in the same size: 5 mm diameter, 30 mm length) were first equilibrated in distilled water at temperatures of 20°C and 50°C for 24 h, respectively, then, quickly frozen in liquid nitrogen, further freeze–dried in a FD-1A-50 Freeze Drier under vacuum at −48°C for 48 h. The freeze–dried hydrogels were fractured carefully, and the interior morphology of the hydrogels was studied by using a scanning electron microscope (SEM) (EOL JSM-5600 LV). Before observation of SEM, all freeze–dried samples were fixed on aluminum stubs and coated with gold.

Swelling kinetics

As-prepared gels rods were cut in the same size (5 mm diameter, 30 mm length) and were immersed in a large excess water at 20°C. The gels were taken out of water at certain time intervals and weighted after wiping off the excess water on the surface with a wet filter paper until they attain a swelling equilibrium. The equilibrium swelling ratio (SR) was calculated with the following equation:

$$\mathrm{SR} = (W_s - W_d)/W_d \quad (1)$$

where W_s is the weight of the swollen hydrogel and W_d is the weight of the dry hydrogel.

Deswelling kinetics

The as-prepared gels (5 mm diameter, 30 mm length) were immersed into deionic water at 50°C. The gels were taken out of water at certain time intervals and weighted after wiping off the excess water on the surface with a wet filter paper. The deswelling ratios (DSR) are represented as follows:

$$\mathrm{DSR} = W_t/W_0 \quad (2)$$

where W_t is the weight of the deswollen hydrogel at time t, and W_0 is the weight of the corresponding initial gels.

Compressive mechanical property

Compression tests were performed for the as-prepared hydrogels with the same size (13 mm diameter, 20 height) using the texture analyses (TA.XT plus, SMSP/100). Compression properties of all gels were obtained under the following conditions: compression speed is 2 mm/s, the same hydrogel sustains repeated compression for four cycles. In every compression cycle, the most compression distance is 12 mm (at 80% strain). The compressive modulus was determined by 2–3.4 mm deformation by the following equations:

$$\Sigma = f/S_0 = E(\lambda - \lambda^{-2}) \quad (3)$$

where σ is the applied stress in Pa m^{-2}, f is the value of measured force, S_0 is the cross-section of the undeformed hydrogel, and λ is the relative deformation of the specimen.

In vitro release of drugs

BSA was chosen as model drug. First, a BSA loading solution was prepared by dissolving BSA (961 mg) in phosphate-buffered solution (PBS) (100 mL, 0.012*M*, pH 7.4). As-prepared hydrogels (5 mm diameter, 30 mm length) were dried at ambient temperature (20°C) for 72 h, and then dried hydrogels were equilibrated in BSA loading solution at 20°C for 72 h to load BSA. Second, the above hydrogels loaded BSA was immersed in a cuvette filled with PBS (8 mL, 0.012*M*, pH 7.4) at 20°C and 37 °C. At a certain time interval, 2.5 mL buffer medium in the cuvette was removed, and the concentration of the BSA was measured by UV/vis spectrophotometer (Lambda 35, Perkin Elmer Co.) at 279 nm. Meanwhile, 2.5 mL fresh buffer solution was added to the cuvette to maintain the same solution volume. The cumulative release (%) was calculated as follows:

$$\text{Cumulative release}(\%) = Mt/(M - Mt) \quad (4)$$

where Mt is the release amount of BSA at time t and M is the estimated amount of BSA loaded in hydrogels. It was determined by the mass change of protein in the solution before and after loading. Each loading experiment was performed in triplicates, according to the approach in the literature.[25]

RESULTS AND DISCUSSION

Preparation of S-P gels

S-P hydrogels were prepared by *in situ*, free-radical polymerization of NIPAAm in the presence of linear PAAm. The resulting hydrogels were all uniform and exhibited no macroscopic phase separation or syneresis through the naked eye observation, regardless of the content of linear PAAm. Generally the interaction between PNIPAAm and clay is regarded as a combination of hydrogen bonding and ionic interaction. The oxygen atoms of the clay surface may be able to form hydrogen bonds with the amide proton of PNIPAAm, and the metal atoms on the clay surface may form a complex with the carboxyl group of NIPAAm.[26,27]

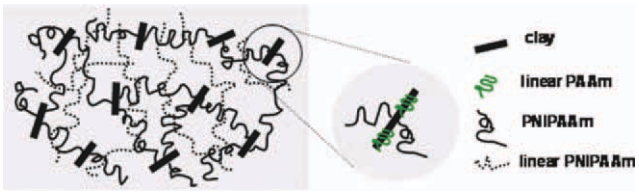

Figure 1 Schematic representation of the structures of S-P gels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

As PAAm molecules and PNIPAAm chain have the same functional group to interact with clay particles, some linear PAAm chains could predominantly link to the surface of the clay platelets by hydrogen bond, ionic interaction or physical entanglement in the prereaction solution. During the subsequent NIPAAm polymerization, the linear PAAm chains were incorporated in PNIPAAm networks. Clay and the predominant absorbed linear PAAm may form typical hydrophilic domains. The network structure of PNIPAAm/clay hydrogels is illustrated in Figure 1. As some of the active sites on the surface of the clay particles were initially taken up by linear PAAm molecules, there might be some PNIPAAm chains leaving two ends dangling chains, which acted as linear semi-interpenetrating chains in the polymer networks. Furthermore, there was still strong hydrogen bond between linear PAAm and PNIPAAm.[28]

Thermal behavior of the S-P hydrogels

Figure 2 shows the differential scanning calorimetry (DSC) thermograms of the gels with different linear PAAm content in the temperature range from 25°C to 45°C. The transition temperature or LCST is determined by the intersecting point of two tangent lines from the baseline and slope of the endothermic peak.[29,30] It was observed that the LCST of S-P hydrogel was almost the same, but the onset temperature of the endothermic peak of S-P hydrogels shifted to a lower value with the increase in amount of linear PAAm (e.g., the LCST is 31.8°C for S3 and 27.9°C for S3P5). According to the report,[31,32] the LCST should increase with increasing hydrophilicity of the polymer. However, the introduction of hydrophilic linear PAAm to PNIPAAm/clay hydrogel network led to more complicated intermolecular hydrogen bond between linear PAAm and clay platelets. The hydrogen bonding protected PNIPAAm from exposure to water, which resulted a sigficant hyrdrophobic contribution to the LCST similar to the result reported by Byung and Jameela.[33,34] Furthermore, it was indicated that the phase transition of S-P gel was gradually weakened as linear PAAm content increased. This may be due to that the space for PNIPAAm chain to realize the coil-globule configuration transition was restricted partially.

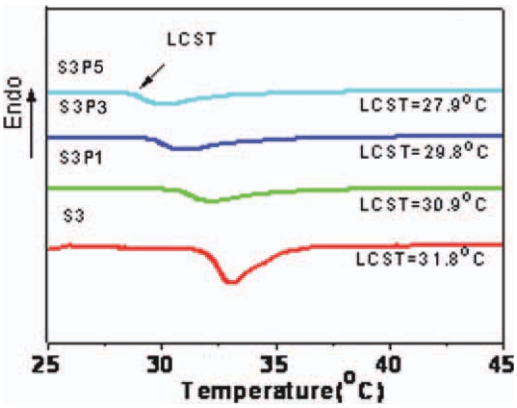

Figure 2 DSC thermograms of the S-P gels with different linear PAAm content at a heating rate of 1°C min^{-1} from 25°C to 45°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Swelling behavior

Figure 3 shows the swelling behavior of S-P gels at 20°C. From the data in Figure 3, it was found that all S-P gels approach to swelling equilibrium after being immersed in 20°C water bath for about 10 h. The swelling rates and swelling ratios of the hydrogels increased with increasing the linear PAAm content. As a rule, the swelling behavior of a hydrogel depends on the hydrophilicity of the polymer chains and the physical structure of the hydrogels.[35] As PAAm chains are more hydrophilic than PNIPAAm, the polymer chains of resulting hydrogels could become more hydrophilic after loading linear PAAm chains in polymer/clay synthesis. On the other hand, aforementioned, linear PAAm predominantly absorbed on the surface of the clay platelets and formed a special microstructure (as shown in Fig. 1), which acted as a strong hydrophilic domain as a

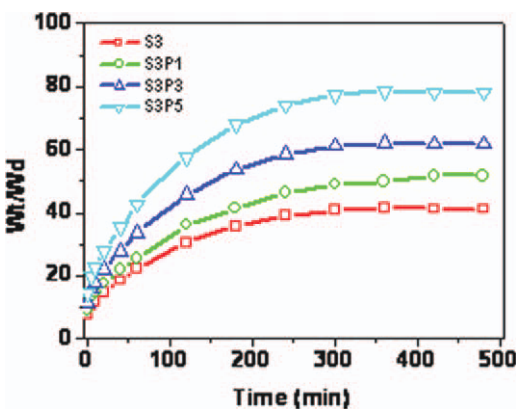

Figure 3 Swelling behavior of S-P gels at 20°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

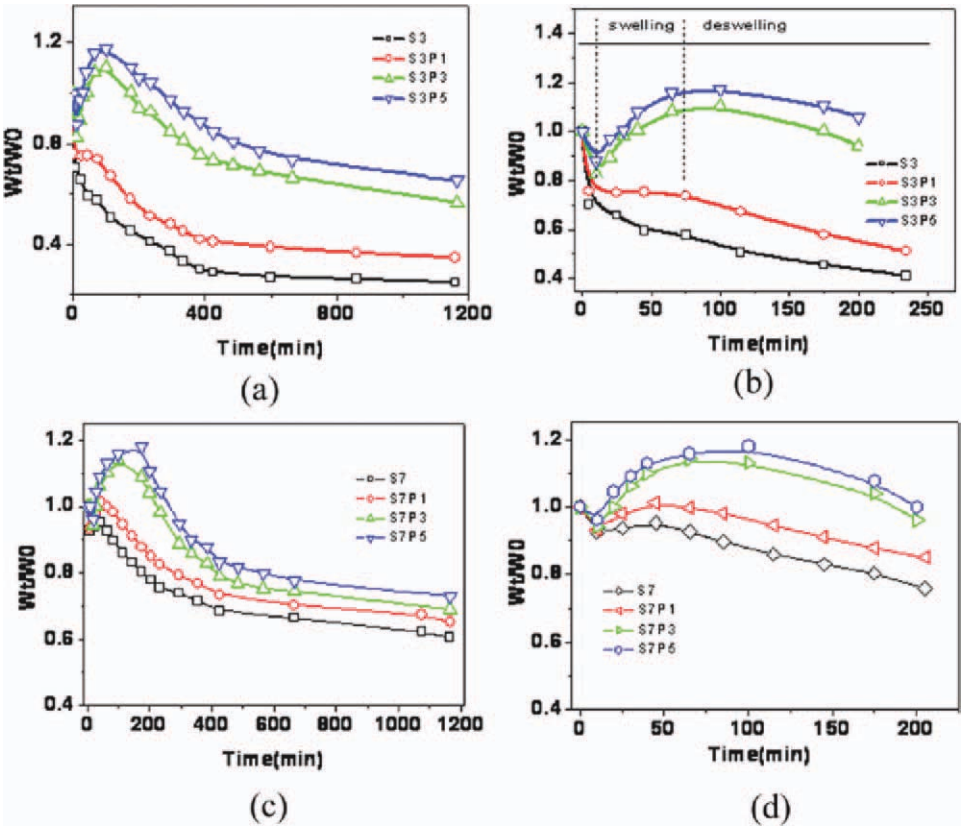

Figure 4 Deswelling behaviors of S-P gels at 50°C: (a) deswelling behavior of S3Px hydrogels for about 20 h; (b) a zoom version of the deswelling behavior of S3Px hydrogels; (c) deswelling behavior of S7Px hydrogels for about 20 h; (d) a zoom version of the deswelling behavior of S7Px hydrogels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

reservoir within the PNIPAAm matrix for water accommodation. As more of these linear PAAm chains were impregnated into PNIPAAm matrix, more extra reservoirs would be available for water accommodation. All these resulted in higher swelling ratios and swelling rates.

Deswelling behavior

Figure 4 exhibits the deswelling kinetics of S-P gels with different linear PAAm content (0%–5%) in two groups (clay content of 3% and 7%) at 50°C water bath. It was found that the deswelling behaviors were greatly dependent on the linear PAAm content. For S3Py gels, the deswelling process was very similar to that of the corresponding PNIPAAm/clay gels when the linear PAAm content was lower than 3 wt %, as shown in Figure 4(a). However, when the content of linear PAAm was up to 3 wt %, deswelling behavior became more complicated-undergoing three processes: deswelling, swelling, and deswelling.

In the deswelling process of the S-P gels, we suppose three factors to determine the kinetics: the aggregation force of PNIPAAm chains, the presence of characteristic hydrophilic groups, and the change of osmotic pressure induced the free ions of clay. The latter two factors acted as a restraint against the volume change of the S-P hydrogel. S-P hydrogel had strong shrinking desire as PNIPAAm/clay NC gels. However, the hydrophilic domains composed of linear PAAm and clay platelets (as described in Fig. 1) could suppress the exclusion of the water as PNIPAAm chains collapse abruptly.

In the previous research,[21] we found the presence of ionic dispersant-tetrasodium pyrophosphate contained in clay for PNIPAAm/clay hydrogels. The high ionic dispersant-tetrasodium pyrophosphate contained in clay makes the ion concentration larger and the osmotic pressure higher, which resulted in a strong swelling trend of hydrogel. The trend is independent on temperature. In this study, the PNIPAAm/clay/PAAm hydrogels are immersed in 50°C water, the high ion concentration trends to make hydrogel swell. As the outermost surface of the hydrogel would be the first region to be affected on the PNIPAAm hydrogels being immersed in 50°C water bath, all the hydrogels initially deswelled, as shown in Figure 4. Meanwhile, the free pyrophosphate anionic groups and sodium ions

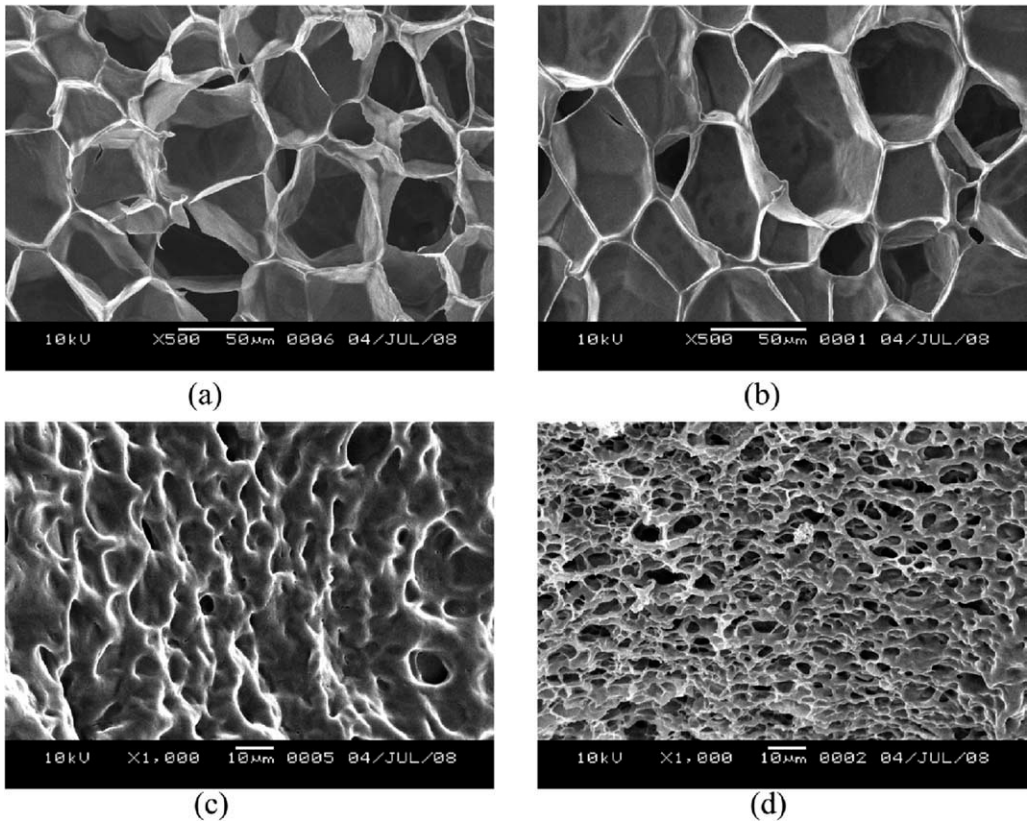

Figure 5 SEM micrographs of freeze–dried S-P gels (all hydrogels were immersed into water bath for 24 h at 20°C or 50 °C before freezing–drying (a) S3 at 20°C, (b) S3P5 at 20°C, (c) S3 at 50°C, (d) S3P5 at 50°C.

of the clay diffused continuously from the surface of gels into water, which caused the ion concentration inside the hydrogels to increase. The increased osmotic pressure made the swelling trend overwhelm the collapsing trend, resulting in subsequent swelling process. It was observed that the retention time of the swelling process increased with increasing the linear PAAm content (i.e., 30–100 min for S3P3 and 20–100 min for S3P5). With the distribution of the free pyrophosphate anionic groups and sodium ions in water from the gel, the ion concentration in gels decreased, which led to a decrease in osmotic pressure. Thus, the phase transition trend of PNIPAAm played a dominant role again, which induced subsequent continuous deswelling process.

Interior morphology by SEM

The interior morphology of S-P gels is shown in Figure 5. From Figure 5(a,b), it was found that the incorporation of linear PAAm into PNIPAAm/clay gel exerted little effect on distribution of the pores. The pores dispersed very uniform with the exception of the slight difference for pore size. For S3P5, the pores were larger than that of S3. This was due to a larger swelling ratio for S3P5 in 20°C water bath. However, the morphology was distinctly different when the gels were immersed in 50°C water bath for 24 h before freezing–drying, as shown in Figure 5(c,d). For S3 gel, absence of linear PAAm chains, it exhibited compact, nonpore structure, while for S3P5 gel, it showed porous morphology structure. As polymerization yields, evaluated from the weights of dried gels,[18] were nearly 100% (>99%) in all cases, we suggested that the porous morphology structure for Figure 5(d) should ascribe to the characteristic hydrophilic domains composed of linear PAAm chains and clay.

As above discussed, linear PAAm predominantly took up some active sites of the surface of clay platelets and many hydrophilic domains surrounded by hydrophobic PNIPAAm chains were formed. When the S-P gels were immersed in 50°C water bath, the PNIPAAm molecules became hydrophobic and might be rearranged and tend to occupy the empty spaces (or pores occupied by water before). However, the hydrophilic domains composed of linear PAAm and clay could act as reservoir and prevent the water be expelled. Consequently, these hydrophilic domains would become pores after freeze–drying, as shown in Figure 5(d). In this sense, the homogenous distribution of pores also illustrated that the dispersion of the clay in the hydrogels was uniform, which was in agreement with the previous report.[27]

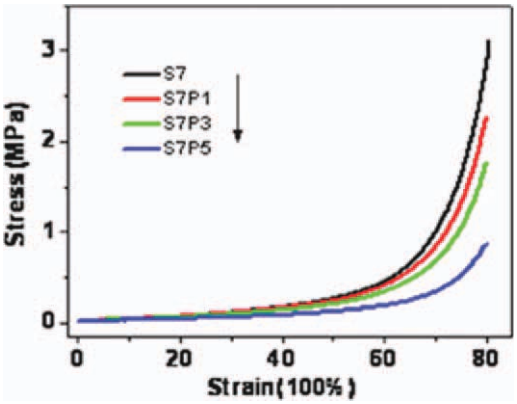

Figure 6 Effect of the linear PAAm content on the stress–strain curves for hydrogels under uniaxial compression. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

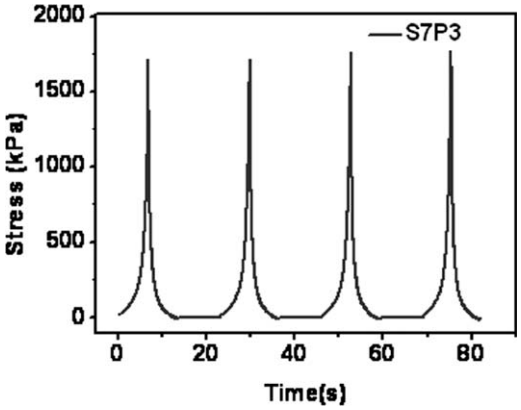

Figure 7 Stress–time curves of S7P3 during four compression cycles.

Compressive properties of S-P gels

Figure 6 shows the typical stress–strain compression curves for S7Py gels with linear PAAm content (0%–5%). It was found that the hydrogels sustained a compression pressure as high as several megapascals despite containing ~ 90 wt % water, for example, the compression stress amounted to 3.12 MPa for S7 and 1.77 MPa for S7P3. This was in stark contrast to most common hydrogels composed of chemical crosslinked PNIPAAm and linear PAAm, which were easily broken either by pressing with a finger or pulling with the hands. The compression strength and modulus were summarized in Table II. It was observed that the compression strength and modulus slightly decreased with increasing the linear PAAm content. On the other hand, the S-P gels exhibited excellent reversibility. All the S-P gels showed some changes in the geometry during compression cycle, but they unrestrained, recovered, and exhibited no appreciable changes (compared with the original size) before the next compression cycle was coming within 20 s. Figure 7 shows the compression strength–time curves of S7P3 during four compression cycles.

In general, the higher crosslinking density and the shorter distance between the crosslinking points produce the higher mechanical strength of a hydrogel.[27] The PNIPAAm/clay gels used in this study are physically crosslinked. The crosslinking density and the distance between crosslinkings are proportional to the clay content.[31,36] As the introducing of linear PAAm, the efficient crosslinking between PNIPAAm and clay platelets decreased. So, crosslinking density decreased and the distance between the crosslinking points increased, which resulted in a slightly suppressed mechanical stress and a higher flexible reversibility.

TABLE II
Compressive Property of S7Py

Hydrogels	Compression strength (MPa)	Compressive modulus (kPa)
S7	3.12	308
S7P1	2.26	276
S7P3	1.77	248
S7P5	0.87	144

In vitro release of BSA

Release at 20°C

The preliminary *in vitro* release data of BSA from the control, S3 and S3Py gels were presented in Figure 8. If drugs were loaded directly into a PNIPAAm/clay hydrogel (S3), they would be released quickly. As shown in Figure 8(a), within the first day, over 36% BSA was released from PNIPAAm hydrogel whether at 20 or 37°C. The overall cumulative release is almost 90% for S3 hydrogel at different temperature. However, when the linear PAAm was incorporated in PNIPAAm/clay hydrogel, BSA release rate and release time was dramatically retarded. Figure 8(b) demonstrated the cumulative releases of BSA (%) from S3P1and S3P5 in PBS at 20°C. The data showed that the release of BSA from S-P gels had a typical biphasic release pattern, i.e., a burst release followed by a slower sustained release. Comparing the release data, it was found that the release device with higher linear PAAm exhibited a slower burst release and slower overall cumulative release percentage. The 12 h initial burst cumulative release % of S3P1 and S3P5 was 11.6% and 9.6%, respectively.

The burst release was attributed to the short diffusion distance for BSA. At the end of the fifth day, the corresponding cumulative releases of BSA% from S3P1 and S3P5 were around 33.1% and 20.9%. Thereafter, the release of BSA slowed down. At the end of the 30th day, cumulative release of BSA

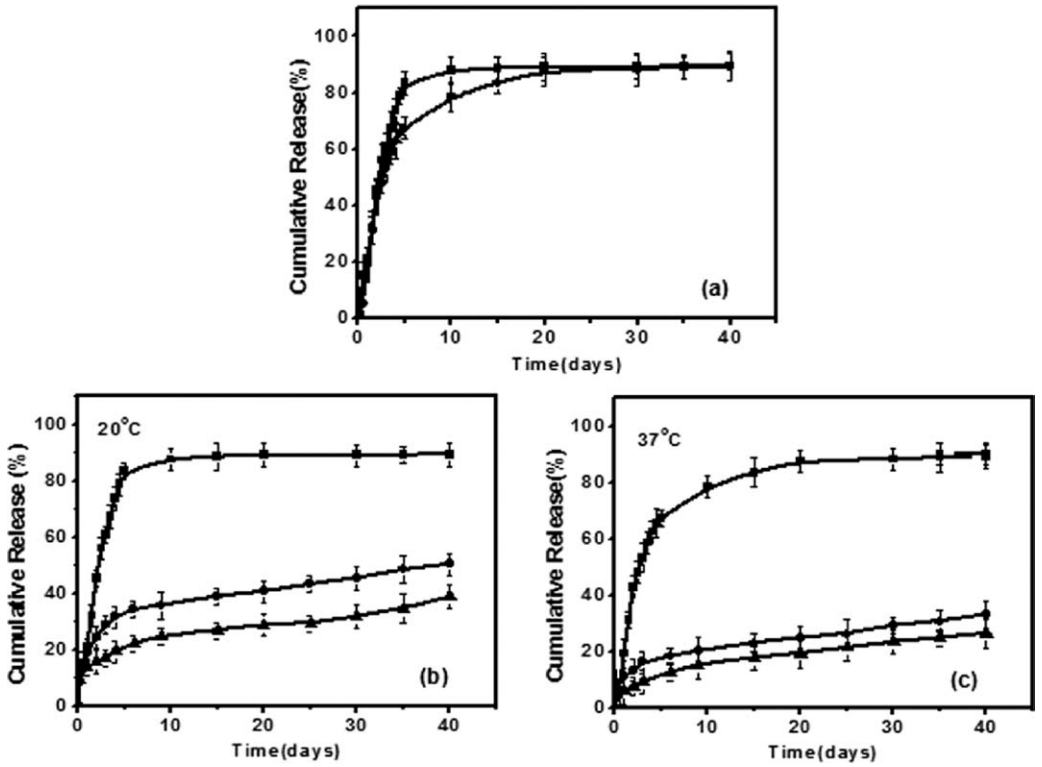

Figure 8 Comparison of the cumulative release of BSA for (a) S3 hydrogels at 20°C (squares) and 37°C (circles), (b) different hydrogels at 20°C, S3 (squares), S3P1 (circles), S3P3 (triangles), (c) different hydrogels at 37°C, S3 (squares), S3P1 (circles), S3P3 (triangles).

reached around 46.1% and 32.1% for S3P1 and S3P5, respectively. The slow release after the initial burst release was due to the specific designing. The special domain consisted of linear PAAm and clay platelets may entrap the residual BSA and hence retard BSA release at a longer period.

Release at 37°C

One of the most attractive features of temperature sensitive S-P gels is the auto-adjustable function to external temperature changes. It is necessary to examine the BSA release data from the S-P gels at another temperature (above LCST), such as the body temperature (37°C). Figure 8(c) presents the cumulative amounts of BSA released at 37°C. The release patterns at 37°C were similar to those at 20°C, but the amounts of the cumulative release at corresponding time periods were different. For instance, at 37°C, 12 h initial burst cumulative release % was 8.6% and 4.6% for S3P1 and S3P5, respectively. The burst cumulative release resulted from the collapsing of rounding PNIPAAm network at 37°C and some BSA was extruded during the collapsing process. Then, due to the fact that the special domain consisted of linear PAAm and clay platelets may entrap the residual BSA in the collapsed matrix and hence retard BSA release at a longer period. At the end of the 30th day, the cumulative release of BSA reached around 29.4% and 23.3% for S3P1 and S3P5, respectively. As mentioned in the introduction part, the prolonged sustained release feature may provide a continuous delivery of the drug and prevent the problems of cyclic variations in the drug concentrations in blood with time and offer a maximum pharmacological efficiency at a minimum drug dose.[29,31] These S-P gels did provide a prolonged sustained drug release with the auto-adjustable function to external temperature changes.

CONCLUSIONS

Fabrication and characterization of a novel nanocomposites hydrogels, S-P gels, used as DDS was described in this study. All the S-P gels have a LCST at around 30°C and with increasing the linear PAAm content, LCST of these gels decreased from 32.8°C to 27.9°C because of the hydrophobic interactions between linear PAAm and isopropyl groups of PNIPAAm. The S-P hydrogel had a higher swelling ratio and swelling rate and a more complicated deswelling behavior undergoing: deswelling, swelling, and deswelling. SEM observations revealed that all the S-P gels have uniform, porous morphology, similar to that of PNIPAAm/clay hydrogels. On the other hand, although the compression

properties of the S-P hydrogels decreased by incorporating linear PAAm into the network of PNIPAAm/clay, they still showed high compression stress and excellent reversibility. In addition, these S-P gels remained smart properties. BSA, preloaded into the S-P gels, was released to examine the release behavior at 20°C and 37°C, respectively. The primary release data exhibited a prolonged release of BSA with the auto-adjustable function to external temperature changes. We are planning to investigate systematically the release behavior of other hydrophilic drug model in the PNIPAAm/clay/PAAm hydrogel in our future research.

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