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Synthesis and stimuli-responsive properties of Polyacrylic acid and Polyacrylamide Trapped with Polysodium-p-styrenesulfonate semi-IPN hydrogels

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Abstract: A series of Polyacrylic acid (PAA)/Poly (Sodium-p-styrenesulfonate) (PSS) and Polyacrylamide (PAAm)/PSS semi-IPN hydrogel with different contents of PSS were prepared. The swelling behaviour of PAA hydrogel in alkaline environment was improved while the swelling ratio of PAAm hydrogel was decreased after PSS was added. With the increase of ionic strength in solution, the swelling ratios of PAA/PSS and PAAm/PSS showed a decreasing trend. Moreover the swelling ratio of PAAm/PSS decreased more quickly than that of PAA/PSS. The swelling speed of PAA and PAAm both decreased after adding PSS and a more rapid responsive speed was found in the former system. The experiment of *in vitro* drug release showed that the drug release speed from PAAM/PSS semi-IPN hydrogel was slower than that from PAA/PSS semi-IPN hydrogel. These results suggested that the polymer composition and the trapped polyelectrolyte made a great influence on the drug release behavior.

Keywords: Polyacrylic acid/Poly (sodium-p-styrenesulfonate), Polyacrylamide/Poly (sodium-p-styrenesulfonate), hydrogel, swelling

Introduction

Hydrogels charged with ionic hydrophilic groups are capable of imbibing large amount of water or biological fluids. They are soft and gentle stimuli-responsive materials that are called “intelligent” polymers. In recent years, the study of swelling property of hydrogels has been expanded rapidly and numerous applications have emerged, including controlled drug release, chemo-mechanical actuator and immobilized enzyme reactor, solute recovery and environment-sensitive membranes [1-7]. All of these functions are based on the response of the hydrogels’ volume change, especially the discontinuous volume phase transition, in response to infinitesimal variations in the surrounding medium. The macroscopic volume change reflects the conformation transition in the network chains of the gel from expanded state to a collapsed state, which can be induced by changing the composition or pH value of the solution or temperature as well as even by applying an electric field or mechanical force and by introducing charged or uncharged linear polymer into the gel system [8-13]. Charged groups attached to the network will play an essential role in this transition [14].

On the other hand, Polyelectrolyte contains many electric charges and could be used in a multitude of traditional applications, such as wet and dry strength additives,

flocculating or dispersing agents, and surfactants. More recent applications include the use of multilayer polyelectrolyte membrane to prepare core-shell particles on hollow capsules for controlled drug delivery. To enhance the hydrogel's responsive property, polyelectrolyte has been used to trap in hydrogel and some work has been done by Y. Tao and Shiga [15, 16]. PSS is one kind of polyelectrolyte containing much charge and the chain is rather rigid. In this paper, we added PSS to the PAA and PAAm and the semi-IPN hydrogel with different content of PSS were prepared. The responsive properties of the two kinds of semi-IPN hydrogel were studied. Silk peptide power (SP) was served as an ideal protein that is often used in cosmetics and had good solubility, excellent moisture absorption and retention. SP could inhibit the formation of melanochrome notably and protect the hair well. On the other hand, SP were generally known as the essential protein for maintaining and improving the health and function of the liver. The trapping of the two kinds of semi-IPN hydrogels with SP and the relevant release behaviour was investigated.

Results and discussions

PAA/PSS and PAAm/PSS pH-responsibility

Fig.1 shows the $Q_{PAA/PSS}$ (the Q value of the PAA/PSS samples) as a function of pH from 1 to 14. As pH increased from 1.0 to 3.0, the $Q_{PAA/PSS}$ did not change much and were equal to about 20 while for pH from 3.0 to 8.0, the $Q_{PAA/PSS}$ increased a little and reached ca. 50. With the further rising of pH from 8.0 to 9.0, the $Q_{PAA/PSS}$ reached a maximum and then gradually decreased to a very low level at pH = 14. Compared to all PAA/PSS samples, the maximum Q of PAA hydrogels trapped with PSS was high. The maximum Q of sample 2 (with 0.05g PSS added in 5mL PAA) was 544, and that of pure PAA hydrogel was only 388. Fig. 2 shows the $Q_{PAA/PSS}$ as a function of pH from 1 to 14 with different contents of PSS. As pH increased from 1 to 10, the Q_{PAAm} (the Q of pure PAAm sample) didn not change much. However, with pH 10 ~ 11, the Q value increased from 28 to 107 and then reached a maximum at pH 11.

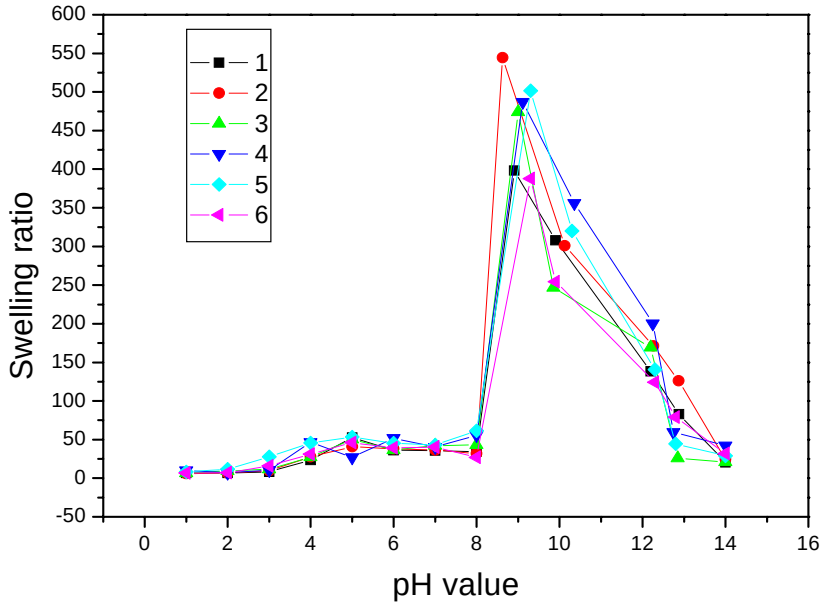

Fig. 1. Q of the PAA/PSS samples as a function of pH.

At pH 14, the Q value gradually decreased to a lower level. Compared with the Q_{PAAm}, the Q of other samples trapped with PSS had the same changing trend with pH. But the maximum Q values of other samples trapped with PSS were obviously lower than that of the pure sample and were only about 70. And the pH value corresponding to the maximum Q values of other samples were higher than that of the pure sample.

The pKa of PAA was equal to 4.75. When pH<3, carboxyl groups in the network chains mainly existed as non-ionic form —COOH [10], hence the electrostatic repulsion between charged groups on the network chains was small and the Q of all samples was not increasing. As pH raised from 3 to 8, a lot of carboxyl groups in the network chains began to change into ionic form and the concentration of $—COO^-$ associated with the network chains increased too. The electrostatic repulsion between charged groups on the network raised gradually and thereby Q increased. When pH=8–9, the concentration of $—COO^-$ reached the maximum and the electrostatic repulsion increased to maximum accordingly. So the Q of all samples increased quickly and reached the maximum. When PSS is added, the electrostatic charges of network increased and hence the Q value. However, with the pH increasing to 14, the concentration of $—COO^-$ was not rising and the ions outside hydrogel flew into the network which intensively enhanced the ionic shielding effect. When the ionic shielding effect prevailed, the Q value decreased.

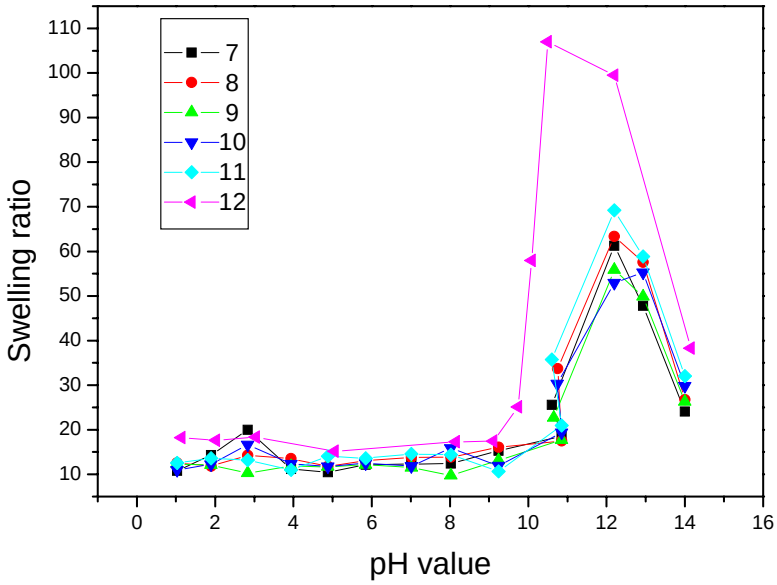

Fig. 2. Q of the PAAm/PSS samples as a function of pH.

When pH<10, PAAm hydrogel mainly existed as acrylamide groups which could not ionize, so the Q_{PAAm} was low. With the growing of pH value, partially the acrylamide groups were hydrolyzed and partially acrylamide were converted to acrylic acid groups. The pKa of PAA was equal to 4.75, so the concentration of $—COO^-$ in PAAm hydrogel network was low. Because of the ionic interaction in the PAAm network, the the Q_{PAAm} grew quickly. With further pH enhancement, the increasing ionic intensity of solution would shield most of the fixed charges, which caused the Q value to fall down.

Compared with $Q_{PAA/PSS}$, the Q value of PAAm/PSS hydrogel was small, because the concentration of —COO^- in PAAm/PSS hydrogel network was less than that in PAA/PSS hydrogel network. With PSS added, the Q of PAAm/PSS hydrogel changed less with pH, which could be explained as follows.

First, compared with PAA hydrogel, there was less —COO^- in the PAAm hydrogel network and the electrostatic repulsion between charged groups of PAAm network was weak. As PSS was added into the PAAm network, the increased electrostatic repulsion between charged groups was weak too. The entangled interaction between the polymer networks would increase dramatically. That is to say, adding little ions in the PAAm hydrogel network would make the Q decrease quickly. With the addition of PSS in PAAm hydrogel, the Q of hydrogel network was not changing much. Adding the polyelectrolyte to the non-ionic hydorgel, the entangled interaction would play an important role in Q.

Second, the volume change of PAAm trapped with PSS shifted to the higher pH value than in the case of pure PAAm , as shown in Fig. 2. This phenomenon proved that the ion shielding effect of PSS was a main factor in decreasing the Q of hydrogel network. The reason of hydrogel volume change was due to the electrostatic charges — the concentration of —COO^- in the hydrogel network. In the same pH, the concentrations of the pure PAAm and the PAAm trapped with PSS were same, so the removal of the volume change of PAAm trapped with PSS comes from the factor of ion strength interaction. When the pure PAAm hydrogel began to have volume change, the PAAm hydrogel trapped with PSS could not do that because of the weak ion strength interaction of PSS. When the pH increased, the networks had much more —COO^- and the electrostatic repulsion would enhance to conquer the negative attribution of ion strength interaction to Q. With further pH increasing, the ion strength would increase too, which caused the decrease in Q.

PAA/PSS and PAAm/PSS slat-responsibility

Tab. 1 shows the Q of samples in the solution of NaCl. The Q of sample 5 was significantly less than that of other samples. Sample 5 contained much PSS in the network of the hydrogel and the entangled interaction was so strong that the network was not easy to swell as other samples. We could see that the swell ratios of all samples were very high (about 200) at low salt concentration and decreased quickly with increasing salt concentration. When the salt concentration increases to 1 M, the swelling ratio of all samples converged to about 20.

Tab. 1. Q_{max} of PAA samples with different ionic strength.

	Q_{max} of PAA with different PSS content (g)					
Ionic strength (mol/L)	Sample6	Sample1	Sample2	Sample3	Sample4	Sample5
0	160.00	142.00	156.00	151.00	138.00	72.00
5.00E-04	207.44	144.64	201.48	155.13	146.54	147.96
0.005	134.44	69.14	115.41	111.33	84.76	94.59
0.05	59.81	31.02	34.56	46.42	42.73	40.64
0.5	46.00	19.62	34.13	23.20	42.90	21.33
1	16.44	13.54	15.66	13.29	23.37	15.12

These phenomena could be attributed to the electrostatic repulsion between charged groups on the network-chains and to the concentration difference of mobile ions inside the hydrogel and the external solution governed by Donnan potential. When the salt concentration was low, the exchange of H^+ from PAA and Na^+ outside hydrogel accelerated the ionization of PAA. The electrostatic repulsions between the networks increased quickly. At the same time, the mobile ions outsides hydrogel afflux into the hydrogel, which caused an electrostatic shielding to certain strength. That made the swelling force to decrease. As the salt concentration increased, the ionic shielding would prevail and make the swelling ratio decrease quickly. So, the presence of PSS had no great influence on the Q values at different salt concentrations.

Tab. 2. Qmax of PAAm samples under the influence of ionic strength.

	Q_{max} of PAAM with different PSS content (g)					
Ionic strength (mol/L)	Sample12	Sample7	Sample8	Sample9	Sample10	Sample11
0	110.0	14.13	14.94	13.85	13.80	16.07
5.00E-04	16.23	15.64	15.89	16.71	15.11	15.66
0.005	15.57	14.41	14.91	14.95	13.98	14.72
0.05	15.62	14.81	14.83	15.97	14.36	14.93
0.5	17.65	16.61	16.21	16.33	15.36	15.79
1	18.75	16.49	17.38	14.73	15.82	16.10

Tab. 2 shows the Q of PAAm/PSS samples in the solution of NaCl. We could see that only when pure PAAm was in pure water, the Q of the sample is above 100. The Q of other samples, whether the samples were trapped with PSS or put into the salt solution, were only about 15. The same as PAA/PSS hydrogel, PAAm/PSS hydrogel in solution exchanged the H^+ from PAAm and Na^+ outside hydrogel. However, little acrylamide groups were converted to acrylic acid groups in the neutral solution and only small H^+ ions were exchanged. So the electrostatic repulsion interaction did not have much influence on Q. On the contrary, the polymer osmotic interaction could not be ignored. Otherwise, the PAAm hydrogel added charge inorganic salt solution would make the chains shrink into loop and the viscosity of the solution would decrease. All PAAm hydrogel trapped with PSS had low Q, because the entangled interaction between PSS and PAAm would slow down the swelling of hydrogels and the PSS could be ionised into a lot of ions that could be compared to the case of NaCl solution.

PAA/PSS and PAAm/PSS hydrogels swelling kinetics

The change in q of PAA/PSS samples upon time is displayed in Fig. 3. The half time of swelling equilibrium ($t_{1/2}$) of pure PAA hydrogel and PAA hydrogel trapped with PSS were about 30min and 130 min, respectively. This could be explained by the fact that adding the polyelectrolyte with a amount of charges into hydrogel network would cause increase of concentration of polyionic and osmotic pressure, which was beneficial to the water molecule afflux into the hydrogel and in turn increased the swelling speed. On the contrary, with PSS added to hydrogel, the entanglements of hydrogel network increased which would decrease the lattice size of hydrogel network and slow down the swelling speed. In general, the influence of the entanglements to the hydrogel network overwhelmed the other effects and the welling speed would decrease after adding PSS.

Fig. 4 showed the q of PAAm/PSS hydrogel changing upon time. The $t_{1/2}$ of pure PAAm hydrogel and PAAm hydrogel trapped with PSS was about 20 min and 35 min, respectively. In the PAAm series hydrogels, the Q of PAA trapped with PSS was more than that of pure PAA. The reason was the same as the PAA/PSS hydrogels, which we have mentioned above. Because the PAA series hydrogels had bigger Q, the q of PAA series was small compared with PAAm series. The physical crosslinking point came into being after PSS was added into PAA or PAAm hydrogel network. The network of hydrogel became small, so the q of hydrogels trapped with PSS decreased.

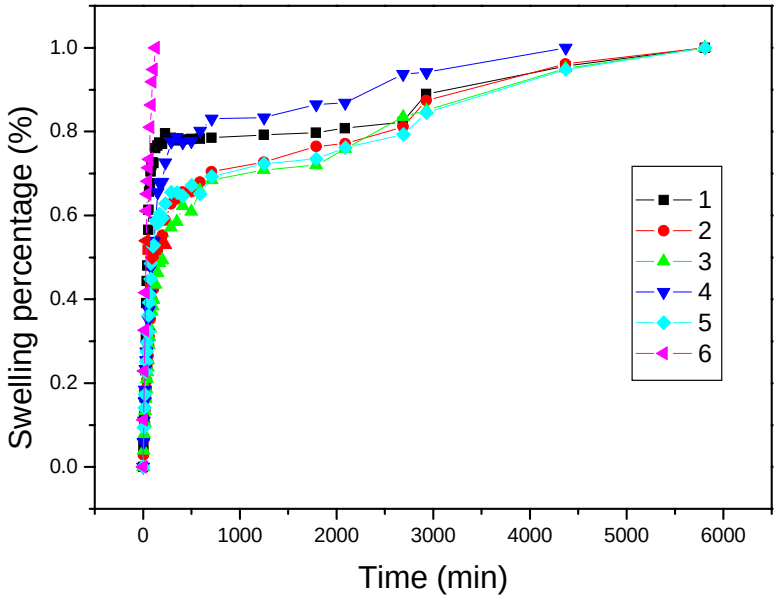

Fig. 3. The q of PAA/PSS samples as a function of time.

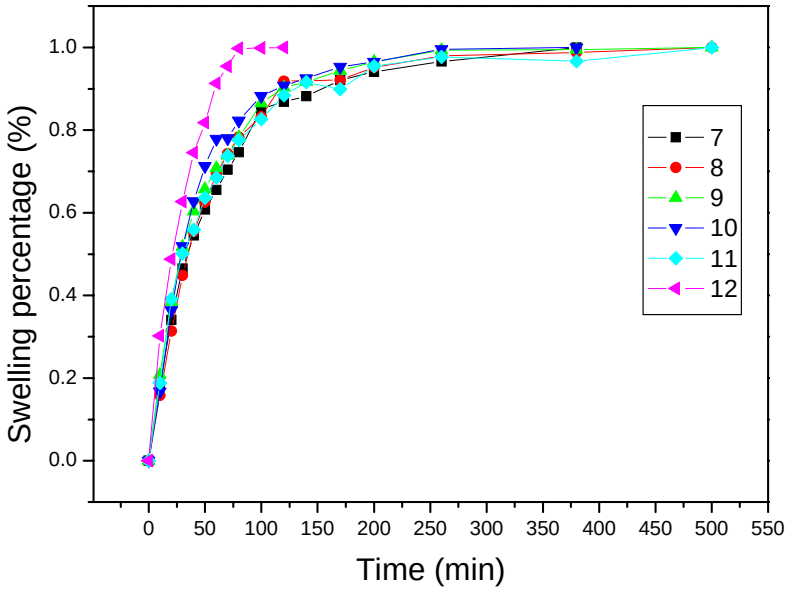

Fig. 4. The q of PAA/PSS samples as a function of time.

SP release

In order to investigate the feasibility, SP, used as a model peptide, was loaded into semi-IPN hydrogels that acted as hydrophilic drug carriers. Fig. 5 shows the release profiles of SP from sample 3 in various pH values and sample 6 at pH 7.1 at various time intervals at 37.1 ^{0}C. An initial burst in release followed by a slow release of SP occurred in pH values of 4.5 and 7.4. Moreover, these semi-IPN hydrogels provided a continuous release of the entrapped peptide for up to 10 days. On the other hand, at pH of 12, the SP release was very fast and about 90% of the loaded SP was released from semi-IPN hydrogels within 24 h. Compared with sample 3 at pH 7.1, SP release in sample 6 was more quick. The hydrophilicity of the sample 3 was strengthened by the trapped PSS. The interaction between SP and hydrogel was enhanced and release became slower. It was obvious that the release of the SP depended on the pH values of the release medium.

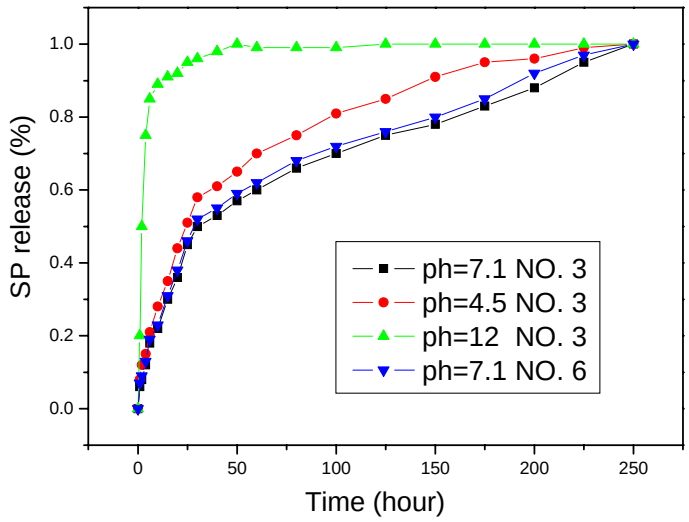

Fig. 5. Release profiles of SP from sample 3 and sample 6 at various pH values at 37.1^{0}C.

The release profile at pH of 7.4 had the slowest release speed. The semi-IPN hydrogels sustained slow release at pH 4.5. This could be explained by the fact that the release of the SP depended greatly on the swelling of the nanoparticles. At a pH of 4.5 and 7.4, there was very limited swelling and the SP entrapped in the semi-IPN hydrogels could not be released easily. However, at a pH of 12, the semi-IPN hydrogels were swollen to a great extent, resulting in a fairly fast release of SP compared with the nanoparticles at pH of 4.5 and 7.4.

Fig. 6 shows the release profiles of SP from sample 9 at various pH values and sample 12 at pH 7.1 at various time intervals at temperature 37.1^{0}C. A continuous release of the entrapped peptide could maintain 15 days. The release speed depended on pH values too, same as Fig. 5. Compared to the release speed of sample 3, the release speed of sample 9 was slow.On the other hand, SP that was composed of some –$CONH_2$ groups had stronger interaction with sample 9 by H-bonds than with sample 3 that ionize in the water. On Comparing with sample 9 at pH 7.1, SP release in the sample 12 was quick too. The reason was the same as what had been explained in

PAA hydrogel. These results were also in good agreement with the effect of the pH values on the Q value samples as mentioned above. We could make a conclusion that the drug release speed of the hydrogels could be adjusted by changing the pH values and the polymer composition.

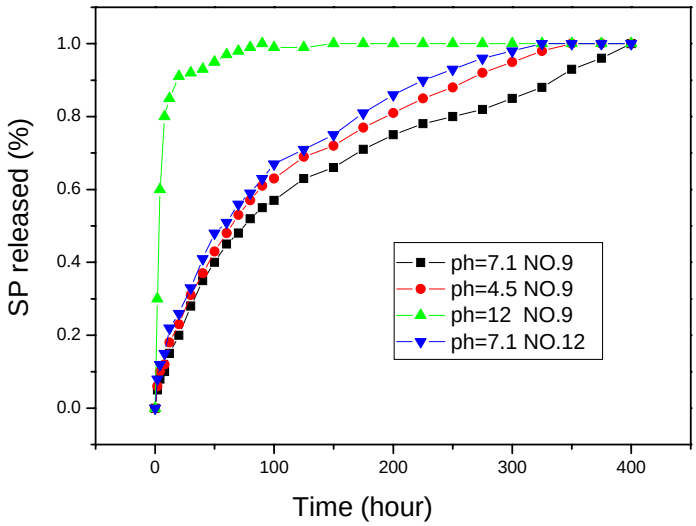

Fig. 6. Release profiles of SP from sample 9 and sample 12 at various pH values at 37.1^{0}C

Conclusions

In the pH sensitive response experiments, the maximum Q of samples increased with the PSS added, because the electrostatic repulsive interaction played an important role in the attribution to Q. Entangled interaction was accompanied with the deformation of polymer network as a result of swelling. The experiments of swelling kinetics showed that the trapped PSS chains would enhance the entangle interaction of hydrogel network and slow down the q changes. In the ionic strength sensitive experiments, the ionic shielding effect would prevail that plays a negative attribution to Q. The experiments of swelling kinetics show that adding the PSS will enhance entangle interaction of hydrogel network and slow down the change of the q. The preliminary results of model drug (silk peptide) loading and release experiments indicate that this system seems to be a very promising vehicle for the administration of hydrophilic drugs peptides. Furthermore, due to their pH-sensitive behaviour, these semi-IPN hydrogel are appropriate carriers for the delivery of drugs in the gastric cavity.

Experimental

Materials

AAm was crystallized from acetone/ethanol mixture (70/30 by volume) below 30 ^{0}C. PSS supplied by Acros Organics Co. Ltd. (New Jersey, USA) had an average molecular weight of 70,000. AA monomer was purified by distillation at 40 ^{0}C /26 mmHg. Silk peptide powder (SP) was supplied by Huzhou Xintiansi Bio-tech Co, Ltd as

a model drug. N, N'-Methylenebisacrylamide (BAAM) used as cross linking agent, the redox pair of N, N, N', N'-tetramethylethylenediamine (TEMED) and ammonium persulfate (APS) as initiator and other chemicals, all are of C. P. grade, were purchased from the local market. Deionised water was used for all experiments.

Preparation of PAA/PSS and PAAm/PSS hydrogels

PSS and AA were dissolved in deionised water along with BAAM and TEMED. APS was then added to the solution to initiate the polymerization. The feed composition and designation of the PAA/PSS blending solutions are listed in Tab.3.

Tab. 3. Preparation and designation of PAA/PSS hydrogels.

Sample No.	1	2	3	4	5	6
Water ml	40	40	40	40	40	40
AA ml	5	5	5	5	5	5
BAAM g	0.130	0.130	0.130	0.130	0.130	0.130
TEMED ml	0.3	0.3	0.3	0.3	0.3	0.3
APS (g/10ml)	0.4	0.4	0.4	0.4	0.4	0.4
PSS g	0.01	0.05	0.1	0.5	1	0
PSS after rinsing (g)	0.0095	0.045	0.092	0.43	0.82	0

The polymerization was maintained at 34-35 ^{0}C for 12 h. After gelation, the samples were thoroughly rinsed to wash out residual monomers and initiator and cut into uniform small pieces. Last, the samples were vacuum dried. After washing, the rinsing solution was measured through ultraviolet spectrometry with the absorbance band at 202 nm. The concentration of PSS was determined by a calibration curve. Then we calculated the content of PSS retained in hydrogel. The results are shown in Fig.1. PAAm/PSS hydrogel was prepared in the same way. The feed composition and designation of the PAAm/PSS blending solution are listed in Table 4.

Tab. 4. Preparation and designation of PAAm/PSS hydrogels.

Sample No.	7	8	9	10	11	12
Water ml	40	40	40	40	40	40
AAm g	5	5	5	5	5	5
BAAM g	0.130	0.130	0.130	0.130	0.130	0.130
TEMED ml	0.3	0.3	0.3	0.3	0.3	0.3
APS (g/10ml)	0.4	0.4	0.4	0.4	0.4	0.4
PSS g	0.01	0.05	0.1	0.5	1	0
PSS after rinsing g	0.0097	0.046	0.093	0.45	0.85	0

pH and ionic strength stimuli-responsive measurement and swelling kinetics test

The dried hydrogel pieces were placed in solutions of pH values from 1 to 14, respectively (The pH values of solution were adjusted by NaOH and HCl). After swelling for 5 days, the samples were taken out of the solutions, blotted out the surface

water and then weighed. The swelling behaviour of the hydrogel was expressed by the weight swelling ratio (Q):

$Q = w_2/w_1$ (1)

where w_1 and w_2 are the weights of the initial dry hydrogel and the swollen hydrogel, respectively. The equilibrium Q value was obtained when the weight of the swollen hydrogel reached constant value.

The dried hydrogel pieces were placed in deionised water (pH=7) with NaCl concentrations of 0 mol/L, 0.0005 mol/L, 0.005 mol/L, 0.05 mol/L, 0.5 mol/L and 1 mol/L, respectively. After swelling for 5 days, the samples were taken out of the solutions and weighed after blotting out the surface water.

The dried hydrogel pieces were placed in deionised water (pH=7), and then taken out to blot the surface water and weighed (w_t) every 10 minutes. The swelling percentage q (%) was calculated as follows:

$q\ (\%) = (w_t - w_1)/ (w_b - w_1) \times 100\%$ (2)

where w_b is the equilibrium-swollen weight. The temperature of all experiments is hold at 25 .

Preparation of drug-loaded semi-IPN hydrogels and In Vitro Drug Release measurement

Using SP as a model drug, the drug-loaded semi-IPN hydrogels were prepared by dissolving 450 mg of SP in mother solutions of sample 3, 6, 9 and 12, respectively. After gelation, samples were incubated for 24 h to make sure the SP had been loaded into the semi-IPN hydrogels. 5 g semi-IPN hydrogels loaded with SP were placed into 500 ml of water medium with various pH values. The entire systems were kept at 37.1 ^{0}C with continuous magnetic stirring. After a predetermined period, 5 ml of the medium was removed and the amount of SP was analyzed by fluorescence measurement, using a JASCO FP-6500 spectrometer with excitation and emission wavelength being 273 nm and 302 nm. The released SP was determined by a calibration curve. In order to maintain the original volume, each time, 5 ml of the medium was replaced with fresh water after every predetermined period. The SP release experiments were repeated three times.

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