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Synthesis, Characterization, and Drug Release Behaviour of Novel Soy Protein/Poly(acrylic acid) IPN Hydrogels

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ABSTRACT

A series of novel interpenetrating polymer network (IPN) hydrogels based on soy protein (SP) and poly(acrylic acid) (PAA) were prepared with glutaraldehyde and *N,N'*-methylenebisacrylamide (BIS) as the cross-linking agents. The structure and properties of the IPN hydrogels were characterized by FTIR, SEM, and DSC. The effects of pH and SP and BIS contents on the behaviour and release mechanism of the model drug bovine serum albumin (BSA) were also investigated in detail. The FTIR data indicated that the absorption of BSA into the IPN hydrogels is purely physical process. The SEM showed that changing the content of SP or BIS can influence the pore size and pore wall thickness of the hydrogels. The DSC data signify that all the hydrogels had good compatibility and miscibility, as well. It was also found that the release profiles of BSA strongly are dependent on the value of pH. The release percentage of BSA decreased with increasing the contents of SP or BIS. The BSA release profile followed Fickian diffusion pattern at pH below the pKa of PAA and the non-Fickian diffusion at pH above the pKa of PAA. The results showed that the IPN hydrogels are suitable candidates for colon drug delivery.

Key Words:

soy protein;
acrylic acid;
drug delivery systems;
hydrogels;
colon.

INTRODUCTION

The intelligent hydrogels, which are three-dimensional hydrophilic polymer networks, can imbibe and hold large amount of water but do not dissolve in the aqueous solution. They can undergo a volume change in response to small variations in external stimuli, such as pH [1-5], temperature [6-8], ionic strength [9,10], biomolecules [11], light and electric field [12,13]. These environmentally sensitive properties have led to the extensive use of intelligent hydrogels, especially in the medical and pharmaceutical fields [14].

With the development of new protein and peptide drugs, it is important to consider how to deliver the drugs to the appropriate site of the body and make them available for use. Therefore, the design of intelligent hydrogels for controlled drug delivery has been extensively investigated [15-17]. Recently, colon-targeted drug delivery systems based on the intelligent hydrogels have attracted more and more attention. Colon is considered as a suitable site for both conventional and labile drugs [18], and for treating special

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diseases such as ulcerative colitis, Crohn's diseases, inflammatory bowel diseases, infectious diseases, and colon cancer [19]. Poly(acrylic acid) (PAA) hydrogel and its composites, which are the typical pH-sensitive synthetic hydrogel with carboxylic acid groups, are highly dependent on the pH of the surrounding medium. Due to the highly pH-sensitivity to the environment, PAA hydrogels are the suitable candidates for the site-specific drug delivery to specific regions of the gastrointestinal tract [20], especially for the colon site-specific delivery of protein and peptide drugs [21,22].

In recent years, great interest has been shown in the use of natural proteins and their composites as the carriers for drug delivery [23,24]. Soy protein (SP) which is a well-known natural polymer and abundantly available from renewable resources and agricultural processing by-products such as oil processing, can endow the soy protein-based composites with structural and mechanical properties for the relative rigidity of polypeptide backbone [25]. Soy protein has good biodegradability and biocompatibility which can make its complexes more similar to tissue constituents. As a result, soy protein-based hydrogels may be regarded as ideal biomaterials for using as drug carriers. However, to the best of our knowledge, the pH-sensitive soy protein/poly(acrylic acid) interpenetrating polymer network (IPN) hydrogels have not been investigated for controlled drug delivery.

Soy protein has a variety of functional groups on its polypeptide primary structure, thus offering the ability to be modified with other polymers. However, the soy protein-based materials are brittle and have poor water holding capacity. These drawbacks limit its applications. To overcome the limitations, blending or grafting with another polymer may be an effective method [26-31]. Particularly, soy protein blending with environmentally sensitive polymers like poly(acrylic acid) through the IPN technology can endow the composites with intelligent features and more biocompatibility, which may be of new potential applications in pharmaceutical field. Therefore, the purpose of this work was accomplished by synthesizing the soy protein/poly(acrylic acid) IPN hydrogels to investigate the possibility of the hydrogels for controlled drug release. The structure and properties of the IPN hydrogels were analyzed by FTIR, SEM, and DSC. The bovine serum albumin (BSA) which was chosen as the model drug was loaded into the IPN hydrogels and the BSA release behaviour was investigated in detail.

EXPERIMENTAL

Materials

Soy protein isolate from Hubei Dupont Yunmeng Protein Ltd., China, was further purified by alkali extraction and acid precipitation. Acrylic acid (AA, A.R. grade) and ammonium persulphate (APS, A.R. grade) were obtained from Tianjin Yongda Chemical Reagent Ltd., China. The former was purified by vacuum distillation. *N,N'*-Methylenebisacrylamide (BIS, A.R. grade) and glutaraldehyde (GA, 25% aqueous solution, A.R. grade) were supplied by Tianjin Kermel Chemical Reagent Ltd., China. Tetramethylethylene-diamine (TEMED, A.R. grade) was purchased from Shanghai Qianjin Chemical Reagent Ltd., China. Bovine serum albumin (BSA, B.R. grade) was provided by Shanghai Sinopharm Chemical Reagent Ltd., China. Other reagents were A.R. grade.

Preparation of IPN Hydrogels

Definite amounts of AA were completely neutralized by using 3.0 M NaOH solution. The pH of each mixture was adjusted to 11 by 0.1 M NaOH solution, and the volume of each mixture was adjusted to 15 mL by adding deionized water. While continuously stirring and bubbling by nitrogen, the SP was added into each mixture to dissolve, and then the BIS, APS, TEMED, GA were added to the mixtures. Finally, the mixtures were immediately injected into PVC tubes (6 mm diameter) to polymerize at 60°C for 24 h. The hydrogels obtained were cut into pieces of 3 mm in length and immersed in deionized water for three days to remove the residual unreacted reagents. The deionized water was refreshed every 4 h during this period. The swollen hydrogels were dried at room temperature for three days and further dried in a vacuum oven for five days. The feed compositions and sample codes are shown in Table 1. The reaction mechanism is illustrated in Scheme I.

Table 1. Feed compositions and sample codes of IPN hydrogels.

Sample codes	SP (g)	GA (mL)	AA (g)	BIS (g)	APS (g)	TEMED (μL)
AS0	0.0	0.0	2.0	0.04	0.02	20
AS1	0.2	0.1	2.0	0.04	0.02	20
AS2	0.4	0.2	2.0	0.04	0.02	20
AS3	0.6	0.3	2.0	0.04	0.02	20
AS4	0.4	0.2	2.0	0.03	0.02	20
AS5	0.4	0.2	2.0	0.05	0.02	20

IR Spectroscopy

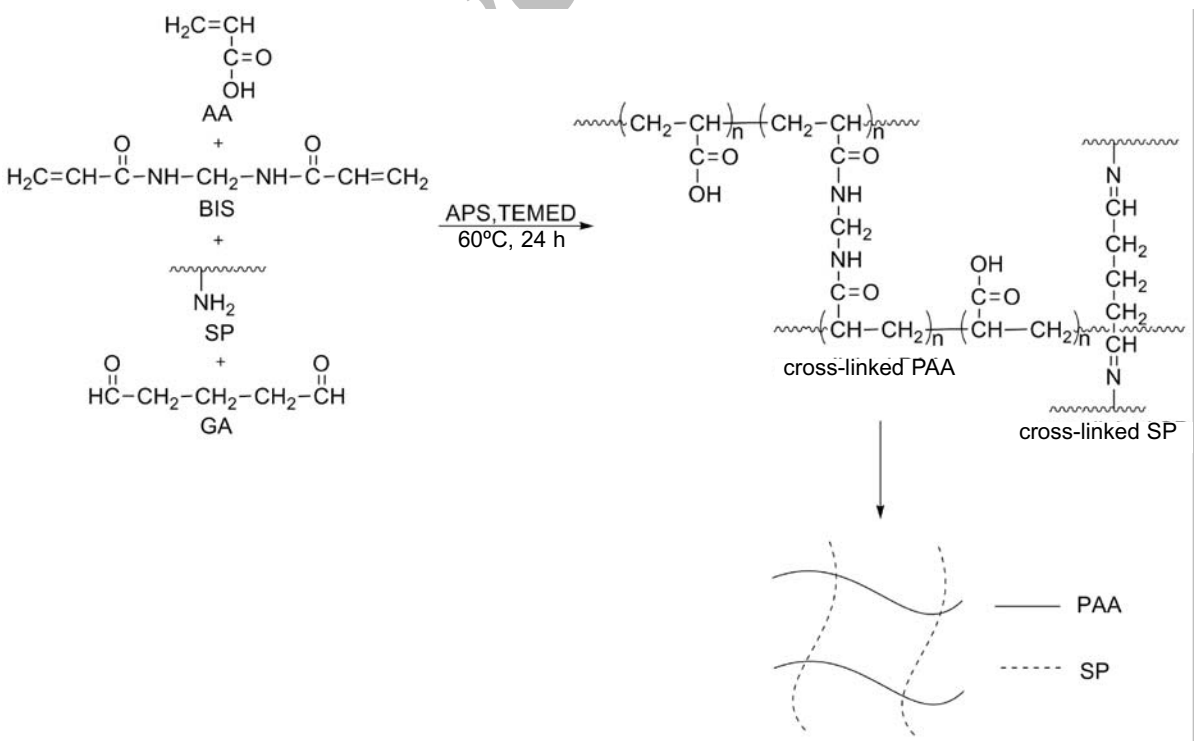
Fourier transform infrared (FTIR) spectroscopy (Equinox 55, Bruker, Germany) was used to record the IR spectra of the BSA, BSA-unloaded and BSA-loaded hydrogels.

Morphology of IPN Hydrogels

The swollen hydrogels were reached equilibrium in deionized water and then they were freeze-dried for 24 h in a freeze drier (LGJ-18, SHKY, China). The freeze-dried gels were coated with gold. The surface morphology of the coated gels was measured using the ESEM (Quanta 400F, FEI, Netherlands) with an acceleration voltage of 20 kV.

Glass Transition Temperature of IPN Hydrogels

The glass transition temperatures (T_g) of dried IPN hydrogels were investigated by differential scanning calorimetry (DSC 204, Netzsch, Germany). All samples were primarily heated from 25ºC to 140ºC at 20°C/min heating rate and then were cooled to 25°C. Second, the samples were reheated to 180°C at 10°C/min. The T_g of the dried hydrogels were determined from the second cycle where the midpoint of



Scheme I. Synthesis of the SP/PAA IPN hydrogels.

the inflection was taken as the T_g.

Drug Loading and In Vitro Release

The model drug (BSA) was loaded into the blank hydrogels by being immersed into the BSA aqueous solution (30 mg/mL) for three days at 4°C. The BSA-loaded hydrogels were dried at room temperature for three days and further dried in a vacuum oven for three days at 40°C to a constant weight.

The dried BSA-loaded hydrogels were immersed in conical vials containing 20 mL of buffer solution of various pHs. The vials were closed and incubated in a thermostatic shaker (HY60, HCBioTch, China) with a speed of 60 rpm at 37°C. At given time intervals, 3 mL of the solution was taken out to measure the amount of released BSA by UV-vis spectrophotometer (760CRT, Lengguang, China) at 280 nm, and then put back into the same vial. The released concentration was obtained from the calibration curve. The release percentage of the BSA from the loaded hydrogels was calculated by the following equation:

$$Release\ of\ BSA\ (\%) = \frac{W_t}{W} \times 100 \quad (1)$$

Where W_t is cumulative mass of BSA released at time t and W is the initial mass of BSA loaded.

RESULTS AND DISCUSSION

Infrared Spectral Analysis

The FTIR spectra of BSA, AS2, and BSA-loaded AS2 are shown in Figure 1. The spectra clearly exhibit a broad band at 3200-3500 cm^{-1} which is due to hydrogen bonding of O-H stretching from a carboxylic group and N-H stretching from an amide group. Peaks at 2800-3000 cm^{-1} were asymmetrical and symmetrical stretching of C-H. As can be seen from spectra 'a' and 'c', peaks near 1560 and 1410 cm^{-1} may be assigned to asymmetrical and symmetrical stretching of COO^- from carboxylic acid salt, and peak around 1650 cm^{-1} represents stretching vibration of C=O from carboxylic groups. As for spectrum 'b', the amide I and II bands have appeared at 1660 and 1534 cm^{-1}, respectively. In contrast to spectra 'a' and 'b', the spectrum 'c' shows a broad band at

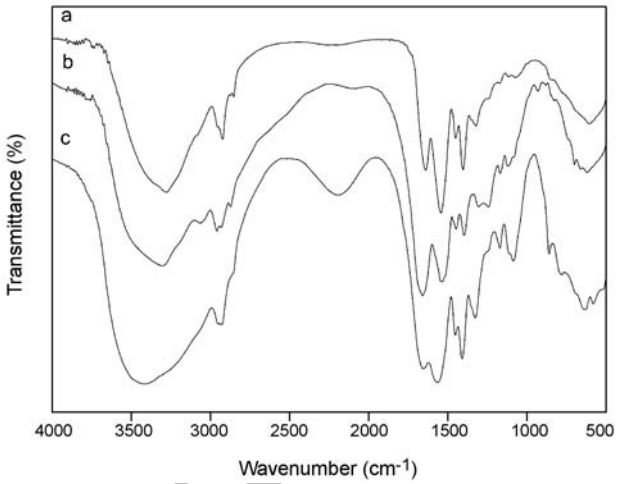


Figure 1. FTIR spectra of: (a) AS2, (b) BSA and (c) BSA-loaded AS2.

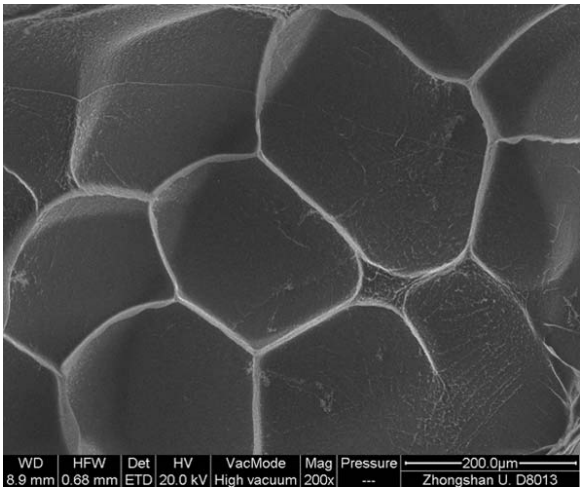
2193 cm^{-1} which may correspond to the presence of C-N from the cross-linker and BSA. All the above IR data give an indication that the absorption of BSA into the IPN polymer matrix has been purely a physical process by hydrogen bonding interactions.

Morphology Analysis

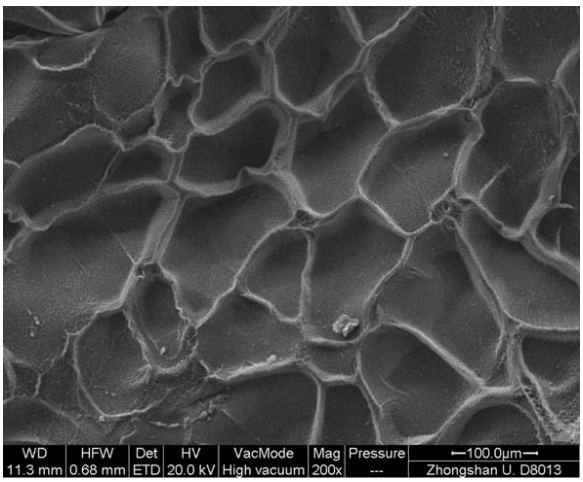
The surface morphology of the freeze-dried gels is shown in Figure 2. It can be seen that all the gels have porous network structure. With the increase of SP content, the pore size of the IPN hydrogels becomes smaller, while the pore wall thickness becomes larger. The similar trends of increasing the cross-linker content can be observed in Figures 2a-2f. This is an indication that changing the content of SP or cross-linker can control the pore size and its wall thickness, which can influence the drug loading and drug release.

Glass Transition Temperature Analysis

The DSC thermograms of the IPN hydrogels are depicted in Figure 3. As it is shown in Figure 3, a single T_g is appeared in all the curves, which suggests that the blend of PAA and SP have good compatibility and miscibility. The T_g of AS0, AS1, AS2, AS3, AS4 and AS5 is 131.0, 133.3, 135.6, 136.8, 132.0 and 137.9°C, respectively. The results show that the T_g has gradually shifted to a high temperature with increasing the content of SP or cross-linker. The value of T_g would be influenced by the



(a)



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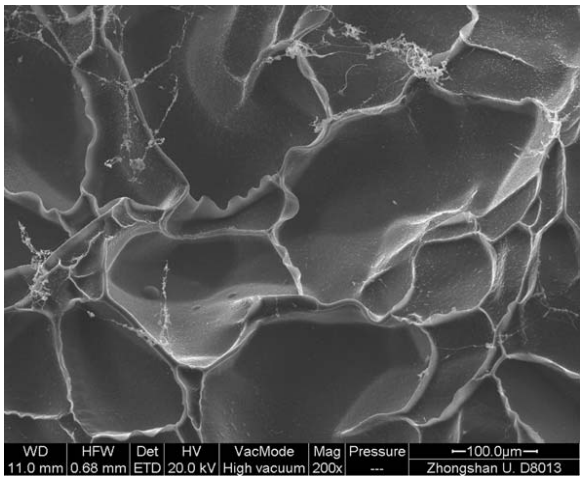
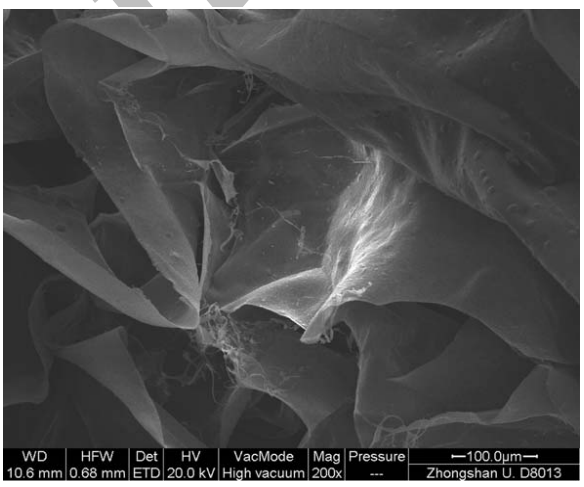
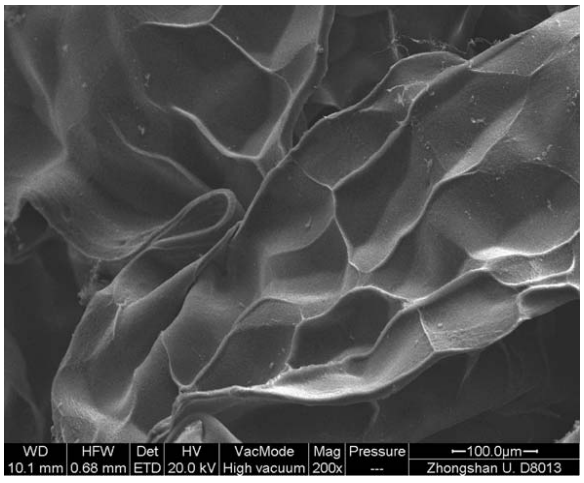


(b)



(e)

(c)



(f)

Figure 2. SEM micrographs of: (a) AS0, (b) AS1, (c) AS2, (d) AS3, (e) AS4, and (f) AS5.

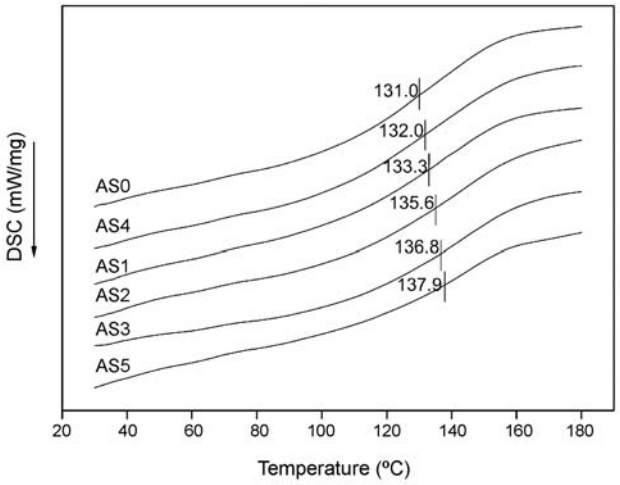


Figure 3. DSC thermograms of the IPN hydrogels.

formation of the hydrogen bonds in the IPN hydrogel [32]. The higher the content of SP or cross-linker, the stronger hydrogen bonds are obtained, which would retard the movement of polymer segment and result into an increased T_g.

Effect of pH on BSA Release

Figure 4 depicts the profiles of dynamic release of BSA from AS2 hydrogel at various pHs at 37°C. As it is observed in Figure 4, the release percentage of BSA is drastically increased with an increase in the external pH which is higher in the buffer medium of pHs 6.0, 7.4, and 9.2 than that in pHs 1.2 and 4.0. This can be explained by the fact that, as the pKa value of PAA

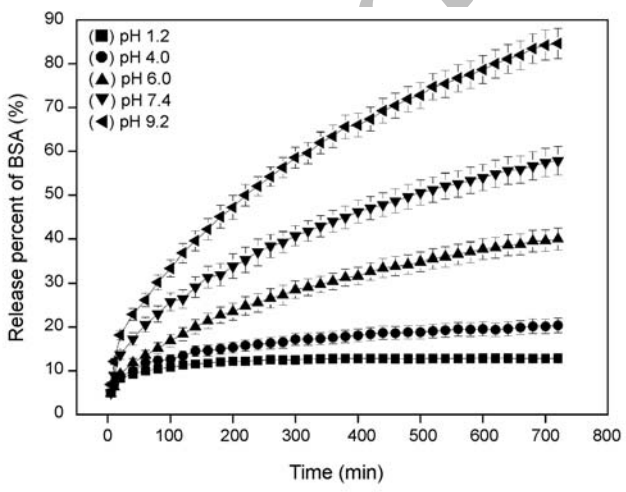


Figure 4. Dynamic release of BSA from AS2 at 37ºC and different pHs.

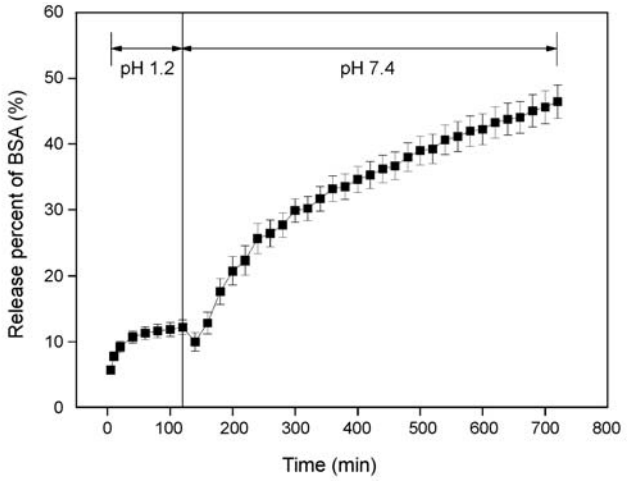


Figure 5. Dynamic release of BSA from AS2 at pH 1.2 and subsequently at pH 7.4.

is known to be 4.8 [33], with pH value below 4.8, PAA acts as carboxylic acid within the IPN network and strong intramolecular and extramolecular hydrogen bondings develop in the polymer matrix. This makes the structure of the hydrogel to be tight, and it results in lower release of BSA at pHs 1.2 and 4.0. However, when the value of pH is above 4.8, the ionization of carboxylic acid groups causes the structure of hydrogel to relax due to mutual repulsion between the similarly charged carboxylic groups within the polymer matrix. Moreover, the ionic osmotic pressure inside the hydrogel increases with an increase of ionized groups. These two factors account for higher release of BSA at higher pH values. It is clearly seen that the release percentage of BSA is higher at pH 7.4 (the pH of colonic fluid), whereas it is at lowest level at pH 1.2 (the pH of gastric fluid). This means that the IPN hydrogels are suitable for colon-targeted drug delivery systems.

In order to simulate the release profile of BSA from stomach to colon, the BSA-loaded AS2 hydrogel is immersed in buffer solution at pH 1.2 and 37°C to release for 2 h and then it is shifted into buffer solution at pH 7.4 and 37°C to release for 10 h. The results, as shown in Figure 5, reveal that the percentage of BSA released at pH 1.2 is very low but increases significantly at pH 7.4. Only about 12% BSA is released within 2 h in simulated gastric fluid (pH 1.2) while, about 48% has been released within 10 h in simulated colonic fluid (pH 7.4). This may

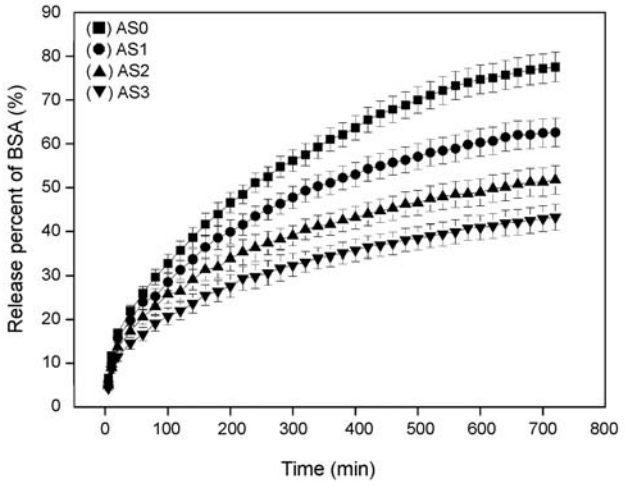


Figure 6. Dynamic release of BSA from AS0, AS1, AS2 and AS3 at pH 7.4 and 37ºC.

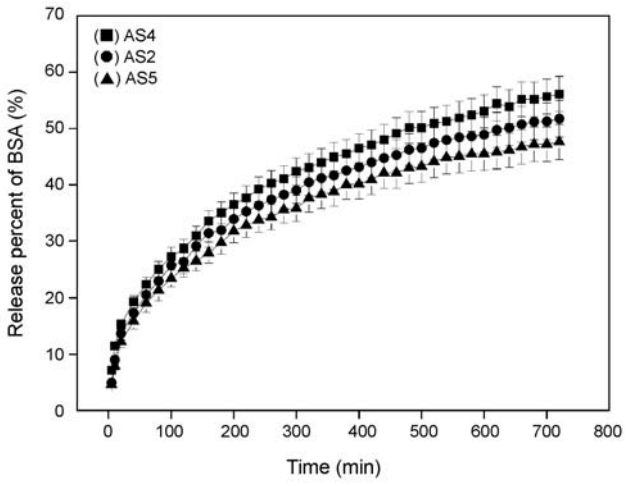


Figure 7. Dynamic release of BSA from AS2, AS4 and AS5 at pH 7.4 and 37ºC.

indicat that the IPN hydrogels can reduce drug leakage in the environment of the stomach and therefore suitable for colon drug delivery.

Effect of SP Content on BSA Release

The effect of SP content on BSA release at pH 7.4 and 37°C are shown in Figure 6. The results demonstrate that, with increasing the amount of SP, the release percentage of BSA is found to be decreased. This may be attributed to the fact that, as the amount of SP increases, the unit content of carboxylic groups fixed in polymer network becomes less and less, which may lead to the electrostatic repulsion effect that would enhance the hydrogel relaxation and expansion to become ever more weaker. In addition, as SP is an amphoteric polyelectrolyte, with an increase in the content of SP, the formation of hydrogen bonds intensifies between SP and PAA, which causes in return the reduction in relaxation of polymer chains. The above phenomena may indicate that the release percentage of BSA can be controlled through modulating the SP content.

Effect of Cross-linker Content on BSA Release

Figure 7 shows the effect of cross-linker contents on the BSA release profile at pH 7.4 and 37°C. It is noticed in Figure 6 that the release percentage of BSA decreases with increasing BIS content. This can be explained on the basis of the fact that, by increasing the amount of BIS, the number of cross-links increases in the polymer network. This would lead to the reduction of voids available within the network chains and the increase of physical entanglements caused by hydrogen bondings between SP and PAA chains. As a result, increasing the amount of BIS can restrain the relaxation of network chains and make the BSA inflexible towards diffusion, which is manifested in decreased BSA release. Therefore, these observations reveal that the release of BSA can be controlled by modulating the amount of BIS.

Release Mechanism of BSA

In order to investigate the release mechanism of BSA from the IPN hydrogels, the release data are analyzed by using eqn (2) for $M_t/M_\infty < 0.6$ as follows [34-36]:

$$M_t / M_\infty = kt^n \quad (2)$$

where M_t is cumulative mass of BSA released at time t, M_∞ is the total mass of BSA released, k is the release constant, and n is the characteristic exponent related to the release mechanism of BSA. For cylinder, when n = 0.45, the release signifies Fickian diffusion mechanism, where the system would be diffusion controlled. When $0.45 < n < 0.89$, the release follows non-Fickian diffusion mechanism where the system are both diffusion and relaxation controlled. While n = 0.89, the mechanism is zero-order release where the system is relaxation controlled. The exponent n can be obtained from the slope of the plot of

$\ln(M_t/M_\infty)$ versus ln t.

The values of n for AS2 at pHs 1.2, 4.0, 6.0, 7.4 and 9.2 are 0.41 (R^2=0.98814), 0.43 (R^2=0.99704), 0.47 (R^2=0.99478), 0.53 (R^2=0.99616) and 0.57 (R^2=0.99662), respectively. And the values of n for AS0, AS1, AS2, AS3, AS4 and AS5 at pH 7.4 are 0.58 (R^2=0.98741), 0.55 (R^2=0.9885), 0.53 (R^2=0.99616), 0.50 (R^2=0.9918), 0.56 (R^2=0.98672) and 0.51 (R^2=0.98563), respectively. These results show that the values of n are increased with an increase in pH.

Moreover, the higher the contents of SP or BIS, the lower is the value of n. According to the data, we can see that the release mechanism of BSA is transferred from Fickian diffusion to non-Fickian diffusion when pH is changed from 1.2 to 9.2. In other words, the release mechanism of BSA at the pH below the pKa of PAA is controlled by diffusion, while above the value of pKa, it is controlled by both diffusion and relaxation. At pH 7.4 (the pH of colonic fluid) the release mechanism of all the samples are diffusion and relaxation controlled, which may be good for the colon drug delivery. The values of n as mentioned above, further confirm that the value of pH, the content of SP, or the cross-linker play important roles in controlled BSA release, and it is approved by corresponding SEM micrographs.

CONCLUSION

The novel SP/PAA IPN hydrogels have been synthesized by free radical copolymerization in presence of GA and BIS as the cross-linking agents and APS as the initiator. The FTIR analysis of IPN hydrogel and BSA-loaded hydrogel demonstrate that the IPN structure is formed and the BSA is successfully loaded in the polymer matrix. SEM micrographs have indicated the pore size and pore wall thickness of the hydrogels can be controlled. DSC thermograms have shown that the IPN hydrogels have good compatibility. The in vitro release profiles of BSA from the IPN hydrogels have also shown minimum release at pH 1.2 (the pH of gastric fluid) but more release at pH 7.4 (the pH of colonic fluid). The release percentage of BSA has decreased with increased SP or BIS content. The investigation of the values of n revealed the release mechanism of BSA is Fickian diffusion controlled mechanism at pH below 4.8 and diffusion and relaxation controlled mechanism at pH above 4.8. The results have confirmed that the IPN hydrogels may be potential candidates for the colon site-specific delivery of protein and peptide drugs.

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