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Calcium Phosphate/Polyacrylamide/Calcium Alginate Hybrid Hydrogel Membranes for the Controlled Release of Bovine Serum Albumin

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ABSTRACT

A polyacrylamide/calcium alginate (PAM/CaAlg) hybrid hydrogel membrane was prepared by UV-initiated free-radical polymerization and subsequent Ca2+ ionic crosslinking. Then the PAM/CaAlg membrane was further treated with diammonium hydrogen phosphate (DHP) solutions to induce calcium phosphate. The resulted calcium phosphate/polyacrylamide/calcium alginate (CP/PAM/CaAlg) hybrid hydrogel membrane was immersed in bovine serum albumin (BSA) aqueous solution for sufficient adsorption. BSA was used as a model protein to investigate the controlled-release behavior of the hybrid hydrogel membranes. The effects of acrylamide/sodium alginate mass ratio, DHP concentration and saline treatment on the swelling behavior and BSA release performance were studied. The morphology of the hydrogel membranes was characterized by scanning electron microscopy (SEM). The results showed that the CP/PAM/CaAlg hybrid hydrogel membranes exhibited a porous structure, which facilitated BSA loading. Meanwhile, the calcium phosphate phase and the hybrid polymer network helped regulate the diffusion pathway of BSA, thereby improving the sustained-release performance. The swelling behavior of the membranes could be regulated by changing the polymer composition and the concentration of DHP. Compared with saline-treated membranes, the phosphate-treated membranes showed better sustained-release performance for BSA in Tris-HCl buffer. The prepared CP/PAM/CaAlg hybrid hydrogel membranes have potential application as protein drug controlled release.

KEYWORDS

Polyacrylamide/Calcium alginate; Hydrogel membrane; Diammonium hydrogen phosphate; BSA; Controlled release

1. INTRODUCTION

Hydrogels are three-dimensional crosslinked polymer networks that can absorb and retain a large amount of water without dissolving, exhibiting soft and elastic properties similar to natural tissues. Hydrogels can be synthesized from a wide range of hydrophilic polymers, including natural polysaccharides, proteins, and synthetic polymers, leading to diverse chemical compositions, adjustable mechanical strength, and excellent biocompatibility. Furthermore, hydrogels can be fabricated into various forms such as slabs, microspheres, microparticles, nanoparticles, films, and coatings, which greatly expand their application scope. As a result, hydrogels have been widely applied in numerous fields, including tissue engineering, controlled drug delivery, enzyme immobilization, artificial muscles, wound dressings, and antibacterial materials [1-5]. Among these

applications, controlled drug delivery has attracted extensive attention due to the urgent demand for safe, efficient, and sustained-release drug carriers.

With the rapid development of biotechnology and recombinant DNA technology, protein and peptide drugs have played increasingly important roles in clinical treatment due to their high specificity, strong efficacy, and low toxicity. However, these drugs often suffer from inherent drawbacks such as short half-life, easy degradation by proteases in vivo, poor oral absorption, and rapid clearance from the bloodstream, which severely limit their clinical application [6-8]. To overcome these limitations, developing suitable delivery systems that can protect protein drugs, prolong their in vivo residence time, and achieve controlled release has become a hot research topic in pharmaceutical science.

Alginate, a natural linear unbranched polysaccharide extracted from brown algae, is composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. Sodium alginate has attracted tremendous attention in the field of controlled drug release because it can form hydrogels under mild pH and temperature conditions through ionic crosslinking with divalent cations (e.g., Ca^{2+}, Ba^{2+}) [9]. Calcium alginate hydrogels are non-toxic, biodegradable, and highly biocompatible, making them ideal carriers for protein drugs, peptides, and even living cells [10]. However, single-network calcium alginate hydrogels still have significant shortcomings. First, they usually exhibit high permeability, leading to an obvious burst release of soluble proteins or drugs at the initial stage of release, which reduces drug efficacy and may cause side effects [11]. Second, single-network alginate hydrogels have weak mechanical properties and poor structural stability during swelling, easily disintegrating in physiological environments, which limits their long-term application [12]. Third, their adsorption capacity for proteins is relatively low, which affects the drug loading efficiency.

To address these drawbacks, various modification strategies have been proposed. Blending alginate with other natural polymers (e.g., gelatin, chitosan) [13], hydrophobic modification [14], biomineralization [15], and graft polymerization [16] have been developed to improve the sustained-release performance and mechanical strength of alginate hydrogels. However, most of these methods can only partially alleviate the burst release problem and cannot significantly enhance the mechanical properties of alginate hydrogels.

Interpenetrating polymer networks (IPNs), which consist of two or more crosslinked polymer networks intertwined at the molecular level, have emerged as an effective strategy to combine the advantages of different polymers [17]. Acrylamide (AM) is a common synthetic monomer that can form polyacrylamide (PAM) with excellent mechanical strength, chemical stability, and hydrophilicity through free-radical polymerization. The IPN of polyacrylamide and calcium alginate combines the high mechanical strength of PAM and the good biocompatibility of calcium alginate, forming a double-network hydrogel with improved structural stability and adjustable swelling behavior [18]. Sun et al. [19] reported that polyacrylamide/calcium alginate double-network hydrogels exhibit extremely high stretchability and toughness, far superior to single-component hydrogels. However, the adsorption capacity of polyacrylamide/calcium alginate hydrogels for proteins is still limited, and their sustained-release performance needs to be further optimized.

Biomineralization, which mimics the natural mineral formation process in organisms, involves the deposition of inorganic minerals in porous organic polymer matrices under mild conditions [20]. This process can effectively regulate the pore structure of hydrogels, reduce the permeability of the matrix, and slow down the diffusion rate of encapsulated drugs, thereby achieving better sustained-release effects [21]. Phosphate ions can interact with Ca^{2+} in calcium alginate networks, inducing the formation of calcium phosphate minerals in the hydrogel matrix, which can modify the internal structure of the hydrogel and improve its drug release performance.

In this study, polyacrylamide/calcium alginate hybrid hydrogel membranes were prepared by UV-initiated free-radical polymerization and subsequent Ca^{2+} ionic crosslinking. The prepared membranes were further treated with diammonium hydrogen phosphate (DHP) solutions of different concentrations to induce biomineralization and regulate their swelling behavior and internal pore

structure. The resulted calcium phosphate/polyacrylamide/calcium alginate (CP/PAM/CaAlg) hybrid hydrogel membrane was immersed in bovine serum albumin (BSA) aqueous solution for loading. BSA was selected as a model protein to systematically evaluate the protein loading and in vitro release behavior of the hydrogel membranes. The morphology of the membranes was characterized by SEM, and the effects of polymer composition, DHP concentration, and saline treatment on the swelling and release properties were investigated in detail. The purpose of this work was to explore the feasibility of phosphate-treated polyacrylamide/calcium alginate hydrogel membranes as high-performance carriers for protein drug-controlled release.

2. MATERIALS AND METHODS

2.1. Materials

The experimental materials used in this study included sodium alginate (SA), acrylamide (AM), N, N′-methylenebisacrylamide (MBAA), ammonium persulfate (APS), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$), calcium chloride ($CaCl_2$), bovine serum albumin (BSA), sodium chloride (NaCl), and Tris-HCl buffer solution, all of which were purchased from reagent companies. All reagents were of analytical or chemical grade and used without further purification. Deionized water was used throughout the experiments.

The main instruments used in this study included a UV-visible spectrophotometer, an electronic balance, a magnetic stirrer, an ultraviolet lamp, and a scanning electron microscope (SEM), all of which were purchased from instrument companies. The UV-visible spectrophotometer was used to determine the absorbance of BSA in the release medium. The electronic balance was used for reagent weighing and swelling measurements of the hydrogel membranes. The magnetic stirrer was used to prepare homogeneous precursor solutions. The ultraviolet lamp was used to initiate the free-radical polymerization of acrylamide. SEM was used to observe the surface morphology of the hydrogel membranes.

2.2. Preparation of Polyacrylamide/Calcium Alginate (PAM/CaAlg) Hydrogel Membranes

The blend solutions containing acrylamide and sodium alginate were prepared with mass proportions of 4:1, 6:1, 8:1, 10:1 and 12:1 by adding ammonium persulphate as photo-initiator as well as N,N-methylenebisacrylamide as the crosslinker for polyacrylamide. In this protocol, the certain amount of Acrylamide was dissolved in distilled water (the water content was fixed at 86 wt. %) under mechanical stirring for 5 min. initiator APS (1% of the mass of acrylamide) and crosslinker N,N-methylenebisacrylamide (0.15% of the mass of acrylamide) was added into the solution gradually and stirring the solution continuously. Then certain sodium alginate powder was added into it until a homogeneous solution was attained. After that, the solutions were allowed to stand until trapped air bubbles were removed. The solutions were poured onto glass plate measuring 75.0 ×150.0×3.0 mm^3, The solutions were cast onto glass plates using a glass rod with a 0.5 mm gap, covered with 3-mm-thick glass plate, then put the glass plates into hermetic bag which was deoxygenated by purging with nitrogen for 10 min. After that, the hydrogel membranes were polymerized under ultraviolet irradiation for 15 min. The obtained hydrogels were crosslinked by immersing them in aqueous solution of calcium chloride (2.5 wt.%). The UV-initiated polymerization ensures rapid and uniform formation of covalent crosslinks in the polyacrylamide network, while subsequent Ca^{2+} crosslinking constructs a stable ionic network of calcium alginate. This dual-crosslinking method effectively combines the advantages of both networks, providing the PAM/CaAlg hydrogel membrane with good structural integrity and adjustable swelling behavior.

2.3. Preparation of CP/PAM/CaAlg Hybrid Hydrogel Membranes

The above prepared PAM/CaAlg hydrogels in Section 2.2 were immersed into the $(NH_4)_2HPO_4$ solution with different concentrations (0.05%, 0.1%, 0.2%,0.3% and 0.5%) for 8h and then the obtained biomineralized CP/PAM/CaAlg hydrogel membranes were washed with deionized water three times and used in subsequent experiments.

2.4. Loading and Release of BSA in Vitro

The CP/PAM/CaAlg hybrid hydrogel membranes prepared in Section 2.3 were cut into circular pieces with a diameter of 20 mm and immersed in 10 mL BSA loading solutions containing 2.5 wt.% $CaCl_2$ until adsorption equilibrium was reached. Unless otherwise specified, the BSA concentration was 40 μmol/L. To investigate the effect of BSA loading concentration, BSA solutions with different concentrations were used under the same loading conditions. To examine whether the biomineralized alginate hydrogel membranes could delay the release of BSA, release profiles of BSA from hydrogels with different mass ratio of sodium alginate and acrylamide in Tris-HCl with pH 8.32 or sodium chloride solutions were determined. The prepared hydrogel membranes were soaked in glass vessels containing 5mL of Tris-HCl with pH 8.32 or sodium chloride solutions. At predetermined time intervals, aliquots of the release medium were withdrawn and analyzed using a UV-visible spectrophotometer at 278 nm to determine the amount of BSA released from the hydrogel membranes. After each measurement, the withdrawn aliquots were returned to the vessels to maintain a constant release volume. All samples were analyzed in triplicate. The amount of BSA released from the hydrogel membranes at time t, Q_t (mg/g), was calculated according to the following equation:

$$Q_t = \frac{(C_0 - C_t)V}{m} \tag{1}$$

Where C_t (mg/mL) is the concentration of BSA in the release medium at time t, V (mL) is the volume of the release medium, and m (g) is the mass of the hydrogel membrane.

2.5. Swelling Studies

The swelling behavior of the polyacrylamide/calcium alginate hydrogels was studied in different mass fraction of diammonium phosphate and in sodium chloride solutions (0.9%) at temperatures of 25 ℃ respectively. Hydrogel discs were made with the help of a metal bore with sharp edges. At predetermined time intervals, the swollen hydrogels were weighed after wiping them with soft paper tissue until no further weight gain of the samples was observed. The degree of swelling for each sample was calculated by using the following expression:

$$SR = \frac{W_t - W_0}{W_0} \times 100\% \tag{2}$$

Where W_0 (g) is the initial mass of the hydrogel film before swelling, and W_t (g) is the mass at different points in time.

2.6. Scanning Electron Microscopy (SEM)

The surface morphology of the hydrogels was observed by scanning electron microscopy (EVO 50, Zeiss, USA). The swollen hydrogel discs of 0.25 cm^2 in area were lyophilized at -80°C and 0.04 mbar for 36 h and observed at 500and 1000magnification after being mounted on the base platform for gold coating using a vacuum sputter coater (EMI TECK, K550X; Carl Zeiss, Thornwood, NY) at a

vacuum pressure of 0.09 mbar. Lyophilization preserves the original porous structure of the swollen hydrogel, and gold coating enhances surface conductivity for clear SEM imaging.

3. RESULTS AND DISCUSSION

In the present study, the hydrogels were prepared by UV initiated free-radical copolymerization of acrylamide and MBAA in the presence of sodium alginate followed with calcium ions crosslinking. The carboxyl groups of alginates reacted with Ca^{2+} to form an ionically crosslinked network. The polyacrylamide chains form a network by covalent crosslinks. Therefore, the hydrogel membrane contained two types of networks: an ionically crosslinked calcium alginate network and a covalently crosslinked polyacrylamide network. Hydrogels with different mass proportions of sodium alginate and acrylamide were swollen in different mediums and show different release curves. The effects of different variables on properties of hydrogels were investigated.

3.1. Scanning Electron Microscopic Analysis

The surface morphology of the PAM/CaAlg hydrogel membranes before and after treatment with diammonium hydrogen phosphate solution was observed by SEM, as shown in Figure 1. Figures 1a and 1b show the morphology of the PAM/CaAlg membrane. The untreated membrane exhibited a relatively compact and smooth surface, and no obvious porous structure was observed. This compact structure may limit the diffusion and adsorption of BSA molecules inside the membrane. Figures 1c and 1d show the morphology of the CP/PAM/CaAlg membrane after treatment with diammonium hydrogen phosphate solution. Compared with the untreated membrane, the treated membrane showed a rougher and more porous surface. The formation of pores may be attributed to the interaction between phosphate ions and Ca^{2+} in the calcium alginate network during the swelling process, which partially changed the original ionic crosslinked structure of the membrane.

The porous structure of the treated membrane is beneficial for BSA adsorption and release. During the loading process, BSA molecules can enter the internal pores of the hydrogel membrane. During the release process, the hydrogel network provides diffusion pathways and resistance for BSA molecules, resulting in sustained-release behavior. Therefore, SEM results indicate that diammonium hydrogen phosphate treatment can regulate the membrane morphology and improve its potential application in protein-controlled release. The interconnected porous structure also provides a larger specific surface area, which is beneficial for increasing the loading capacity of BSA.

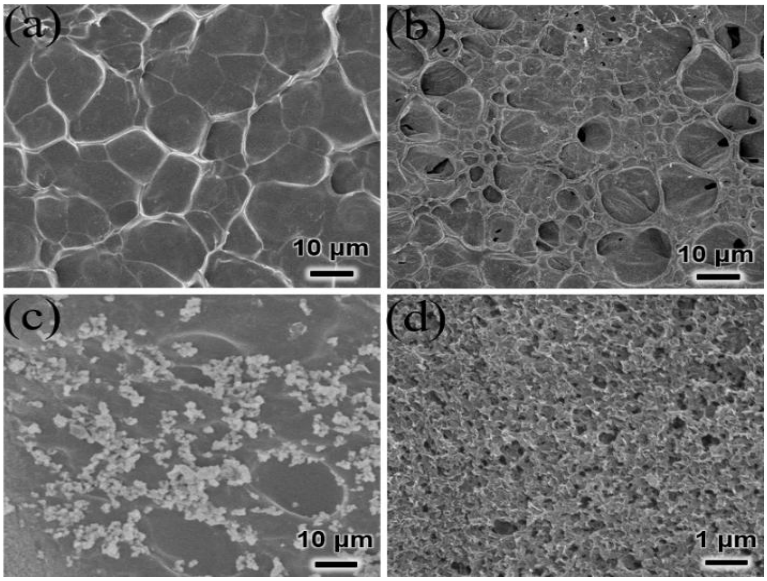

Figure 1. SEM images of PAM/CaAlg membrane (a, b) and CP/PAM/CaAlg membrane (c, d) at different magnifications

3.2. Swelling Studies

Equilibrium swelling and swelling rate play important roles associated with release of proteins. Figure 2 shows the swelling behavior of the CP/PAM/CaAlg hydrogel membranes with different AM:SA mass ratios in diammonium hydrogen phosphate solutions with different mass fractions. The swelling ratio in different mass fraction of diammonium phosphate media showed a dependence on blend composition of the IPN. The overall swelling ratio of the hydrogels decreased gradually with the decrease in polymer blend ratio of AM-SA. Formulations prepared with a higher amount of SA exhibited higher % swelling ratio than those containing a smaller amount of SA. Compared with Hydrogels with smaller amount of SA, more calcium ions participated in crosslinking to form hydrogels with higher amount of SA. In the process of swelling, Ca^{2+} and the alginate macromolecules were gradually released from the hydrogel matrix, chelating action between calcium ion and phosphate ions occurred. Therefore, a higher alginate content leads to more Ca^{2+} involved in ionic crosslinking. During phosphate treatment, more Ca^{2+} can be chelated by phosphate ions, weakening the ionic network and resulting in a higher swelling ratio. Besides, all hydrogels with different blend ratio of SA-AM disintegrated in diammonium phosphate with mass fraction of 0.5%, while hydrogels swelling in low mass fraction of diammonium phosphate were almost no erosion. In the polyacrylamide/calcium alginate hybrid hydrogel, the calcium alginate network and the polyacrylamide network were physically intertwined. The alginate chains were ionically crosslinked by Ca^{2+}, while the polyacrylamide chains were covalently crosslinked by MBAA. Therefore, even when part of the Ca^{2+} ions interacted with phosphate ions during swelling, the covalently crosslinked polyacrylamide network could still help maintain the membrane structure.

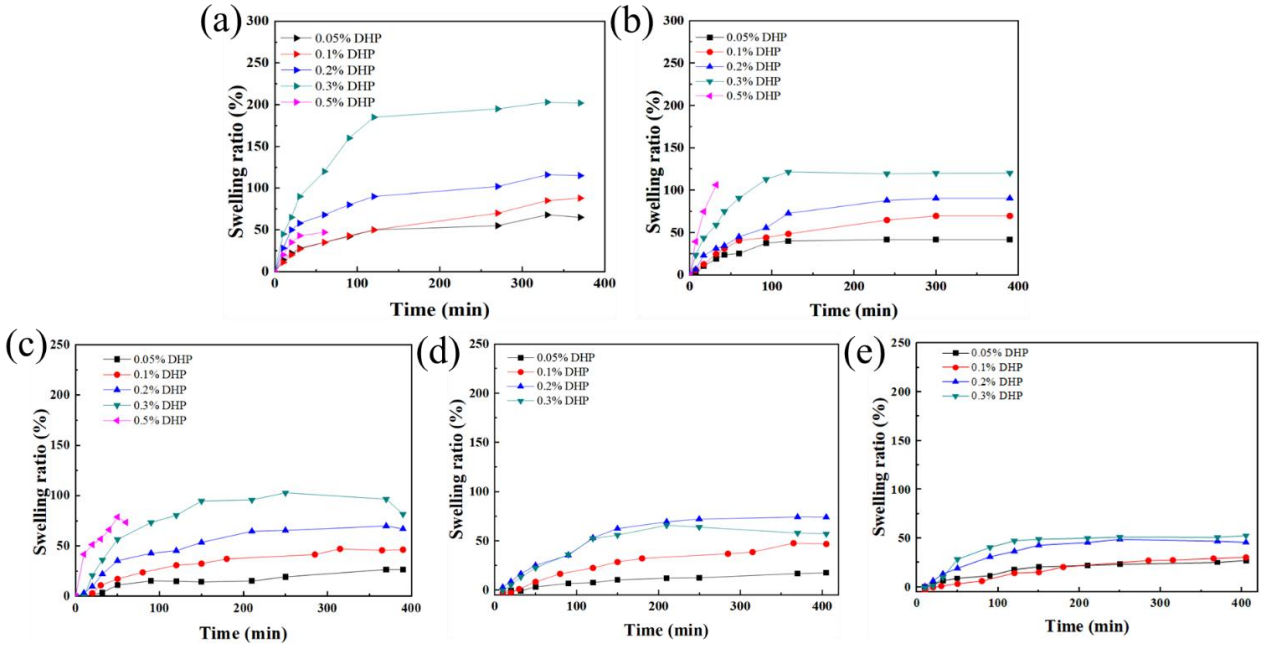

Figure 2. Swelling behavior of CP/PAM/CaAlg hydrogel membranes with different AM:SA mass ratios in diammonium hydrogen phosphate solutions with different mass fractions: (a) AM:SA = 4:1; (b) AM:SA = 6:1; (c) AM:SA = 8:1; (d) AM:SA = 10:1; (e) AM:SA = 12:1

At high diammonium hydrogen phosphate concentrations, a large number of phosphate ions diffused into the hydrogel network and interacted with Ca^{2+}, which weakened the calcium alginate ionic crosslinks and caused hydrogel disintegration. In contrast, at low phosphate concentrations, only part of the Ca^{2+} ions was complexed by phosphate ions. Therefore, the covalently crosslinked polyacrylamide network remained intact and helped maintain the overall membrane structure.

Figure 3 compares the swelling behavior of CP/PAM/CaAlg hydrogel membranes in diammonium hydrogen phosphate solutions and in 0.9% saline solution. For the representative AM:SA mass ratio

of 8:1, the swelling ratio increased with increasing DHP concentration, indicating that phosphate ions progressively weakened the Ca^{2+}-crosslinked calcium alginate network. The hydrogel was disintegrated in diammonium phosphate with mass fraction of 0.5% less than one hour, which resulted from the high content phosphate ions acting as Ca^{2+} complexing agents result in disintegration of hydrogels. In the case of hydrogels swelling in saline, the swelling ratio from the AM -SA mass ratio 4:1 was the highest compared with other mass ratio of SA-AM. calcium ions were partly exchanged by the non-gelling sodium ions.

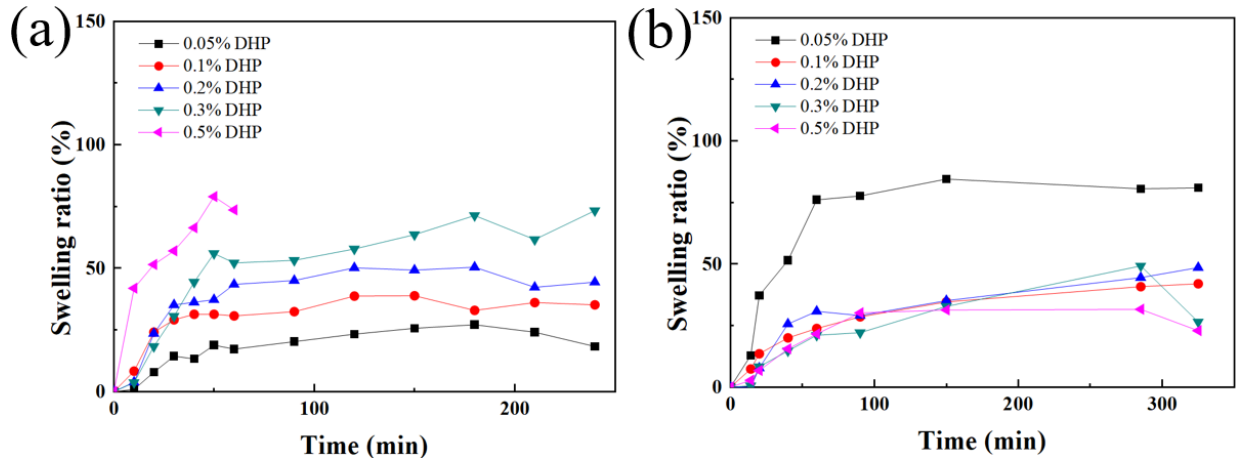

Figure 3. Swelling behavior of CP/PAM/CaAlg hydrogel membranes in different swelling media: (a) diammonium hydrogen phosphate solutions with different mass fractions; (b) 0.9% saline solution

3.3. The BSA Release in Vitro

Based on the above swelling and morphological characterizations, the sustained release behavior of representative hydrogels with the mass ratios of acrylamide and sodium alginate 4:1, 6:1, 8:1, 10:1 and 12:1 was investigated in Tris-HCl with pH 8.32.

3.3.1. BSA release of CP/PAM/CaAlg hydrogel membranes prepared with different DHP

Figure 4 presents the BSA release profiles of the CP/PAM/CaAlg hydrogel membranes with different AM:SA mass ratios after swelling in diammonium hydrogen phosphate solutions. The release experiments were carried out in Tris-HCl buffer at pH 8.32. The studied hydrogels were loaded with BSA after being swollen in different mass fractions of diammonium phosphate. As to all formulations, the release was characterized with an initial BSA burst, followed by a continuous release phase. Hydrogels displayed different release profiles depending on their composition. The BSA release behavior was closely related to the AM:SA mass ratio. At relatively high SA content, more Ca^{2+}-crosslinked calcium alginate domains were present in the hydrogel network, which could restrict BSA diffusion and lead to a lower release rate after the initial burst. At a moderate AM:SA ratio, such as 8:1, the hydrogel possessed a more balanced network structure, allowing sufficient BSA loading while maintaining an appropriate diffusion resistance. Among the tested samples, the membrane with an AM:SA ratio of 8:1 showed the highest cumulative BSA release of 81.24%, suggesting that this composition provided a suitable balance between BSA loading capacity and diffusion control. However, at very low SA content, the calcium alginate component was insufficient to provide effective BSA retention and regulated diffusion pathways, resulting in a lower total release.

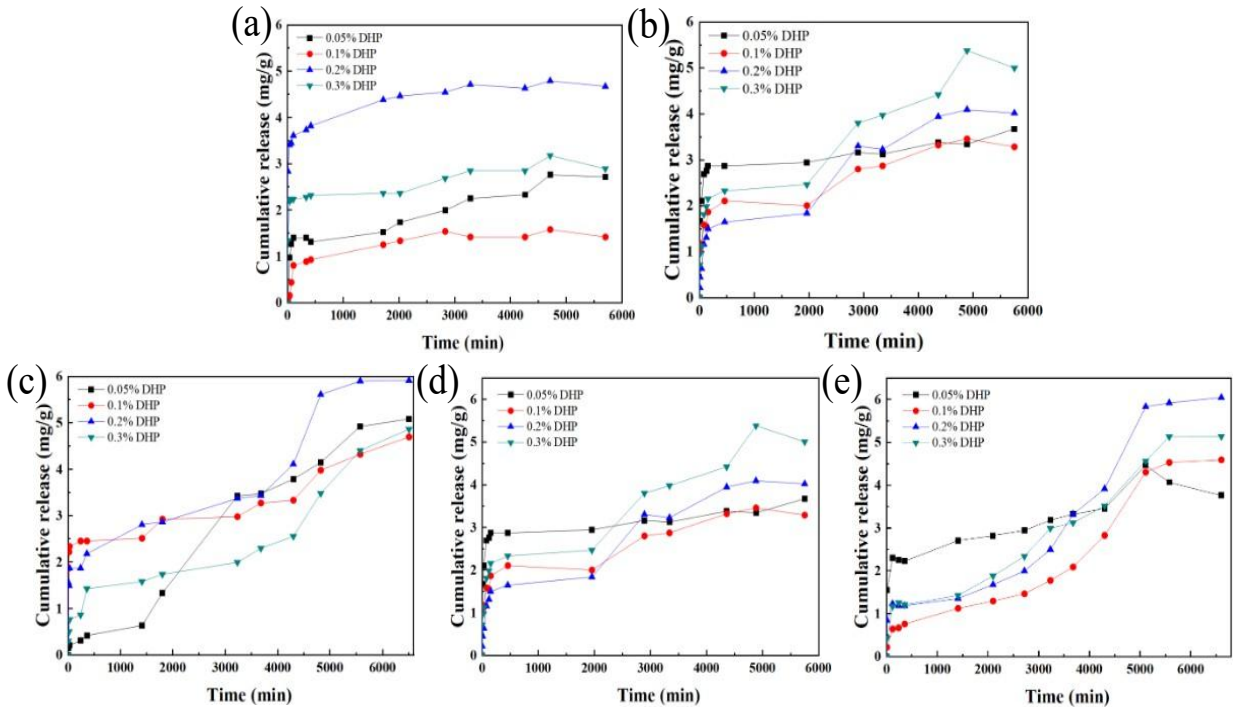

Figure 4. BSA release profiles of CP/PAM/CaAlg hydrogel membranes with different AM:SA mass ratios after swelling in diammonium hydrogen phosphate solutions with different mass fractions: (a) AM:SA = 4:1; (b) AM:SA = 6:1; (c) AM:SA = 8:1; (d) AM:SA = 10:1; (e) AM:SA = 12:1

3.3.2. BSA release of hydrogels after swelling in saline

Figure 5 shows the BSA release profiles of PAM/CaAlg hydrogel membranes after swelling in 0.9% saline solution. As shown in Figure 5a, the saline-treated membranes exhibited relatively rapid BSA release behavior compared with the phosphate-treated membranes. This result indicates that saline treatment did not provide an effective sustained-release effect for BSA. The rapid release behavior may be attributed to the ion exchange between Na^+ in saline solution and Ca^{2+} in the calcium alginate network. The replacement of Ca^{2+} by non-gelling Na^+ weakened the ionic crosslinked structure of calcium alginate, resulting in a looser network and faster diffusion of BSA from the membrane into the release medium.

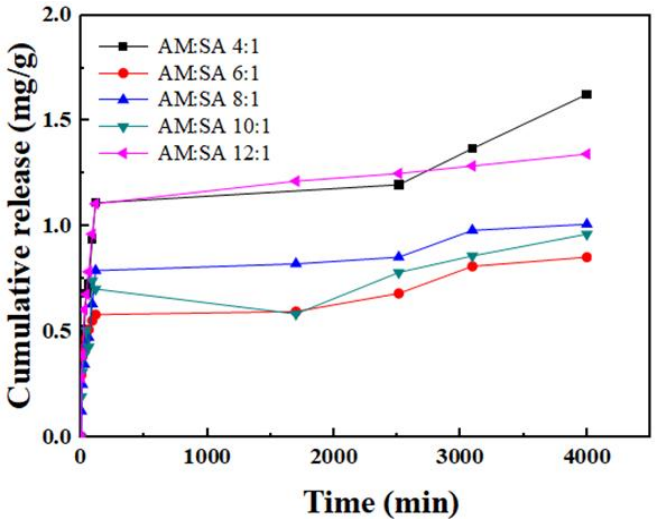

Figure 5. BSA release profiles of PAM/CaAlg hydrogel membranes after swelling in 0.9% saline solution

3.3.3. Effect of BSA loading concentration on BSA release

The CP/PAM/CaAlg hydrogel membrane with an AM:SA mass ratio of 8:1 was selected as a representative sample to investigate the effect of BSA loading concentration on release behavior, as shown in Figure 6. The release rate increased with increasing BSA loading concentration. Membranes with higher BSA loading exhibited faster release, while those with lower BSA loading showed slower release. This may be because more BSA molecules were located near the membrane surface at higher loading concentrations, making them more easily exposed to the release medium.

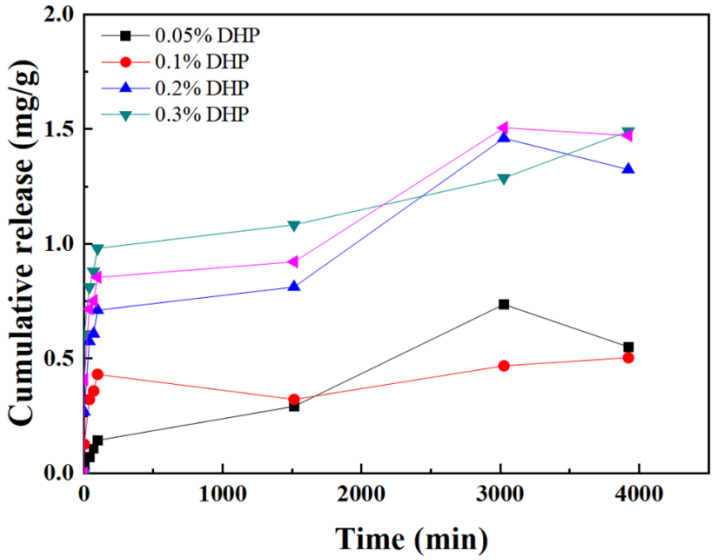

Figure 6. Effect of BSA loading concentration on the BSA release behavior of CP/PAM/CaAlg hydrogel membranes with AM:SA = 8:1

4. CONCLUSION

Polyacrylamide/calcium alginate hybrid hydrogel membranes were successfully prepared by UV-initiated free-radical polymerization and Ca^{2+} ionic crosslinking. The prepared membranes were further treated with diammonium hydrogen phosphate solutions with different concentrations, and their swelling behavior and BSA release performance were investigated. SEM observation showed that the phosphate-treated hydrogel membranes possessed a porous structure, which was favorable for BSA adsorption and diffusion. The polyacrylamide/calcium alginate hydrogel membrane contained both a covalently crosslinked polyacrylamide network and an ionically crosslinked calcium alginate network, which helped maintain the membrane structure during swelling and release.

The swelling results showed that the swelling behavior of the hydrogel membranes was affected by both the acrylamide/sodium alginate mass ratio and the concentration of diammonium hydrogen phosphate. At suitable phosphate concentrations, the membranes could maintain their integrity and exhibit controllable swelling behavior. However, excessive phosphate concentration could weaken the calcium alginate ionic crosslinked network and lead to membrane instability.

The BSA release experiments demonstrated that the CP/PAM/CaAlg hydrogel membranes exhibited better sustained-release performance than the saline-treated membranes. The sustained release of BSA was mainly attributed to the porous structure, the regulated swelling behavior and the hybrid network of polyacrylamide/calcium alginate. These results suggest that the CP/PAM/CaAlg hybrid hydrogel membranes have potential application as protein drug controlled-release carriers.

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