Preparation of CMC/HEC Crosslinked Hydrogels for Drug Delivery

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A novel crosslinked hydrogel was prepared from sodium carboxymethyl cellulose (CMC) and hydroxyethyl cellulose (HEC) using ammonium persulfate as an initiator and methylenebisacrylamide as a crosslinker for drug delivery. The chemical structure of the copolymer was characterized by Fourier transform infrared spectroscopy and X-ray diffraction, and the morphology was observed under scanning electron microscopy. The swelling behavior of the hydrogels confirmed the pH- and ionic strength-sensitivity. The reversibility of the hydrogels and the on-off switching behavior were also investigated, providing the potential for drug delivery. The release of bovine serum albumin (BSA) from drug-loaded hydrogels was studied at different pH conditions to simulate gastrointestinal conditions. The amount of BSA released from the hydrogels at pH 1.2 was relatively low (17.8%), while 85.2% was released at pH 7.4. According to the results, the CMC/HEC hydrogel has the potential for use in the controlled release of oral medication.

Keywords: Hydrogel; Carboxymethyl cellulose; Hydroxyethyl cellulose; Controlled release; pH sensitivity; Bovine serum albumin

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INTRODUCTION

Hydrogels are three-dimensional, water-swollen, polymeric networks containing chemical or physical crosslinks such as ionic interaction, hydrogen bonding, or hydrophobic interaction (Peppas *et al.* 2000; Bakass *et al.* 2002; Jao *et al.* 2009). Hydrogels made from synthetic polymers such as polymethacrylates, polyacrylates, and polyacrylamides have been extensively reported (Chen and Zhao 2000; Krul *et al.* 2000). However, the toxicity and carcinogenicity of the residual monomers in these hydrogels might pose problems for their use in drug delivery, tissue engineering, and personal hygiene products (Anbergen and Oppermann 1990; Pourjavadi *et al.* 2006).

Due to a number of exceptional properties including biocompatibility, biodegradability, renewability, and non-toxicity, polysaccharides have received a lot of attention regarding the preparation of hydrogels, especially smart hydrogels sensitive to pH, temperature, ionic strength, electricity, *etc*. (Chen *et al.* 2004b; Liang *et al.* 2004; Sannino *et al.* 2005; Coviello *et al.* 2007). These responsive hydrogels have become an important area of research and development in the fields of medicine, pharmaceuticals, and biotechnology (Hoffman 2002).

Cellulose is one of the most important polysaccharides due to its economic advantages and versatility (Tomšič *et al.* 2007). Sodium carboxymethyl cellulose (CMC), the only anionic polyelectrolyte among most water-soluble cellulose derivatives, contains many hydrophilic hydroxyl and carboxyl groups, which give it the potential for use in preparing pH-responsive hydrogels (Huang *et al.* 2003; Sannino *et al.* 2009; Akar *et al.* 2012). Hydroxyethyl cellulose (HEC), another cellulose ether with advantageous properties similar to CMC (Wang *et al.* 2011), possesses abundant reactive hydroxyl groups for the production of hydrogels. Moreover, HEC can effectively improve the swelling capability of hydrogels because of its excellent water retention ability (Gorgieva and Kokol 2011). In recent decades, the preparation of hydrogels has been focused on grafting and copolymerization (Madsen and Peppas 1999; Marsano *et al.* 2000). In the present study, a novel crosslinked pH-responsive hydrogel with high water-retention ability was prepared from CMC and HEC. The properties of the prepared CMC/HEC crosslinked hydrogel were characterized using Fourier transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), and scanning electron microscopy (SEM). The swelling capacity of the hydrogels was measured in various solutions with a wide range of pH values. The pH- and ionic strength-sensitivity and reversibility were also investigated. The release of bovine serum albumin (BSA) from drug-loaded hydrogels was examined in simulated gastric fluid (pH 1.2) and intestinal fluid (pH 7.4).

EXPERIMENTAL

Materials

CMC with different molecular weights (expressed with viscosity 2500 to 4500, 800 to 1200, and 300 to 800 mPa•s, denoted as CMC-1, CMC-2, and CMC-3, respectively) and HEC with a viscosity of 80 to 125 mPa•s were obtained from Aladdin Reagent Co. (Shanghai, China). BSA was obtained from Boao Biological Technology Co., Ltd. (Shanghai, China). Ammonium persulfate (APS) and methylenebisacrylamide (MBA) were purchased from Lingfeng Chemical Reagent Co., Ltd. (Shanghai, China). Na_2HPO_4, NaH_2PO_4, and all other chemicals were obtained from Guangzhou Chemical Reagent Factory (Guangdong, China). CMC and HEC were of USP grade, and all other chemicals were of analytical grade. All chemicals were used as received without any purification.

Preparation of CMC/HEC Hydrogel

Crosslinking polymerization of CMC and HEC was carried out using APS as a free radical initiator and MBA as a hydrophilic crosslinker, according to the following procedure:

HEC was dispersed into distilled water in a 100 mL three-neck flask in an oil bath with magnetic agitation for 5 min at 70 °C. CMC was introduced into the clear HEC dispersion. The mass ratio of CMC to HEC was 3:1, and the total concentration of CMC and HEC was 2 wt%. The resulting mixture was stirred overnight to obtain a clear and highly viscous solution. Then, the initiator APS (0.5% based on the total polymer CMC and HEC), previously dissolved in 5 mL distilled water, was added dropwise into the CMC/HEC solution. Crosslinker MBA (5%), also previously dissolved in 5 mL distilled water, was added 10 to 15 min later, and the reaction was carried out at 85 °C under N_2 atmosphere for 30 min. After the required time, the mixture was cooled to ambient temperature. The resultant gel was immersed in 300 mL ethanol for 24 h, which was

repeated twice to completely remove water. The product was dried to a constant weight at 50 °C, cut into small pieces, and stored away from moisture, heat, and light before use. The hydrogels prepared from CMC-1, CMC-2, and CMC-3 were denoted as Gel-1, Gel-2, and Gel-3, respectively.

Swelling and Sensitivity Measurements

A certain amount of dry sample was put in a nylon bag (400 mesh size) and immersed in ultrapure water or phosphate-buffered saline (PBS) at 20 °C. The bags were removed from water or PBS buffer at regular intervals and surface water was carefully blotted with filter paper without applying pressure. The swollen hydrogels were weighed and the degree of swelling was measured by the following equation (Kumar *et al.* 2010),

$$\text{Degree of swelling} = (W_t - W_o)/W_o \times 100\% \quad (1)$$

where W_t and W_o are the weight of the swollen hydrogel at time t and the weight of dry samples, respectively.

The swelling capacity of the crosslinked hydrogels was investigated at different pHs (pH 1.2 to 8.8). The maximum degree of swelling was determined as swelling capacity at the corresponding pH values.

The pH sensitivity and reversibility was investigated by alternately immersing in buffer solutions with pH 1.2 and 5.5. The pH values were precisely monitored by a pH meter and 0.1 ±0.0001 g of the dry sample was used for the swelling measurements according to above-mentioned method.

The ionic strength sensitivity and reversibility were investigated by alternately immersing in ultrapure water and 0.1 M PBS buffer. The dry sample (0.1 ±0.0001 g) was used for the swelling measurements according to above-mentioned method.

Characterization of the Crosslinked Hydrogels

The physico-chemical properties of the crosslinked hydrogels were characterized with FT-IR, XRD, and SEM, according to previous publications (Lan *et al.* 2011; Chen *et al.* 2013).

BSA Loading and Release

Drug loading was carried out according to the published method (Chen *et al.* 2004a) at 4 °C by swelling the crosslinked hydrogels in BSA/purified water solution until an equilibrium swelling state was achieved. The samples were then taken out, dried, and weighed. To confirm the percentage of drug loading in hydrogels, the amount of BSA solution left in the loading medium was detected at a wavelength of 280 nm using a UV spectrophotometer.

The release of BSA from drug-loaded hydrogels was performed at 37 °C by suspension in 50 mL PBS buffer (pH 7.4, simulated intestinal fluid) and HCl (pH 1.2, simulated gastric fluid) at room temperature in a shaking water bath. Samples were removed from the release media at regular intervals and the release of BSA was estimated using a UV spectrophotometer. The same volume of fresh PBS buffer or HCl was added to the release media after each sampling to keep the total release media constant.

RESULTS AND DISCUSSION

Preparation of Crosslinked CMC/HEC Hydrogel and FT-IR Characterization

This work presents the optimized synthesis of a novel hydrogel through crosslinking of CMC and HEC in a homogeneous medium using APS as a free radical initiator and MBA as a crosslinker. The possible mechanism of the crosslinking reaction is illustrated in Fig. 1. The sulfate anion-radicals generated from thermal decomposition of APS extracted hydrogen from the hydroxyl groups of the polysaccharide substrate to form the corresponding alkoxy radicals (1 and 2 from CMC; 3 and 4 from HEC) on the substrates. Then, the hydrogel formation could be carried out by the free radical reactions with MBA by crosslinking between CMC and HEC or by self-crosslinking of the free radicals on HEC or CMC. A similar crosslinking mechanism has been reported between CMC and sodium alginate (Chen and Zhao 2000).

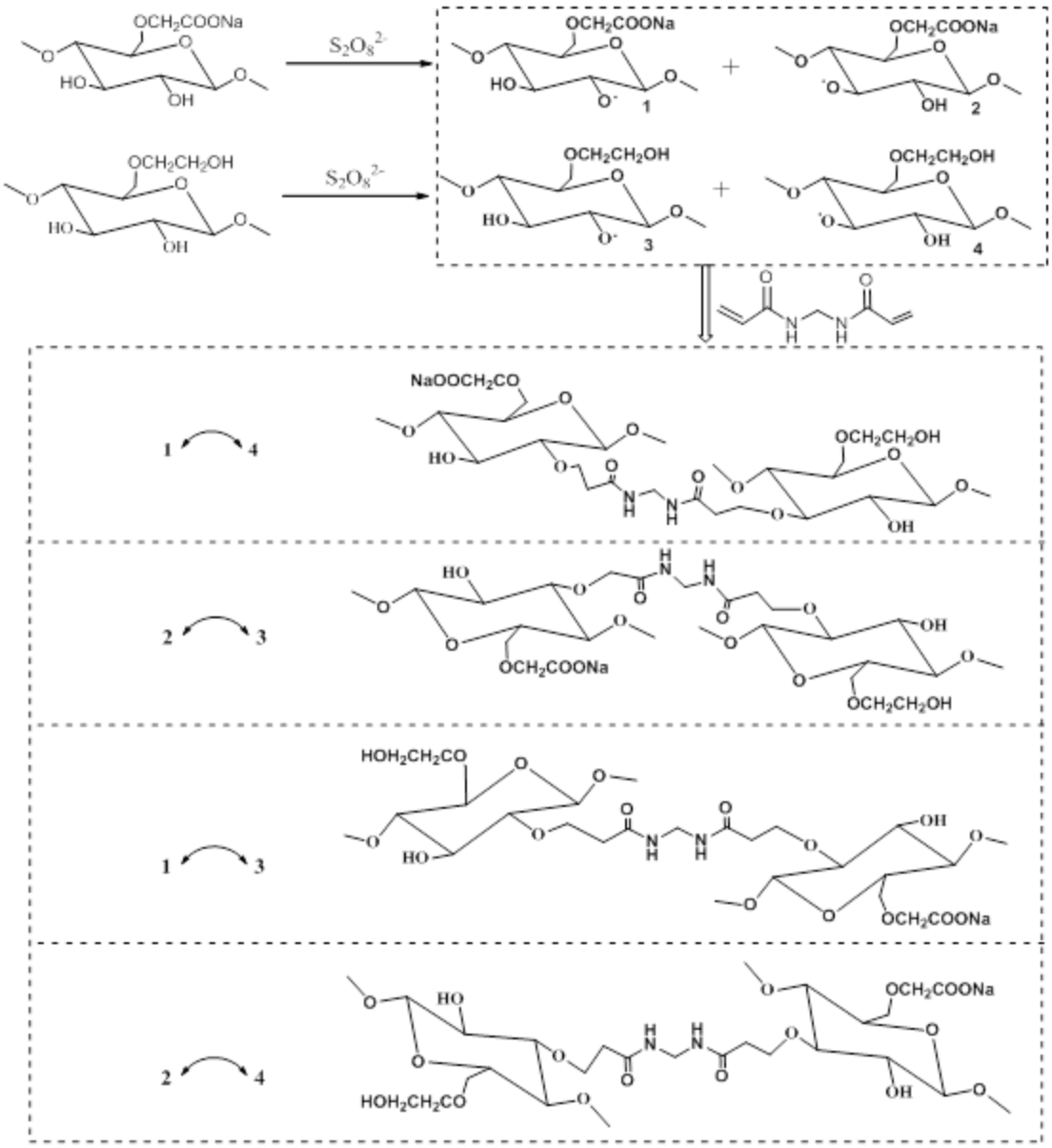


Fig. 1. Crosslinking mechanism of CMC and HEC in the presence of APS and MBA

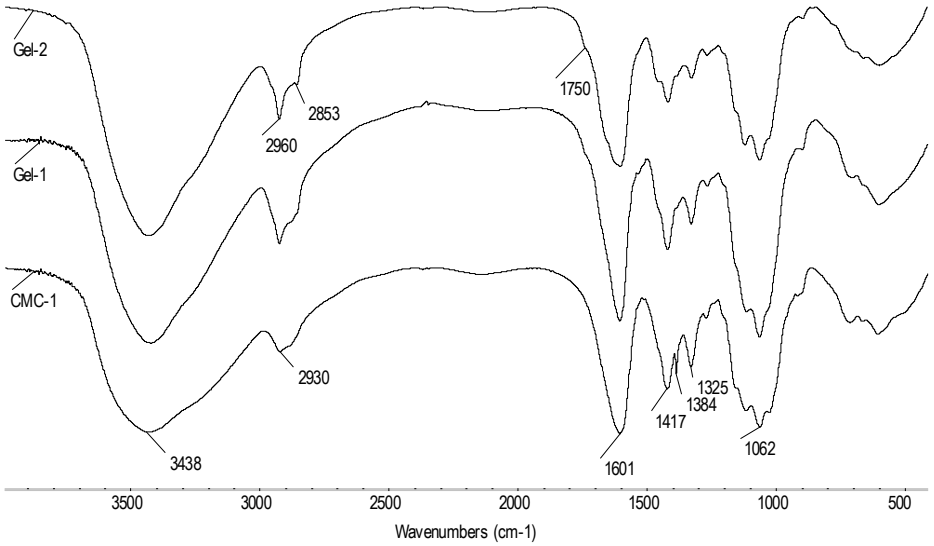


Fig. 2. FT-IR spectra of CMC-1 and the CMC/HEC crosslinked hydrogel samples Gel-1 and Gel-2

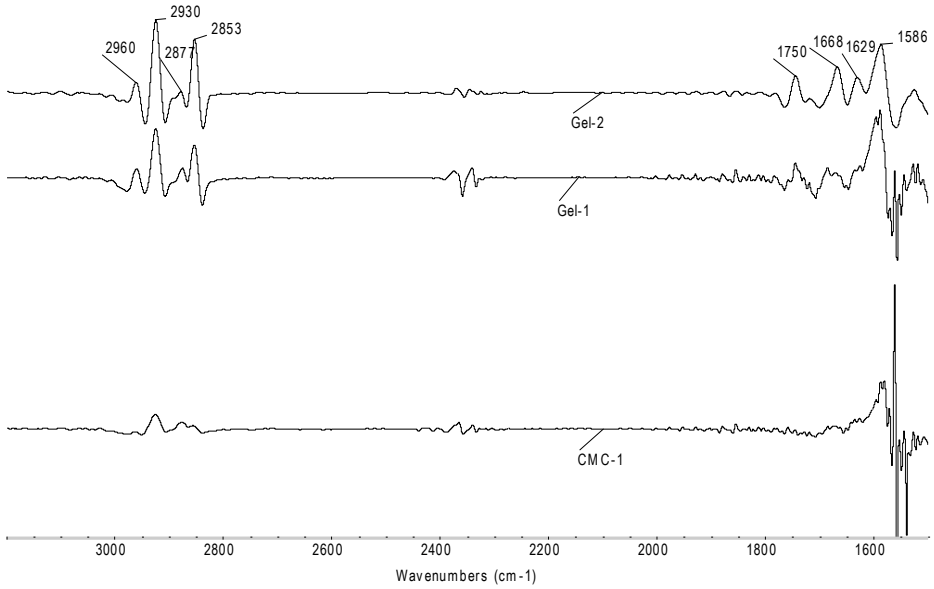


Fig. 3. Second derivative FT-IR spectra of CMC-1 and the CMC/HEC crosslinked hydrogel samples Gel-1 and Gel-2

Figure 2 shows the FT-IR spectra of CMC-1 and the hydrogel samples Gel-1 and Gel-2. In the spectrum of CMC-1, the characteristic absorbance at 3438 cm^{-1} originated from O-H stretching. The absorbance at 2930 cm^{-1} is related to C-H stretching. The strong signal at 1601 cm^{-1} is due to C=O stretching. The bands at 1417 and 1384 cm^{-1} are attributed to O-H bending, and the band at 1325 cm^{-1} is assigned to C-H bending. The prominent band at 1063 cm^{-1} corresponds to the C-O-C pyranose ring vibration. A new shoulder appeared at 1750 cm^{-1} from the amide group in the spectra of Gel-1 and Gel-2, indicating the successful attachment of amide onto CMC after crosslinking CMC and HEC with MBA as a crosslinker. To further confirm the detailed position of absorption bands and their changes, second derivative transformations of the FT-IR spectra of CMC-1 and the

crosslinked hydrogels were studied, as illustrated in Fig. 3. In the C-H stretching region, the bands at 2930, 2877, and 2853 cm^{-1} were observed in the spectra of CMC and hydrogels. In addition, a new absorption at 2950 cm^{-1} appeared in Gel-1 and Gel-2, which was probably due to crosslinking with MBA and HEC. In the C=O stretching region, more detailed absorption information was observed in the second derivative FT-IR spectra than in the FT-IR spectra. The overlapped band at 1601 cm^{-1} in Fig. 2 was derived from the bands at 1668 cm^{-1} from the stretching of carbonyl groups, 1629 cm^{-1} from the bending of absorbed water, and 1586 cm^{-1} from the stretching of carboxylates, as shown in Fig. 3. Compared with the spectrum of CMC-1, the presence of the absorption band at 1750 cm^{-1} from the amide group in the spectra of Gel-1 and Gel-2 clearly indicated the occurrence of crosslinking.

X-ray Diffraction (XRD)

The X-ray diffraction curves of the CMC and the crosslinked hydrogels are shown in Fig. 4. A strong broad crystalline peak in the range 20.3° to 21.1° present in all the curves was assigned to the (110) plane of cellulose II crystals, indicating the typical cellulose II structure in CMC and the crosslinked hydrogels. Noticeably, this crystalline peak shifted towards a higher 2θ direction at 21.1° in Gel-1 compared with that at 20.3° in CMC-1. Similar results were also reported in the preparation of hydrogels from CMC crosslinked with fumaric acid (Akar *et al.* 2012).

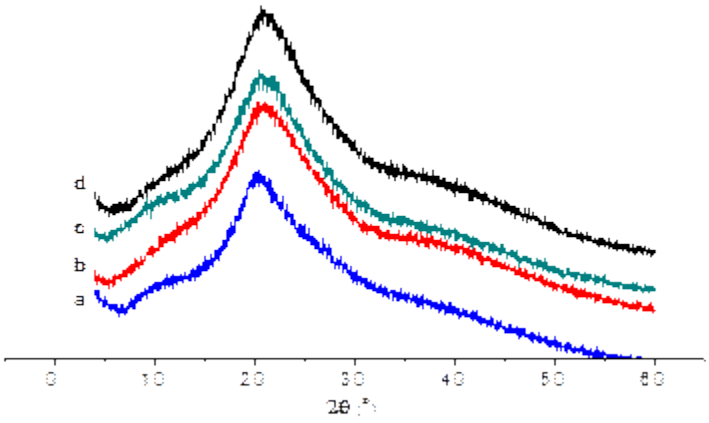
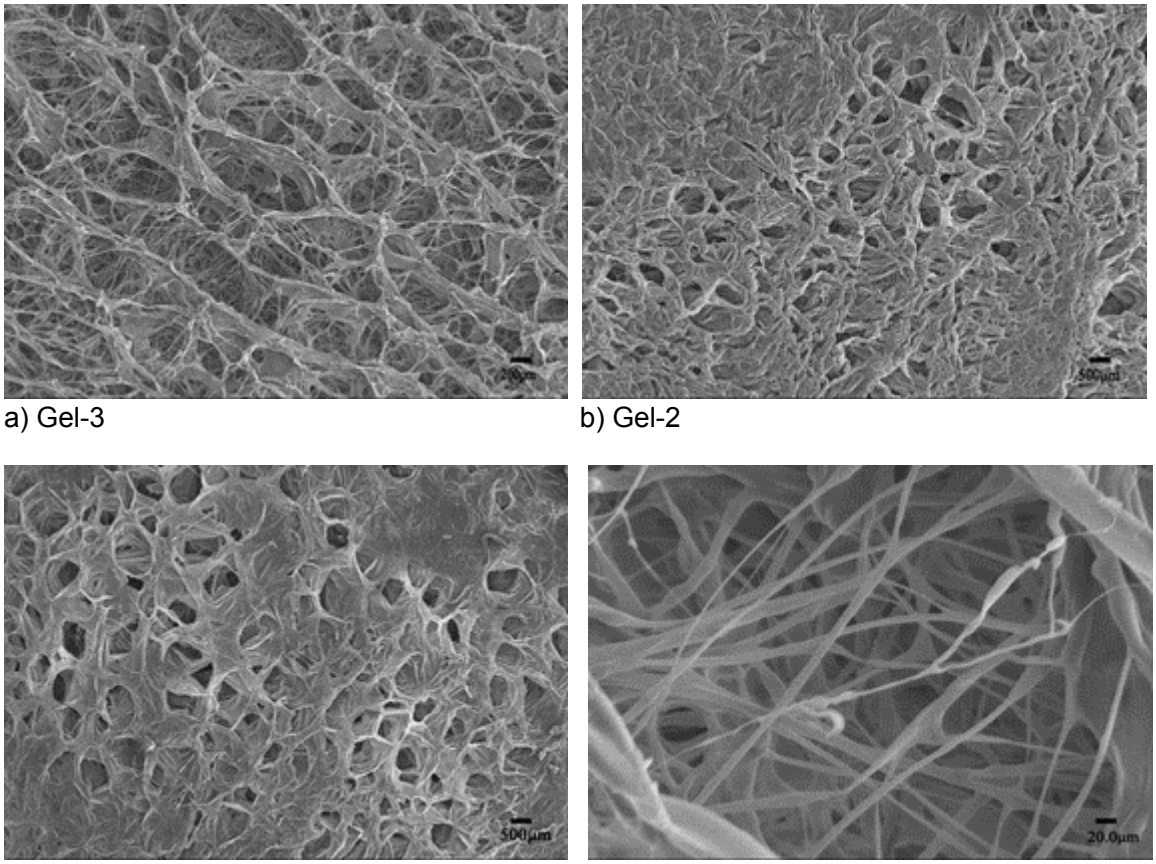


Fig. 4. X-ray diffraction curves of CMC-1 (a), Gel-1 (b), Gel-2 (c), and Gel-3 (d)

Scanning Electron Microscopy (SEM)

The SEM micrographs of the freeze-dried samples are shown in Fig. 5. These micrographs confirmed the macroporous structure of the crosslinked hydrogels (Fig. 5A-C). It is supposed that these macropores are regions of water permeation and interaction sites. The inner interwoven structure of the pores is shown in Fig. 5D. These macroporous architectures provided large specific surface area, resulting in better matrix-water interaction and easier water absorption. The average pore size of crosslinked CMC/HEC hydrogels was about 20 to 100 µm. It was also noted that the higher molecular weight of CMC caused more orderly three-dimensional structures of crosslinked hydrogels with relatively large and uniform pores (Fig. 5A-C). It was inferred that the degree of swelling of the crosslinked hydrogels should be enhanced with the improved molecular weight of the CMC used.



a) Gel-3 b) Gel-2

c) Gel-1 d) Gel-1: Inner structure of pore (× 2000)

Fig. 5. SEM images of the crosslinked hydrogels

Swelling Studies

The swelling capacity of crosslinked CMC/HEC hydrogels was investigated in different solutions with a wide range of pH values. Figure 6 reveals the effect of pH on the swelling capacity of Gel-1 at various pH solutions ranging from 1.2 to 8.8. The maximum swelling capacity was observed at about pH 5. The pKa of carboxylic groups was reported to be approximately 4.6 (Taleb *et al.* 2009). Under very acidic conditions (pH 1.2), most of carboxylate anions were protonated, eliminating the main anion-anion repulsion (Kabiri *et al.* 2010) and leading to a remarkable decrease in swelling capacity. At higher pH (pH > 5), some of the carboxylate groups were ionized, and the enhanced electrostatic anion-anion repulsion caused a dramatically improved swelling capacity. However, the swelling ratio began to decrease at pH > 5, which was probably due to the "charge screening effect" of Na^+, preventing effective anion-anion repulsion by shielding carboxylate anions. Similar pH-dependent swelling was reported in hydrogels prepared by grafting copolymerization from acrylic acid and acrylamide onto chitosan in the presence of potassium persulfate (KPS) and MBA (Mahdavinia *et al.* 2004).

Since the CMC/HEC crosslinked hydrogels showed different swelling behavior in various pH solutions, the reversible swelling-deswelling behavior of the hydrogels was explored in buffer solutions with pH 1.2 and 5.5. Figure 7 illustrates the pH-responsive on-off switching behavior of Gel-1. At pH 5.5, Gel-1 swelled due to the high electrostatic anion-anion repulsion, while it shrank at pH 1.2 within several minutes due to the protonation of carboxylate anions, indicating that the pH-responsive swelling-deswelling

behavior of the hydrogels occurs quickly and reversibly. This on-off switching behavior makes them suitable candidates for potential drug delivery systems.

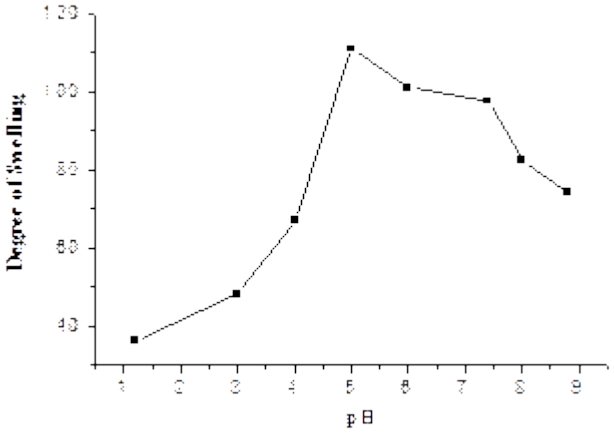


Fig. 6. Swelling capacity of the crosslinked Gel-1 in various pH solutions

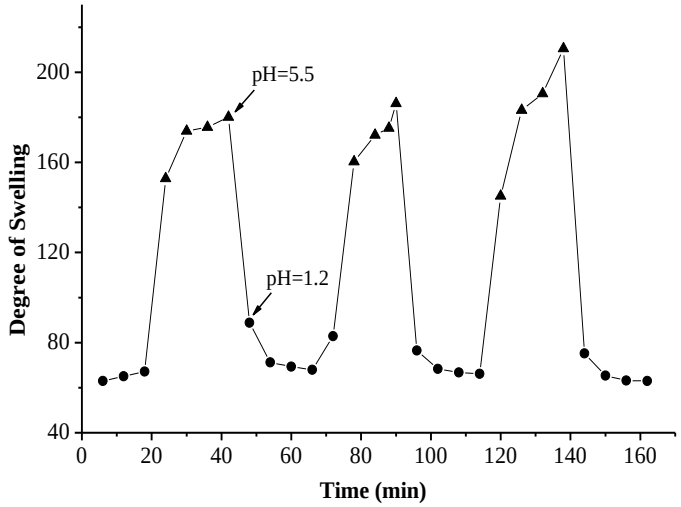


Fig. 7. On-off switching behavior as reversible swelling (pH 5.5) and deswelling (pH 1.2) of Gel-1

Moreover, the ionic strength-responsive swelling-deswelling behavior of the hydrogels was examined in ultrapure water and 0.1 M PBS buffer. Figure 8 shows the on-off switching behavior of Gel-1. The swelling capacity of Gel-1 in 0.1 M PBS buffer (about 60 g/g) was expectedly lower than in ultrapure water (about 90 g/g), probably due to the "charge screening effect" of cations in PBS buffer, which led to the reduction of osmotic pressure and subsequent loss of swelling. In ultrapure water, Gel-1 easily swelled with increased time. As expected, the swollen Gel-1 deswelled slowly when immersed in 0.1 M PBS buffer. More importantly, the PBS loaded in Gel-1 was slowly replaced by water when the shrunken Gel-1 was immersed again in ultrapure water, resulting in slow enhancement of swelling. This ionic strength-responsive on-off switching behavior of hydrogels with the alternative treatment with ultrapure water and 0.1 M PBS buffer is a result of the ion exchange ability of the carboxylate group.

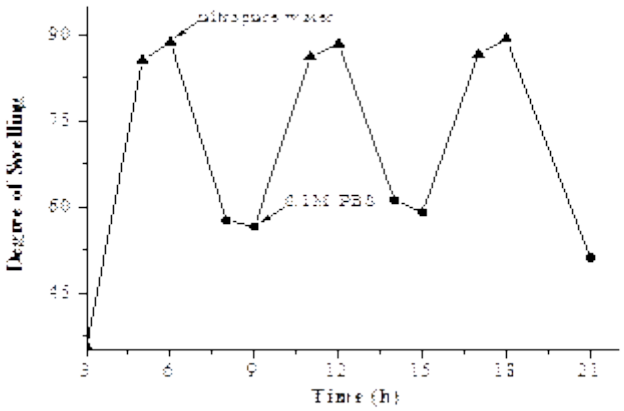


Fig. 8. On-off switching behavior as reversible swelling (ultrapure water) and deswelling (0.1 M PBS buffer) of Gel-1

BSA Loading and Release

Due to the pH sensitivity and reversibility of the crosslinked hydrogels, the incorporation of BSA as a model drug was performed, and the subsequent release of BSA was investigated in simulated gastric fluid (pH 1.2, HCl) and intestinal fluid (pH 7.4, PBS buffer). Figure 9 illustrates the cumulative release of BSA from Gel-1 in PBS buffer (pH 7.4, a) and HCl (pH 1.2, b) at room temperature. As shown in Fig. 9, the initial burst release of BSA was followed by a slow release and another increased release. About 16.8% of the loaded BSA was released within the first hour during the burst release stage from Gel-1 at pH 7.4. The slow release of BSA over 27 h cumulatively released 50% of the loaded BSA. The subsequent increased release, probably due to the partial dissolution of hydrogels, lasted for another 23 h. The total release of the loaded BSA from Gel-1 at pH 7.4 was 85.2% within 50 h of the entire release stage. However, the release of BSA at pH 1.2 was much simpler than that at pH 7.4. The BSA release only lasted for 6 h, including the initial burst release within the first 2 h and a slow release in the following 4 h. The cumulative BSA release in the initial burst release stage was 10.5% within 0.5 h and 15.7% within 2 h. Only 2% BSA was released during the 4 h of the following slow release stage and almost no BSA was released at pH 1.2 after 6 h. The total release of the loaded BSA was only 17.8%, which was much lower than the 85.2% BSA released at pH 7.4. This decreased release behavior of BSA at pH 1.2 was consistent with the results from swelling studies in different pH solutions.

As shown in the lower right corner inset of Fig. 9, the cumulative BSA release at the initial burst release stage is proportional to the square root of time, indicating that the size of the pores in hydrogels was larger than the hydrodynamic radius of BSA and that the release of the unbound BSA followed Fickian diffusion (Ritger and Peppas 1987; Cadée *et al.* 2002; Chen *et al.* 2004a). At this stage, the crosslinked hydrogels served as diffusion barriers, and BSA was released mainly by a diffusion mechanism (Cadée *et al.* 2002). More than 85% of the loaded BSA was still trapped in hydrogels after the initial burst release, suggesting that most of the BSA loaded in hydrogels was bound to the hydrogel network due to the intermolecular interactions between BSA and the crosslinked hydrogel network.

The total release of the loaded BSA was 17.8% and 85.2% in simulated gastric fluid (pH 1.2) and intestinal fluid (pH 7.4), respectively, as shown in Fig. 9. The higher release of BSA in simulated intestinal fluid was attributed to pH sensitivity of the prepared

CMC/HEC hydrogels. The significant differences in BSA release between simulated gastric fluid and intestinal fluid implied a potential for controlled release of oral medication and a desirable protection for delivery in the stomach before being transferred to the intestines.

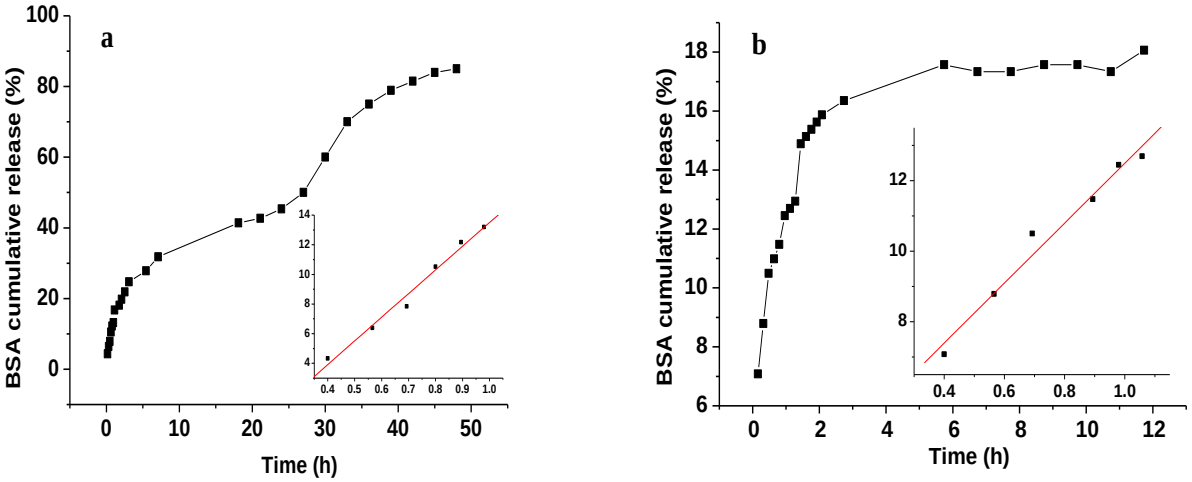


Fig. 9. Cumulative release profiles of BSA from a) Gel-1 in PBS buffer (pH 7.4) and b) HCl (pH 1.2)

CONCLUSIONS

1. A novel hydrogel was successfully prepared from two cellulose derivatives, CMC and HEC, using APS as an initiator and MBA as a crosslinking agent. The structure and morphology of the crosslinked hydrogels was characterized using FT-IR, XRD, and SEM.
2. The sensitivity, reversibility, and the on-off switching behavior of the hydrogels were also confirmed at different pHs and ionic strengths, indicating potential application as pH- and ionic strength-responsive hydrogels.
3. The significantly different release of BSA in simulated gastric fluid with pH 1.2 (17.8%) and intestinal fluid with pH 7.4 (85.2%) suggested the desirable protection in stomach before being transferred to intestine and the potentially controlled release of oral medication.

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REFERENCES CITED

Akar, E., Altınışık, A., and Seki, Y. (2012). "Preparation of pH- and ionic-strength responsive biodegradable fumaric acid crosslinked carboxymethyl cellulose," *Carbohydr. Polym.* 90(4), 1634-1641. DOI:10.1016/j.carbpol.2012.07.043

Anbergen, U., and Oppermann, W. (1990). "Elasticity and swelling behaviour of chemically crosslinked cellulose ethers in aqueous systems," *Polymer* 31(10), 1854-1858. DOI:10.1016/0032-3861(90)90006-K

Bakass, M., Mokhlisse, A., and Lallemant, M. (2002). "Absorption and desorption of liquid water by a superabsorbent polymer: Effect of polymer in the drying of the soil and the quality of certain plants," *J. Appl. Polym. Sci*. 83(2), 234-243. DOI:10.1002/app.2239

Cadée, J. A., de Groot, C. J., Jiskoot, W., den Otter, W., and Hennink, W. E. (2002). "Release of recombinant human interleukin-2 from dextran-based hydrogels," *J. Controlled Release* 78(1-3), 1-13. DOI:10.1016/S0168-3659(01)00483-7

Chen, J., and Zhao, Y. (2000). "Relationship between water absorbency and reaction conditions in aqueous solution polymerization of polyacrylate superabsorbents," *J. Appl. Polym. Sci*. 75(6), 808-814. DOI:10.1002/(sici)1097-4628(20000207)75:6<808::aid-app10>3.0.co;2-3

Chen, L., Tian, Z., and Du, Y. (2004a). "Synthesis and pH sensitivity of carboxymethyl chitosan-based polyampholyte hydrogels for protein carrier matrices," *Biomaterials* 25(17), 3725-3732. DOI:10.1016/j.biomaterials.2003.09.100

Chen, M. J., Chen, C. Y., Liu, C. F., and Sun, R. C. (2013). "Homogeneous modification of sugarcane bagasse with maleic anhydride in 1-butyl-3-methylimidazolium chloride without any catalysts," *Ind. Crops Prod*. 46, 380-385. DOI:10.1016/j.indcrop.2013.02.023

Chen, S.-C., Wu, Y.-C., Mi, F.-L., Lin, Y.-H., Yu, L.-C., and Sung, H.-W. (2004b). "A novel pH-sensitive hydrogel composed of N,O-carboxymethyl chitosan and alginate cross-linked by genipin for protein drug delivery," *J. Controlled Release* 96(2), 285-300. DOI:10.1016/j.jconrel.2004.02.002

Coviello, T., Matricardi, P., Marianecci, C., and Alhaique, F. (2007). "Polysaccharide hydrogels for modified release formulations," *J. Controlled Release* 119(1), 5-24. DOI:10.1016/j.jconrel.2007.01.004

Gorgieva, S., and Kokol, V. (2011). "Synthesis and application of new temperature-responsive hydrogels based on carboxymethyl and hydroxyethyl cellulose derivatives for the functional finishing of cotton knitwear," *Carbohydr. Polym*. 85(3), 664-673. DOI:10.1016/j.carbpol.2011.03.037

Hoffman, A. S. (2002). "Hydrogels for biomedical applications," *Adv. Drug Delivery Rev*. 54(1), 3-12. DOI:10.1016/S0169-409X(01)00239-3

Huang, H., He, P., Hu, N., and Zeng, Y. (2003). "Electrochemical and electrocatalytic properties of myoglobin and hemoglobin incorporated in carboxymethyl cellulose films," *Bioelectrochemistry* 61(1-2), 29-38. DOI:10.1016/S1567-5394(03)00057-4

Jao, W.-C., Chena, H.-C., Lin, C.-H., and Yang, M.-C. (2009). "The controlled release behavior and pH- and thermo-sensitivity of alginate/poly(vinyl alcohol) blended hydrogels," *Polym. Adv. Technol*. 20, 680-688. DOI:10.1002/pat.1318

Kabiri, K., Zohuriaan-Mehr, M. J., Mirzadeh, H., and Kheirabadi, M. (2010). "Solvent-, ion- and pH-specific swelling of poly(2-acrylamido-2-methylpropane sulfonic acid)

superabsorbing gels," *Journal of Polymer Research* 17(2), 203-212. DOI:10.1007/s10965-009-9306-7

Krul, L. P., Nareiko, E. I., Matusevich, Y. I., Yakimtsova, L. B., Matusevich, V., and Seeber, W. (2000). "Water super absorbents based on copolymers of acrylamide with sodium acrylate," *Polym. Bull*. 45(2), 159-165. DOI:10.1007/pl00006832

Kumar, P. T. S., Abhilash, S., Manzoor, K., Nair, S. V., Tamura, H., and Jayakumar, R. (2010). "Preparation and characterization of novel β-chitin/nanosilver composite scaffolds for wound dressing applications," *Carbohydr. Polym.* 80(3), 761-767. DOI:10.1016/j.carbpol.2009.12.024

Lan, W., Liu, C. F., Yue, F. X., Sun, R. C., and Kennedy, J. F. (2011). "Ultrasound-assisted dissolution of cellulose in ionic liquid," *Carbohydr. Polym*. 86(2), 672-677. DOI:10.1016/j.carbpol.2011.05.013

Liang, H.-F., Hong, M.-H., Ho, R.-M., Chung, C.-K., Lin, Y.-H., Chen, C.-H., and Sung, H.-W. (2004). "Novel method using a temperature-sensitive polymer (methylcellulose) to thermally gel aqueous alginate as a pH-sensitive hydrogel," *Biomacromolecules* 5(5), 1917-1925. DOI:10.1021/bm049813w

Madsen, F., and Peppas, N. A. (1999). "Complexation graft copolymer networks: Swelling properties, calcium binding and proteolytic enzyme inhibition," *Biomaterials* 20(18), 1701-1708. DOI:10.1016/S0142-9612(99)00071-X

Mahdavinia, G. R., Pourjavadi, A., Hosseinzadeh, H., and Zohuriaan, M. J. (2004). "Modified chitosan 4. Superabsorbent hydrogels from poly(acrylic acid-co-acrylamide) grafted chitosan with salt- and pH-responsiveness properties," *Eur. Polym. J*. 40(7), 1399-1407. DOI:10.1016/j.europolymj.2004.01.039

Marsano, E., Gagliardi, S., Ghioni, F., and Bianchi, E. (2000). "Behaviour of gels based on (hydroxypropyl) cellulose methacrylate," *Polymer* 41(21), 7691-7698. DOI:10.1016/S0032-3861(00)00142-7

Peppas, N. A., Bures, P., Leobandung, W., and Ichikawa, H. (2000). "Hydrogels in pharmaceutical formulations," *Eur. J. Pharm. Biopharm.* 50(1), 27-46. DOI:10.1016/s0939-6411(00)00090-4

Pourjavadi, A., Barzegar, S., and Mahdavinia, G. R. (2006). "MBA-crosslinked Na-Alg/CMC as a smart full-polysaccharide superabsorbent hydrogels," *Carbohydr. Polym*. 66(3), 386-395. DOI:10.1016/j.carbpol.2006.03.013

Ritger, P. L., and Peppas, N. A. (1987). "A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs," *J. Controlled Release* 5(1), 23-36. DOI:10.1016/0168-3659(87)90034-4

Sannino, A., Demitri, C., and Madaghiele, M. (2009). "Biodegradable cellulose-based hydrogels: Design and applications," *Materials* 2(2), 353-373. DOI:10.3390/ma2020353

Sannino, A., Pappadà, S., Madaghiele, M., Maffezzoli, A., Ambrosio, L., and Nicolais, L. (2005). "Crosslinking of cellulose derivatives and hyaluronic acid with water-soluble carbodiimide," *Polymer* 46(25), 11206-11212. DOI:10.1016/j.polymer.2005.10.048

Taleb, M. F. A., El-Mohdy, H. L. A., and El-Rehim, H. A. A. (2009). "Radiation preparation of PVA/CMC copolymers and their application in removal of dyes," *J. Hazard. Mater*. 168(1), 68-75. DOI:10.1016/j.jhazmat.2009.02.001

Tomšič, B., Simončič, B., Orel, B., Vilčnik, A., and Spreizer, H. (2007). "Biodegradability of cellulose fabric modified by imidazolidinone," *Carbohydr. Polym*. 69(3) 478-488. DOI:10.1016/j.carbpol.2007.01.003

Wang, W., Wang, J., Kang, Y., and Wang, A. (2011). "Synthesis, swelling and responsive properties of a new composite hydrogel based on hydroxyethyl cellulose and medicinal stone," *Compos. Part B- Eng*. 42(4), 809-818. DOI:10.1016/j.compositesb.2011.01.018

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