Preparation and Properties of Physically Crosslinked Sodium Carboxymethylcellulose/Poly(vinyl alcohol) Complex Hydrogels

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ABSTRACT: A series of physically crosslinked complex hydrogels of poly(vinyl alcohol) (PVA) and sodium carboxymethylcellulose (CMC) were prepared via physical mixing and a freeze/thaw technique. The morphology of the CMC/PVA complex gels was analyzed with differential scanning calorimetry and wide-angle X-ray diffraction. It was found that the crystallinity and melting temperature of the complex gels decreased, whereas the glass-transition temperature increased, with an increase in the content of CMC. The reswelling of the complex gels was pH-responsive and relied on the content of CMC and the freeze/thaw cycles. A network structure model of the complex gel was presented. PVA crystalline regions served as physical crosslinks; the interaction between CMC and PVA resulted in intramolecular entanglements. It was also found that the model drug hemoglobin was released completely from the complex hydrogels in 4 h, and its release rate increased with an increase in the content of CMC. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 1568–1572, 2008

Key words: drug delivery systems; hydrogels; stimuli-responsive polymers; structure-property relations; water-soluble polymers

INTRODUCTION

Biodegradable hydrogels are important scaffolds for tissue engineering and are widely used as matrices for drug delivery systems.[1–4] It is well known that sodium carboxymethylcellulose (CMC) is nontoxic, biocompatible, biodegradable, and abundant.[5–8] CMC-based hydrogels are mainly prepared by chemical crosslinking or radiation-induced crosslinking.[9–11] Poly(vinyl alcohol) (PVA) is water-soluble and biocompatible.[12] Consequently, much attention has been paid to the applications of PVA hydrogels in biomedical and pharmaceutical fields.[13] Both chemical and physical crosslinking can be used to form PVA hydrogels.[14] The freeze/thaw technique is a mild physical process in the sense that the use of crosslinking agents and organic solvents can be avoided, and this is especially useful for preparing PVA hydrogels.[15–17]

Unfortunately, the reswelling property of physically crosslinked PVA gels from the dry state is quite poor,[18] and it is inert to the stimuli of environmental changes. One strategy for preparing intelligent hydrogels and taking advantage of the freeze/thaw process is mixing functional components with PVA. CMC is an ionic polyelectrolyte that contains carboxyl groups and exhibits pH sensitivity.[19] Thus, it can be anticipated that a mixture of CMC and PVA probably will present the advantages of both components.

The aim of this study was to prepare physically crosslinked CMC/PVA complex hydrogels of different ratios by the freeze/thaw technique. Then, the effects of the compositions on the morphology and pH-responsive swelling properties of the complex hydrogels were investigated. A preliminary study of the complex used as a drug release carrier for oral administration was also performed.

EXPERIMENTAL

Materials

PVA (with a degree of hydrolysis of 99% and number-average molecular weight of 2000) was kindly donated by Fujian Chemical Fiber and Chemical Factory (Yonqan, Fujian, China). Hemoglobin (Hb) was purchased from Shanghai Kejie Biotechnology Ltd. Co. (Shanghai, China). CMC (300–800 mPa s) and hydrochloric acid (HCl) were analytical-grade reagents; they were purchased from Shanghai Chemical Agents, Ltd. Co. (Shanghai, China) and used as received.

Preparation of CMC/PVA complex hydrogels

A 1-g mixture of PVA and CMC in different ratios was dissolved in 15 mL of distilled water. The

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solution was cooled to room temperature and poured into molds. Then, it was subjected to two repeated freeze/thaw cycles, 10 h at −16°C and 2 h at 25°C. The obtained hydrogels were dried under vacuum at 37°C to a constant weight.

Preparation of CMC/PVA/Hb complex hydrogels

PVA (0.5 g) and CMC (0.5 g) were dissolved in 10 mL of distilled water. Hb (0.1 g) was added under stirring to form a homogeneous solution. The solution was transferred into molds and subjected to two repeated freeze/thaw cycles, 10 h at −16°C and 2 h at 25°C. The obtained hydrogels were dried under vacuum at 37°C to a constant weight.

X-ray measurements

X-ray diffraction profiles of dried CMC/PVA complex gel powder were collected with a Bruker (Bruker, AXS Inc., Madison, WI) D8-Advanced diffractometer, which used nickel-filtered Cu Kα radiation (λ = 0.15406 nm) and scanned from 2 to 60° at a scan speed of 3°/min.

Thermal analysis

The differential scanning calorimetry (DSC) analyses were carried out with a TA Instruments (New Castle, DE) SDT 2960 simultaneous DSC/thermogravimetric analysis analyzer. CMC/PVA complex gels were heated from 0 to 250°C at a heating rate of 20°C/min, kept 5 min at 250°C, cooled to 0°C at the same rate, and kept 5 min at 0°C. Then, the samples were heated from 0 to 250°C at the same rate to record DSC curves.

Reswelling of the CMC/PVA complex gel

Dried CMC/PVA complex gels (0.040 g) were placed in vials that contained 3 mL of HCl (0.1*M*, pH 1.2) and maintained at 37°C for 2 h. Then, the samples were removed and immersed in phosphate-buffered saline (PBS; 0.1*M*, pH 7.4) at the same temperature. At timed intervals, the samples were removed, the surface liquid of the samples was blotted with filter paper, and the samples were weighed. The swelling ratio (SR) of the samples was calculated from the weight of the sample at equilibrium swelling (W_e) and the weight of the dried sample (W_d): $SR = (W_e - W_d)/W_d$. An average of three measurements was taken.

In vitro release of CMC/PVA/Hb complex gels

Hb-loaded CMC/PVA complex gels (0.040 g) were placed in vials that contained 10 mL of PBS (0.1*M*, pH 7.4) and maintained at 37°C. At timed intervals, a 3-mL sample of the liquid was removed to be analyzed with a Shimadzu (Shimadzu Instruments (Suzhou) Co., Ltd., Suzhou, China) UV2450 ultraviolet–visible spectrophotometer at 405.5 nm, and 3 mL of fresh PBS was added in the meantime.

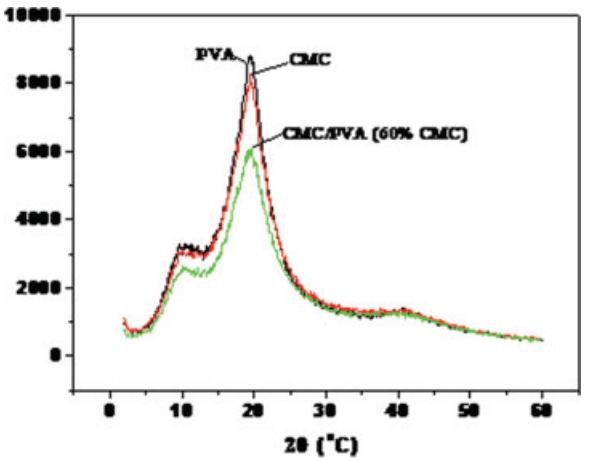

Figure 1 WAXD profiles of CMC powder, dried PVA gel, and dried CMC/PVA (60% CMC) gel. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

RESULTS AND DISCUSSION

Formation and morphology of CMC/PVA complex hydrogels

CMC and PVA in different ratios can be mixed homogeneously in an aqueous solution. After being subjected to two freeze/thaw cycles, the solution can be transferred into soft and elastic CMC/PVA hydrogels. No evident phase separation in the hydrogels can be found, and this can be attributed to the interaction between the components.

Wide-angle X-ray diffraction (WAXD) and DSC analysis have been used to investigate the morphology of the complex hydrogels. There are two peaks around 10 and 19.6°on the WAXD patterns of both PVA and CMC. The peaks of CMC/PVA appear at the same angles, but they are weakened (Fig. 1). The WAXD analysis results indicate that the components and their blend are semicrystalline. However, the hydrogen bonds that form between the carboxylic groups of CMC and hydroxyl groups of PVA hinder the crystallization of the components. As a result, the crystallinity of CMC/PVA is lower than that of CMC or PVA.

DSC analysis shows that the melting points of CMC/PVA complex hydrogels decrease with an increase in the content of CMC, and the melting peaks are widened (Fig. 2). The melting points of the gels are 212.1°C for 0% CMC, 213.1°C for 30% CMC, 211.1°C for 40% CMC, 192.7°C for 50% CMC, and 174.77°C for 60% CMC. Evidently, the interaction between CMC and PVA weakens the interaction between PVA chains and hinders the crystallization

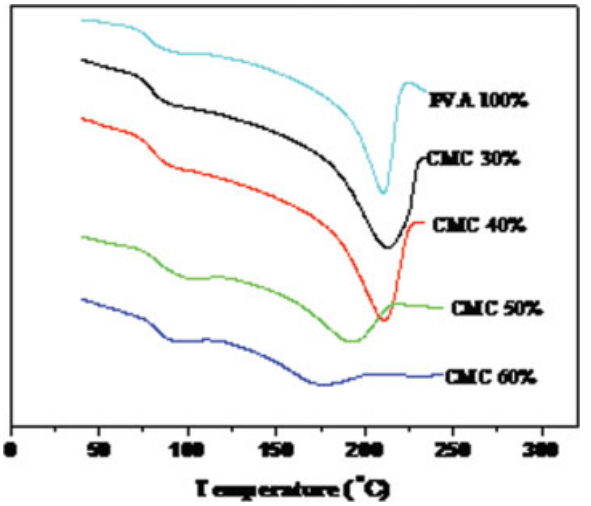

Figure 2 DSC curves of CMC/PVA complex hydrogels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of PVA. The crystallinity of CMC/PVA can be calculated from the DSC curves as follows: crystallinity = $100 \times \Delta H_m/150$.[20] The degree of crystallinity of a PVA gel was determined as the ratio between the heat of fusion, ΔH_m, of the PVA gel sample and the thermodynamic enthalpy of melting of a 100% crystalline PVA, ΔH_{m0} (150 J/g). The crystallinity of CMC/PVA decreases from 25.6 to 4.9% as the CMC content increases from 30 to 60%. In other words, the crystallinity of the blends depends on the composition, and this is consistent with the WAXD analysis results and suggests that the components are compatible.[21] In addition, the glass-transition temperature of the complex gels increases from 78.5 to 82.3°C with the CMC content increasing from 0 to 60%. Increasing the content of CMC will enhance the interaction between CMC and PVA, and this renders PVA chains more rigid and increases the glass-transition temperature of the gel.

According to the WAXD and DSC analysis results, it can be assumed that the formation mechanism of physically crosslinked CMC/PVA hydrogels is the same as that of PVA hydrogels.

pH-responsive swelling of CMC/PVA complex gels

There are a lot of carboxylic groups on CMC chains. Thus, it can be expected that the complex gel will behave in a pH-sensitive fashion. As shown in Figure 3, SR of the CMC/PVA gel is much greater than that of PVA and relies on the pH value of the medium. After immersion in HCl for 2 h, SR of PVA reaches the maximum and stays the same when it is transferred into PBS. In other words, only the crosslinked structure affects the swelling of PVA. It is attributed to the incorporation of CMC that the complex gels show pH sensitivity. CMC/PVA gels swell quickly in the first 30 min and then slow down when they are immersed in HCl, but the swelling rate will increase evidently when the gels are transferred into PBS. The higher the CMC content is, the greater the pH sensitivity will be (Fig. 3). In addition, the swelling of the complex gel is also affected by the physical crosslinking degree. CMC/PVA gels can be regarded as semi-interpenetrating polymer networks. Increasing freeze/thaw cycles will enhance the crosslinking degree, CMC chains will be firmly anchored in the gel, and fewer CMC molecules will be diffused into the medium when the samples are immersed in HCl or PBS. As a result, more water will be held in the network, and SR will be increased. The maximum SR values of CMC/PVA gels obtained by two and eight freeze/thaw cycles are 1.76 and 2.52 in HCl for 2 h and 6.17 and 8.07 in PBS for 12 h, respectively (Fig. 4).

The swelling behavior of CMC/PVA gels can be explained as shown in Figure 5. Hydrogen bonds

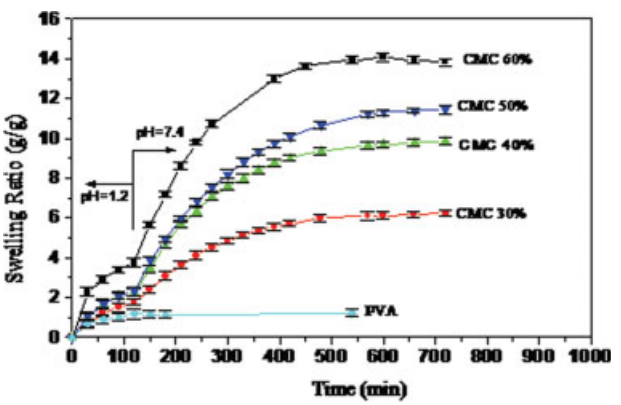

Figure 3 pH-responsive swelling of CMC/PVA complex gels in HCl (0.1*M*, pH 1.2) and PBS (0.1*M*, pH 7.4). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

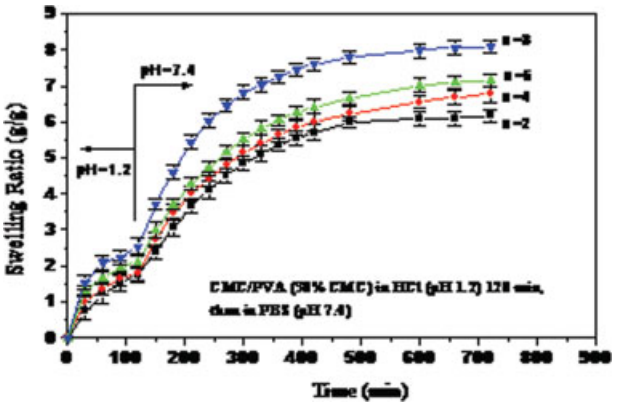

Figure 4 Effect of freeze/thaw cycles on the pH-responsive swelling of CMC/PVA complex gels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

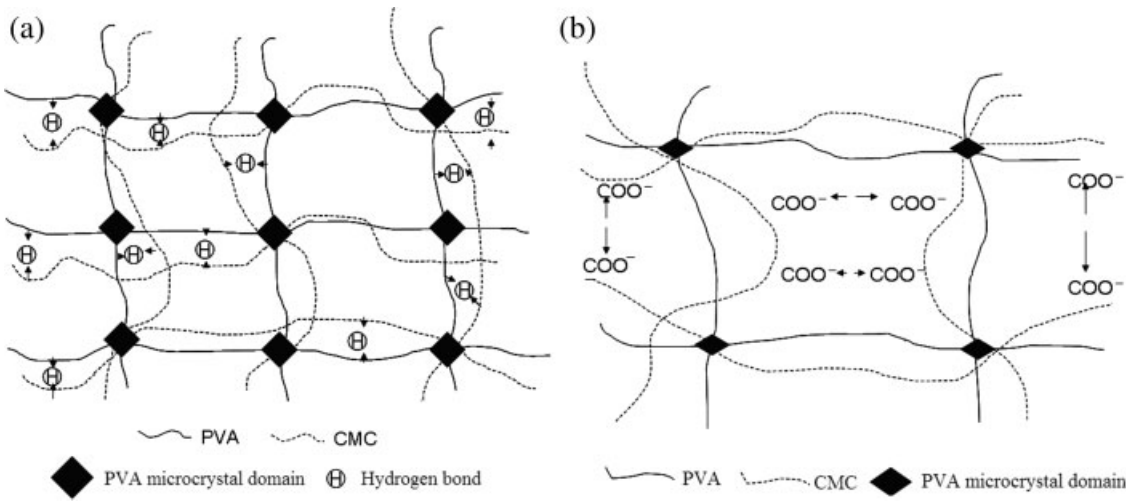

Figure 5 Network models of CMC/PVA complex gels (a) in HCl (0.1*M*, pH 1.2) and (b) in PBS (0.1*M*, pH 7.4).

are formed [Fig. 5(a)], and the attraction between chains reduces SR when the gels are immersed in HCl. Some of the carboxylic groups become ionic [Fig. 5(b)], and the repelling effect increases SR when the gels are immersed in PBS.[22]

In vitro release of CMC/PVA/Hb complex gels

After the soaking of a dried CMC/PVA/Hb gel in PBS for 2 h, the UV absorption peak of the solution still appears at 405.5 nm, and this indicates that Hb remains active. Thus, Hb can be used as a model drug to examine the release behavior of the complex gel. No burst release is found, and this suggests that Hb is well entrapped in the complex gel. In addition, Hb will be released completely in 40 h, and its release rate depends on the composition of the complex gel (Fig. 6). As mentioned previously, SR increases with the content of CMC, which can be used to modulate the release rate of the model drug.

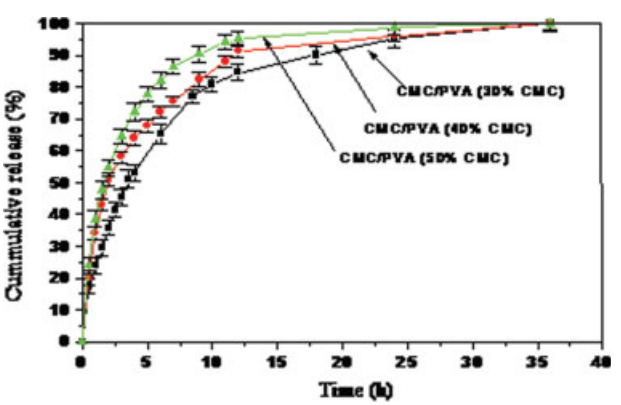

Figure 6 Release behavior of CMC/PVA/Hb complex gels in PBS (0.1*M*, pH 7.4) at 37°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

On the contrary, the reswelling capacity of the dried PVA gel is so poor that it is difficult for Hb to diffuse out. No UV absorption at 405.5 nm is found after the soaking of the dried PVA/Hb gel in PBS for 24 h at 37°C.

The UV absorption peak of the solution deviates from the original at 405.5 nm just after the immersion of the dried CMC/PVA/Hb gel in HCl for 30 min. In other words, the structure of Hb has changed. Now that Hb is an acid-sensitive protein, protein determination with a protein–dye binding assay[23] is unavailable. Thus, the process[24] that is usually used to examine the pH-responsive release behavior of a protein-loaded matrix by immersion in an acid medium for some time and then in a higher pH is doubtful. To find a solution, it is necessary to well investigate the *in vitro* release behaviors of different pH-responsive matrices containing a series of model drugs in various media.

CONCLUSIONS

Physically crosslinked CMC/PVA complex hydrogels of different compositions have been prepared under mild conditions. The morphology analysis reveals that the crystalline microdomains of PVA serve as crosslinks of the complex hydrogels. It is assumed that the CMC chains are entangled with PVA chains via hydrogen bonds and that the gels are semi-interpenetrating polymer networks. Because of the incorporation of carboxylic groups, the swelling property of the complex hydrogel behaves in a pH-sensitive fashion. However, the pH-responsive release of a protein model drug (Hb) cannot be determined by the classical method because the

structure of the protein will be changed once it comes up against acid. As CMC and PVA are water-soluble and biocompatible, a CMC/PVA complex hydrogel could be a potential candidate for pH-responsive drug release carrier.

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