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Carboxymethyl cellulose/polyethylene glycol superabsorbent hydrogel crosslinked with citric acid

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Abstract Carboxymethyl cellulose/poly(ethylene glycol) (CMC/PEG) hydrogels crosslinked with citric acid (CA) are synthesized to evaluate the effect of CMC molecular weight (Mw), PEG and CA concentration on the optical property, swelling rate (SR), degradation rate (DR), and cytotoxicity and cell proliferation of hydrogels. For crosslinked CMC/PEG hydrogels, the FT-IR peak intensity associated with hydroxyl groups decreases due to PEG intercalation (esterification crosslinking) between CMC chains in a similar manner as the concentration of CA crosslinker increases. Crosslinked CMC (Mw = 90,000)/PEG hydrogels with 10 % CA dissolve regardless of PEG content. However, the SR of the CMC (Mw = 250,000)/PEG hydrogels decrease from 4923 % to 168 % with increasing PEG and CA concentrations from 0 to 20 % and from 0 to 25 %, respectively. As the Mw of CMC increases, the DR of the hydrogel is greatly improved. CMC (Mw = 250,000)/PEG10 hydrogels with 10 % CA exhibit the optimum properties of high absorbing capacity (3,200 %) with moderate DR (54 %), stiffness (1.39 ± 0.19 GPa), and cell viability (94.8 ± 1.3 %). CA-crosslinked CMC/PEG hydrogels are highly suitable for wound dressing or personal care applications due to their non-toxicity, good cell proliferation, SR, and mechanical properties.

Key words Carboxymethyl cellulose (CMC), Polyethylene glycol, Citric acid, Crosslink, Superabsorbent hydrogel

1. Introduction

Because of their excellent healing properties, hydrogels have been widely used as candidates for the treatment of bad injuries such as accidents, burns, trauma, and diabetic ulcers [1-12]. Recently, the scope of its application is expanding to personal care (diapers and napkins), pharmaceuticals (drug delivery system), and agriculture (water storage and controlled release) [2-6]. Polymer blending of natural and synthetic polymers is one of the most effective methods to provide novel hydrogel dressings with properties tailored to specific applications. Among various candidates for natural polymers, sodium carboxymethyl cellulose (CMC) and its derivatives are abundant natural raw materials and are widely used for the production of hydrogels and composite materials in various fields such as wound dressing, personal care, and drug delivery, because of low cost [2]. CMC is an ionic cellulose ether with multiple carboxyl groups and a polysaccharide in a double helix structure [1-9].

Superabsorbent hydrogels (SAHs) based on CMC and its derivatives are attracting great attention due to their ability to absorb large amounts of water, saline or physiological solutions [2,10]. SAH is a crosslinked hydrophilic polymer that can absorb large amounts of water through the swelling process but is insoluble in water [7]. However, the low water-solubility of polymer precursors and the intrinsic cytotoxicity of chemical crosslinker limit the widespread clinical application of wound dressings due to the presence of unreacted crosslinking agents. Attempts to overcome the aforementioned shortcomings include the formation of chemically modified CMC derivatives to improve biocompatibility and water solubility using environmentally friendly crosslinkers of citric acid (CA) [2,11]. Polyethylene glycol (PEG) is incorporated into the CMC derivatives to promote water solubility of hydrogels [2-6]. PEG is an amphiphilic polyether that is dissolved in water and many organic solvents [3-6,13,14]. It also has the potential to inhibit surface binding of proteins, platelets, and cells for blood compatibility [15]. The shortcomings of PEG, such as lack of cell affinity and surface cell recognition sites, can be solved by enhancing cell-scaffold interactions by mixing with CMC crosslinked with CA. CMC/PEG hydrogels were obtained by esterification crosslinking mechanism [2-4,8]. After absorbing water, the hydrogels swell and stay for a long time [16]. In this study, superabsorbent CMC/PEG hydrogels containing CMCs of two dif-

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ferent MWs (90,000 and 250,000) are prepared by carboxymethyl-functionalization and chemical crosslinking with CA. The objective of this study is to synthesize a biocompatible CMC/PEG hydrogel crosslinked with CA to evaluate the effect of CMC Mw, PEG and CA concentration on the optical property, SR, DR, and cytotoxicity and cell proliferation of hydrogels.

2. Materials and Methods

2.1. Materials

CMC ($[C_6H_7O_2(OH)_2OCH_2COONa]_n$, Mw 90,000, Mw 250,000), PEG solution ($[H(OCH_2CH_2)_nOH]$, Mw 2,000), CA (≥ 99.5 %) were purchased from Sigma-Aldrich, USA and used as received. Distilled (DI) water with a resistivity of 18.4 MΩ·cm was used as the solvent throughout the experiment.

2.2. Synthesis of hydrogel

2 % w/v CMC and CMC/PEG solutions containing CMC/PEG weight ratio ranging from 10/0 to 8/2 were prepared by stirring in DI water. CA, a crosslinking agent, was dissolved in the CMC and CMC/PEG precursor solutions at intervals of 5 wt% in the range of 10 to 25 wt%, and homogenized for 20 min. 10 mL of the precursor solution was cast into a plastic mold with a diameter of 50 mm. After drying overnight at 40°C, the sample was slowly evaporated for 24 h at 80°C for crosslinking.

2.3. Characterization

Fourier transform infrared spectroscopy (FT-IR, Spectrum Two, PerkinElmer, UK) was used to investigate the chemical structure of the hydrogel [14,15,17-19]. Differential scanning calorimetry (DSC) and thermogravimetric (TG, STAS 409C/31F, Netzsch, Germany) studies were done at temperatures up to 400°C with a heating rate of 10°C/min. The elastic modulus of a CMC/PEG hydrogel with a size of 1.5 × 3 cm^2 was examined at room temperature using an Instron 5564 with a 1000 N force cell at a loading rate of 10 mm/min [15,19].

2.4. Swelling and degradation rate

Prior to the experiment, the hydrogel (W_d, dried mass) was initially gauged. The hydrogel with a dimension of 10 × 10 mm^2 is immersed in distilled (DI) water for 1 h. The specimen was removed and gently wiped with gauze to remove excess liquid on the sample surface (W_s, swollen mass). The specimens are then dried at 40°C until the mass has stabilized and the final weight is measured (W_f, final mass). The swelling rate (S) is determined using the equation, $S(\%) = \frac{(W_s - W_d)}{W_d} \times 100$, where W_s and W_d represent the weight of the swollen hydrogel and the weight of the dried hydrogel, respectively [1,3,4]. The degradation rate (D) is examined by the equation, $D(\%) = \frac{(W_d - W_f)}{W_d} \times 100$.

2.5. Cytotoxicity and cell proliferation

The extract test method was performed on CMC/PEG hydrogel to evaluate their cytotoxic behavior based on the International Organization for Standardization (ISO 10993-5) [13-15,17-21]. Cell counting kit-8 (CCK-8, Dojindo Molecular Technologies, Inc., Japan) was used for cell proliferation assay. Detailed experimental procedure is explained elsewhere [1,3,4,19].

2.6. Statistical analysis

All experiments were carried out in triplicate. Statistical analysis was done using IBM SPSS software, version 23.0 for windows (IBM Korea Inc., Seoul, Korea). The results obtained were assayed by one-way analysis of variance (ANOVA) followed by Tukey's test [21-23]. Test values were given as the mean ± standard deviation, and $p < 0.05$ was considered statistically significant.

3. Results and Discussion

As the PEG content increased from 0 % to 20 %, the

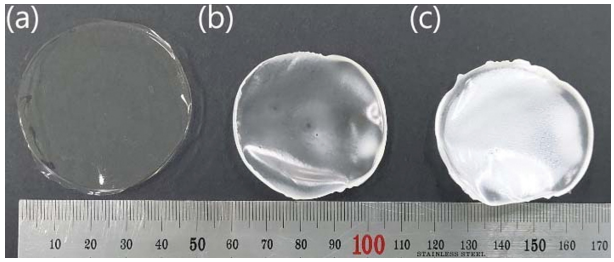

Fig. 1. Optical photographs of CMC/PEG hydrogels as a function of PEG concentration: (a) 0 %, (b) 10 %, and (c) 20 %, respectively. Note that the CA concentration was fixed at 10 wt%.

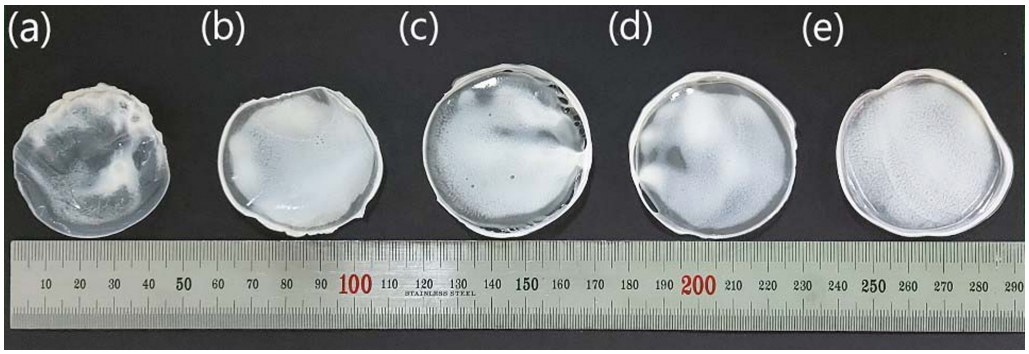

Fig. 2. Optical photographs of CMC/PEG20 blends as a function of CA concentration: (a) 0 %, (b) 10 %, (c) 15 %, (d) 20 %, and (e) 25 %, respectively.

optical transparency of the CMC/PEG hydrogel membrane deteriorated dramatically, as depicted in Fig. 1. Adding more PEG with the help of CA (10 wt%) showed a white opaque structure due to chemical crosslinking between CMC and PEG. The same results were observed for CMC/PEG20 hydrogel membranes with higher CA concentrations. When the CA content was increased from 0 % to 25 %, the translucency of the CMC/PEG20 film was enhanced due to the higher crosslinking network containing PEG and CMC functional groups, as displayed in Fig. 2 [2].

FT-IR spectra of CMC (Mw = 250,000)/PEG(10 %) hydrogels with different amount of CA (0 to 25 %) are shown in Fig. 3(a). CMC is a polymer with multiple carboxyl groups (-COOH). C=O, C-O, C-H, and O-H are partially found in CMC, which occurs due to the existence of numerous hydroxyl and carboxylic groups [1-4]. Carboxylates (-COO, 1586 cm^{-1}, 1413 cm^{-1}, and 1322 cm^{-1}) and carboxylic groups (-COOH, 1720 cm^{-1} and 1244 cm^{-1}) coexist in the CMC hydrogel due to the substitution of Na^{+} by H^{+} in the CMC polymer chain during the acidification catalyzed by CA [1]. The peak located at 1586 cm^{-1} is related to the contribution of the carboxymethyl groups (-CH_2-COOH) inserted into the cellulose polymer chain. The slight increase in peak intensity at 1720 cm^{-1} with increasing CA content is attributed to the construction of ester bonds [2]. The spectra of CMC/PEG hydrogel exhibit main peaks at 3000~3700 cm^{-1} and 2800~3000 cm^{-1} due to the -OH groups and C-H stretching common to both CMC and PEG, respectively [1,2]. The decrease in the intensity of the O-H peak present at 3000~3700 cm^{-1} is due to the consumption of hydroxyl groups in CMC as a result of the chemical crosslinking with CA to form ester bonds [2]. For the PEG polymer, bands associated with C-O (alcohol) and C-O-C were detected at 1244 cm^{-1} and 1100 cm^{-1}, respectively [2-6,13,15]. For the crosslinked CMC/PEG hydrogel, the PEG peak associated with crystallinity at 1345 cm^{-1} disappeared and other band intensities of PEG also decreased. C-O vibrations of primary and secondary alcohols were observed at 1053 cm^{-1} and 1014 cm^{-1}, respectively. β-1,4-glycosidic bonds between glucose units were observed at 889 cm^{-1}. The peak intensity associated with hydroxyl groups decreased dramatically due to PEG intercalation between the CMC chains in a similar way

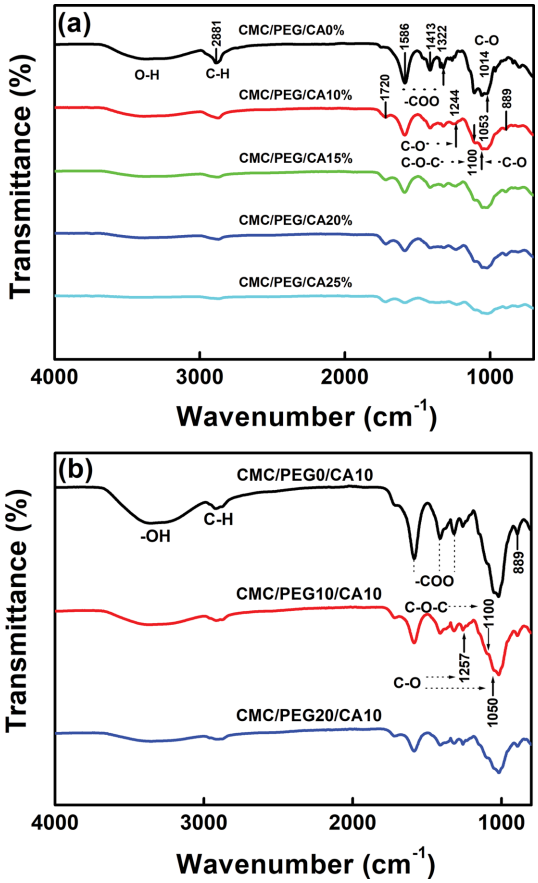

Fig. 3. FT-IR spectra of (a) CMC (Mw = 250,000)/PEG(10 %) hydrogels with different amount of CA (0 to 25 %) and (b) CMC/CA10 hydrogels containing different PEG concentration.

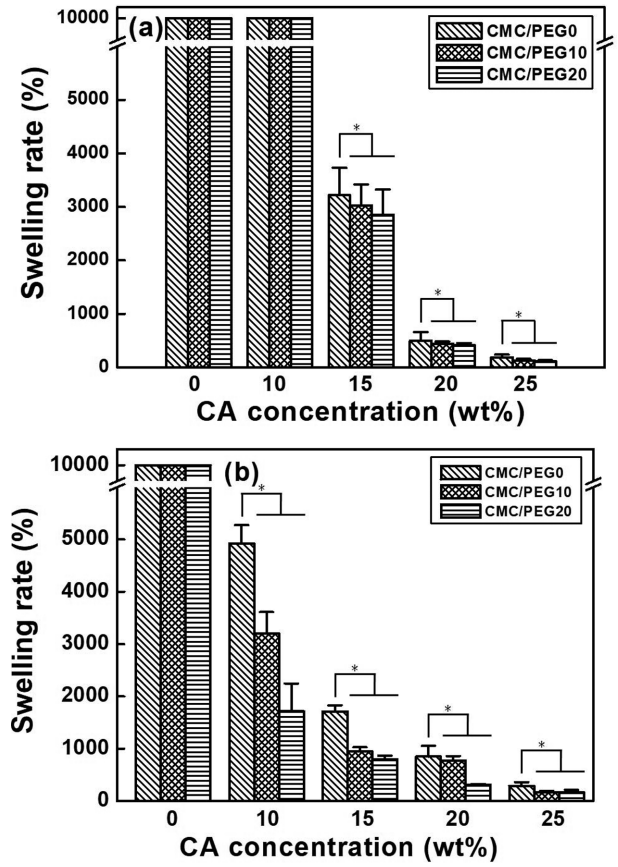

Fig. 4. The variation of swelling rates of (a) CMC (Mw = 90,000)/PEG and (b) CMC (Mw = 250,000)/PEG hydrogels with CA concentration ranging from 0 % to 25 %. Note that PEG concentration was fixed at 10 wt%. Results are expressed as mean ± standard deviation (* $p < 0.05$).

as the concentration of CA crosslinker increased with increasing PEG concentration from 0 % to 20 %, as shown in Fig. 3(b) [2-6].

The swelling rates (SR) of CMC (Mw = 90,000 and 250,000)/PEG hydrogels as a function of CA concentration are displayed in Fig. 4. SR is determined by measuring the change in weight over time after soaking it in DI water for 1 h at room temperature. Uncrosslinked CMC/PEG hydrogel completely dissolved regardless of PEG content and CMC molecular weight. As shown in Fig. 4(a), crosslinked CMC (Mw = 90,000)/PEG hydrogels with CA concentration of 10 wt% also dissolved regardless of PEG content. However, the SR of the CMC/PEG20 hydrogel decreased dramatically from 1860 % to 116 % as the CA concentration increased from 15 % to 25 %. The dramatic decrease in SR is likely due to the presence of covalent bonds linking functional groups in the polymer chain and increased shrinkage of the CMC/PEG membrane [2]. The increase in crosslinker concentration and the low Mw of CMC are attributed to the dramatic decrease in SR of CMC/PEG hydrogel. The reason is that the number of covalent bonds bridging the functional groups in the polymer chain is proportional to the Mw of the CMC. A similar trend was observed for CMC/PEG hydrogels when the Mw of CMC was increased from 90,000 to 250,000. Uncrosslinked CMC (Mw = 250,000)/PEG hydrogel completely dissolved regardless of PEG content. When the PEG and CA concentrations were raised from 0 to 20 % and from 0 to 25 %, respectively, the SR decreased dramatically from 4923 % to 168 %. With the help of CA crosslinker, the SR was significantly reduced by adding PEG to CMC due to the higher crosslinking network containing CMC and PEG functional groups [2]. The introduction of PEG and CA is ascribed to the stiffness of the hydrogel due to the densification of the hydrogel network. The elastic modulus of the skin was reported to average 0.4 GPa as measured by an atomic force microscope using force indentation measurements [24]. The elastic modulus of the CMC (Mw = 250,000) hydrogel was more than doubled from 0.08 GPa to 1.2 GPa through the addition of 10 % PEG to the CMC hydrogel and chemical crosslinking (CMC/PEG10/CA15) [2]. The elastic modulus of the CMC/PEG10 hydrogels loaded with 10 % and 15 % CA was found to decrease from 1.39 ± 0.19 GPa to 0.79 ± 0.02 GPa, which was similar to the results reported elsewhere [2]. However, when the CA concentration is increased by more than 20 %, the specimen becomes brittle due to chemical crosslinking, which leads to premature fracture in the grip during the experiment. The SR of the CMC/PEG membrane can be adjusted according to the concentration of CA and PEG to produce SAHs. SAHs with hydrophilicity ranging from 168 % to 4923 % can be tailored as wound dressings, skin tissue substitutes, and personal care applications, where swelling behavior is important to promote a moist environment that helps the wound healing process. They are commonly used in the later stages of natural healing for partial thickness burns, especially small areas with small burns. Dressings are widely applied in the treatment of ulcerative diseases such as pressure sores and lower excruciating ulcers [25,26].

The degradation rate (DR) of CMC/PEG hydrogel as a function of CA concentration is shown in Fig. 5. CMC/PEG hydrogels with low Mw of CMC (Mw = 90,000) and low concentrations of crosslinker (0~10 %) were completely degraded (DR = 100 %), as depicted in Fig. 5(a). The DR of CMC/PEG10 progressively decreased from 81 % to 34 % with increasing CA concentration from 15 % to 25 % due to the stable hydrogel formation.

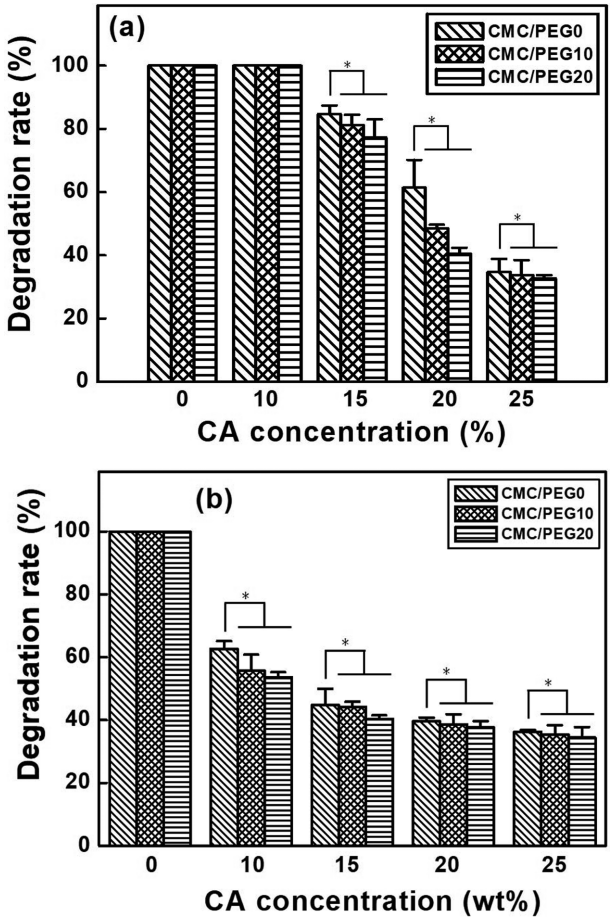

Fig. 5. Histogram of degradation rate of (a) CMC (Mw = 90,000)/PEG and (b) CMC (Mw = 250,000)/PEG hydrogels with CA concentration ranging from 0 % to 25 %. Results are expressed as mean ± standard deviation (* $p < 0.05$).

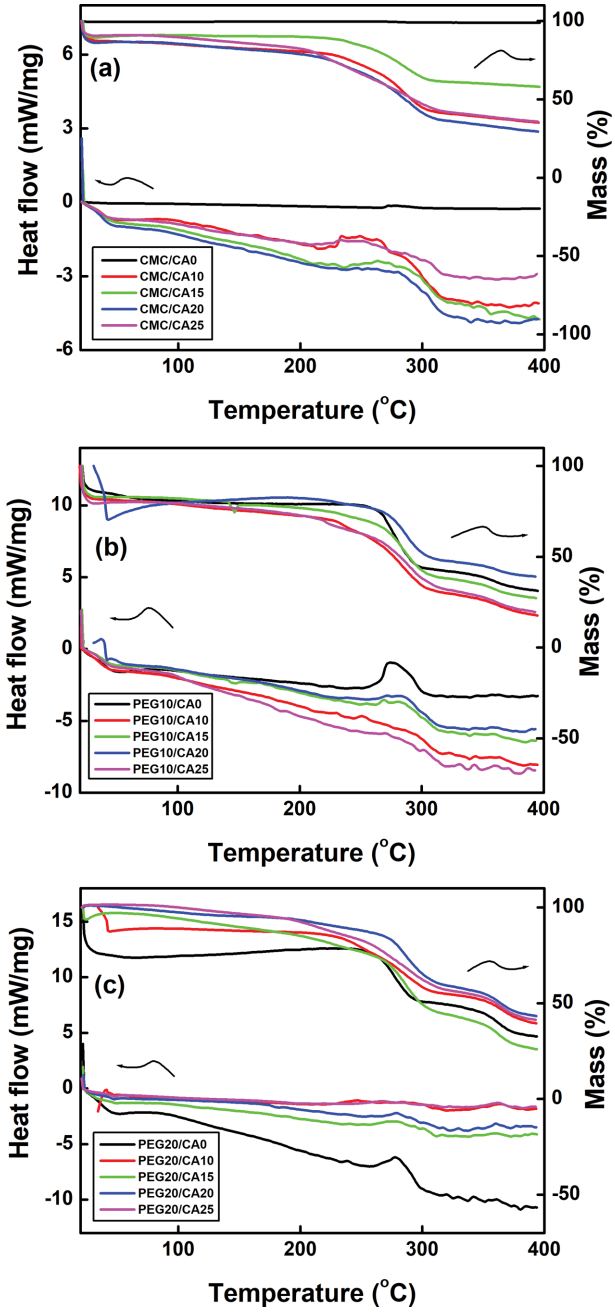

Fig. 6. DSC and TG curves of (a) CMC/CA, (b) CMC/PEG10/CA, and (c) CMC/PEG20/CA hydrogels. Note that CA was used as a crosslinker.

As the Mw of CMC increased from 90,000 to 250,000, the DR of the hydrogel was significantly improved. The degradation is related to hydration of the remaining polymer chains that are not effectively crosslinked [2]. The high Mw of CMC corresponds to the polymer chain and the chemical stability of the CMC/PEG hydrogel is improved, which reduces its degradability. The DR of CMC (Mw = 250,000)/PEG10 gradually decreased from 55 % to 35 % as the CA concentration increased from 15 % to 25 %. Moreover, the loading effect of PEG and CA was more synergistic for higher crosslinking networks containing CMC functional groups, resulting in more stable hydrogels. The concentration of crosslinker and PEG, CMC Mw for SAH production are attributed to the chemically stable CMC hydrogel. SAH with a broad range of SR (168 to 4923 %) is important for promoting a moist environment that supports the wound healing process. In the present study, CMC (Mw = 250,000)/PEG10 with 10 % CA had a high absorption capacity of ~3200 %, moderate degradation (54 %), and good stiffness (1.39 ± 0.19 GPa) for potential skin tissue repair or wound dressing application [2]. It exhibited customizable properties of hydrophilicity and degradability and retained the structural integrity of the hydrogel [27]. With biological functions including protein adsorption, cell adhesion, and immunological response, PEG served as a secondary crosslinker between CMC polymer chains in CMC/PEG hydrogel. CMC/PEG hydro-

gel with structural stability and moderate degradability can be controlled by adjusting the CMC and PEG concentrations.

DSC and TG were investigated to examine the state of CMC/PEG hydrogel, as shown in Fig. 6. No appreciable change in mass was detected for the uncrosslinked CMCs (Mw = 250,000). For crosslinked CMC, severe mass loss was observed with decomposition, vaporization, and removal of volatile products in the temperature range of 210°C to 360°C, as displayed in Fig. 6(a). A dramatic reduction in mass loss was observed in crosslinked CMC hydrogels due to the evaporation of bound water tightly attached to the polymer backbone compared to uncrosslinked CMC. CMC crosslinked with CA arose from the consumption of hydroxyl groups, resulting in fewer hydrophilic groups that can interact with water molecules. The exothermic peak indicates the degradation of the polymeric chain. Carboxymethylation interferes with the packing of higher-order cellulose polymers by steric hindrance and electrostatic repulsion, resulting in poor thermal stability [2]. The crosslinking-related esterification reaction can reduce hydrogen bonding of CMC, which can lower the decomposition temperature of the crosslinked hydrogels. However, a higher amount of CA is expected to increase the esterification reaction, thereby increasing the thermal stability of CMC/CA25 compared to CMC/CA20. When PEG was added to the CMC hydrogel (Figs. 6(b) and (c)), the endothermic peak associated with PEG melting (50°C) was severely weakened due to the strong bond between the multifunctional groups of the two molecules [7,8]. The addition of PEG and CA not only increased the total number of -OH groups available for esterification reaction, but also increased the bonds between terminal hydroxyls, C-O-C of PEG, and -OH of CMC, as previously verified in Fig. 3. As the PEG content increased from 0 % to 20 %, the SR and DR decreased dramatically due to the more stable hydrogel as a result of a higher crosslinking network containing PEG and CMC functional groups.

The cytotoxicity of CMC (Mw = 250,000)/PEG/CA hydrogels determines whether a product or compound may have a toxic effect on living cells [18]. Test extracts with CMC/PEG10/CA hydrogels as a function of CA content (0~25 %) show no evidence of inducing cytotoxicity. All experiments are performed in triplicate. Quantitative cell viability of CMC/PEG10/CA0, 10, 15, 20, and 25 hydrogels were 90 %, 94 %, 95 %, 100 %, and 90 %, respectively, compared to the negative control. Cell viability of CMC/CA10, CMC/PEG10/CA10, and CMC/PEG20/CA10 were 92 %, 94 %, and 92 %, indicating that the CMC/PEG/CA hydrogel was not cytotoxic under the conditions of this study. Cell proliferation results of L-929 cells on CMC/PEG hydrogels are shown in Fig. 7. Test values ($p < 0.05$) was considered statistically significant. The experimental results suggested that L-929 cells adhered well to the hydrogel and continued to proliferate with increasing time regardless of CMC concentration. The CMC/PEG/CA hydrogel was highly considered as wound dressing due to their non-cytotoxicity and excellent cell proliferation under the conditions of this study.

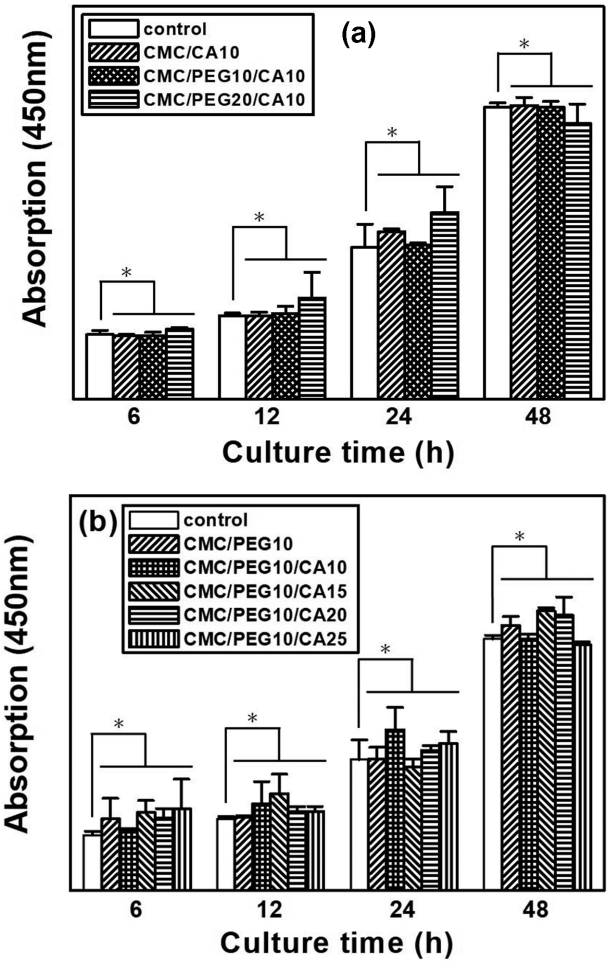

Fig. 7. Proliferation of L-929 cells on (a) CMC/CA10 hydrogels with different concentration of PEG (b) CMC/PEG10 hydrogels containing different amount of CA with time. Results are expressed as mean ± standard deviation (* $p < 0.05$).

4. Conclusions

CA-crosslinked CMC/PEG hydrogels are synthesized to study the effect of PEG and CA concentration on the

optical, chemical, mechanical properties, and biocompatibility of the hydrogel. The optical transparency of the CMC/PEG hydrogel decreased dramatically as the PEG content increased from 0 % to 20 %. Adding more PEG with the help of CA (10 wt%) resulted in a white opaque structure due to chemical crosslinking between CMC and PEG. The FT-IR results show that the hydroxyl peak intensity decreases due to PEG intercalation between the CMC chains in a similar way as the CA concentration increases. The SR and DR of crosslinked CMC (Mw = 90,000)/PEG hydrogel are inferior to CMC (Mw = 250,000)/PEG hydrogel. The SR and DR of the CMC (Mw = 250,000)/PEG hydrogel decreased from 4923 % to 168 % and from 62 % to 34 %, respectively, when PEG and CA concentrations were increased from 0 to 20 % and from 0 to 25 %, respectively. CMC (Mw = 250,000)/PEG10 hydrogels with 10 % CA exhibited the optimal characteristics of high absorbing capacity (3200 %), moderate degradation (54 %), stiffness (1.39 ± 0.19 GPa), cell viability (94.8 ± 1.3 %), and good cell proliferation. CMC/PEG hydrogels are well suited for wound dressing or personal care applications. SAHs with structural and chemical stability and biocompatibility can be tuned by adjusting CMC (Mw = 250,000) and PEG concentrations.

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