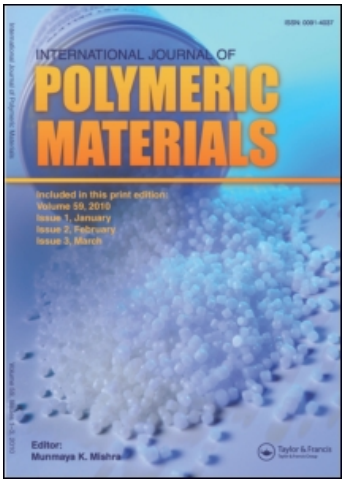

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Preparation and Release Properties of a pH-Tunable Carboxymethyl Cellulose Hydrogel/Methylene Blue Host/Guest Model

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pH-sensitive carboxymethyl cellulose hydrogel beads were prepared in spherical form by a suspension-crosslinking technique with epichlorohydrin as a crosslinking agent and fluid wax as the suspending solvent. The hydrogel beads are spherical in shape with a diameter of about 4 mm, which exhibits reversible pH-sensitive behavior. The hydrogel beads have good behavior for adsorption and release. The ability of the hydrogel beads to uptake and release a positively charged cationic guest molecule, such as methylene blue, could be tuned by controlling the extent of carboxylate ionization via pH. At 25°C, the maximum loading amount for methylene blue exceeded 1350.6 g/g with 56.27% adsorption ratio.

Keywords absorption, carboxymethyl cellulose, hydrogel, pH tunable, release

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INTRODUCTION

Hydrogels are attractive chemical functionalities that have been the subject of wide-ranging interest recently [1]. They are three-dimensional crosslinked network polymers spanning a wide range of compositions that do not dissolve in water, but are able to swell to a water absorption capacity that is many times their weight. They can be synthesized in a variety of physical forms including microparticles [2], nanoparticles [3], and macroparticles [4, 5] that can model, for example, drug delivery processes [6]. However, it is well known that uniform particle size and shape are critical in the successful development of stimuli-responsive drug delivery hydrogels [7].

The typical preparation of hydrogels consists of a bulk formation via graft copolymerization [8], that is mechanically disintegrated to the desired size. However, irregularly shaped hydrogel particles, not surprisingly, often display nonuniform drug release. A potential solution to the problem can be obtained by employing an inverse suspension crosslinking method. Inverse suspension crosslinking is a process in which polymer solutions are dispersed in the form of liquid droplets in a continuous nonsolvent medium by stirring and then crosslinked with the crosslinking agent. O'Connor et al. [9] were able to prepare uniform thermally responsive hydroxypropyl methylcellulose gel particles via inverse suspension crosslinking. Inverse suspension crosslinking is a highly simple and powerful method to control final particle size and distribution by stirring speed or phase ratio.

As has been already alluded, pH-sensitive hydrogels have shown some success for use in the site-specific delivery of drugs [10]. Much work has involved the study of carboxymethyl cellulose (CMC) in hydrogel applications. Carboxymethyl cellulose (CMC) is an ionic polysaccharide that contains carboxyl groups that can prepare pH sensitive hydrogels [11]. Not only can drug delivery applications benefit from the use of CMC, principally because of its biocompatibility, biodegradability and nontoxicity [12, 13], but so can cosmetics [14] and food [15]. Xiao [16] synthesized a fast pH-responsive carboxymethyl cellulose/poly(vinyl alcohol) hydrogel with ferric ions as the crosslinker that exhibited pH-responsive release behavior.

We report herein for the first time the successful preparation of a novel pH-sensitive hydrogel based on CMC that uses epichlorohydrin (ECH) as the crosslinker via inverse suspension crosslinking. The structure and morphology of the hydrogel were analyzed by FTIR and SEM, respectively, the thermal behavior of the hydrogel was characterized by differential scanning calorimetry (DSC), and the swelling kinetics and pH-dependent behavior were also studied. Finally, to evaluate the ability of the hydrogel for potential drug release applications, the absorption and release behavior of a model guest molecule (cationic methylene blue, MB) was examined.

EXPERIMENTAL

Reagents and Chemicals

CMC was purchased from Aladdin-Reagent Inc. The molecular weight and total degree of substitution of CMC were 250,000 and 1.2, respectively. All other reagents used in this study were supplied from China Corporation and were of analytical grade and used without further purification.

Hydrogel Particle Synthesis

The CMC hydrogel particles were synthesized by an inverse suspension crosslinking technique. 5 wt% CMC solutions were prepared by directly mixing 5 g of solid NaOH and 5 g of CMC with 90 ml deionized water. 10 ml epichlorohydrin (ECH) was added to 90 ml CMC solutions under stirring (400/rpm) for 20 min. The mixtures were dispersed in a continuous phase of 1000 ml liquid wax. The crosslinking reaction was conducted under stirring (300/rpm) at 0°C for 48 h. The resulting particles were washed with deionized water and acetone until the unreacted substance and liquid wax were completely removed.

FTIR Spectroscopy Analysis

The dried samples were compressed into KBr pellets. FTIR spectra of the samples were recorded with a Thermo-Nicolet FTIR spectrometer (SX-170) from 4000 to 500 cm^{-1}.

Thermal Analysis of Hydrogels

The hydrogel samples reached a swollen equilibrium by immersion in deionized water at room temperature for 24 h. Approximately 8 mg of the equilibrated sample was placed inside an aluminum pan and hermetically sealed with an aluminum lid after removing excess water on the surface with a filter paper. The thermal analysis was performed on DSC Q200 (TA Instruments, USA) from −20°C to 120°C under the nitrogen flow 40 ml/min and the heating rate 2°C/min.

Morphology of Hydrogels

The equilibrated hydrogel samples were freeze-dried under vacuum until all the water was sublimed. The freeze-dried samples were fractured carefully in liquid nitrogen, and then fixed on plates by sputter-coating with gold before analysis. The morphology of external and fractured surface of samples was

obtained by scanning electron microscopy (S-3700 N, Hitachi Company) under an accelerating voltage of 10 kV.

Swelling Behavior of Hydrogels

The swelling ratios of the hydrogel samples were measured at 25°C in the pH range 1.2 to 9.2 using a gravimetric method. The hydrogel samples were immersed in deionized water or buffer solution. Masses of swollen hydrogels at different times were weighed after wiping off excess water on the hydrogel surfaces with filter paper. The average value of three measurements from three parallel specimens in the same hydrogel was taken for each sample. The swelling ratio, SW_t, of the hydrogels was expressed as follows:

$$SW_t = (W_t - W_d)/W_d \tag{1}$$

where, W_d is the weight of dry hydrogels and W_t is the weight of swollen hydrogels at different times. The equilibrium swelling ratio of hydrogels was measured by immersing dried hydrogels in deionized water or buffer solution. After reaching equilibrium, hydrogels were weighed after removing their surface water. SW_{eq} (equilibrium swollen ratio) was calculated by the following equation:

$$SW_{eq} = (W_{eq} - W_d)/W_d \tag{2}$$

where, W_d is the weight of dry hydrogels and W_{eq} is the weight of the swollen equilibrium hydrogels.

Adsorption and Release Behavior

Methylene blue (MB) is a cationic dye with a high affinity for negatively charged polymers. This criterion was the rationale for choosing it as a model molecule for evaluating CMC/ECH hydrogels absorption and release capacity, because the negatively charged carboxylate groups in the CMC/ECH hydrogels can easily entrap positively charged guest molecules (such as many drugs), and release them under controlled conditions [17, 18]. The dried hydrogels (in 1 g units) were soaked in various concentrations of aqueous MB (1 L) for 48 h at room temperature. The maximum of the UV-visible absorption of MB, 664 nm, was the spectral signature used in these experiments [19]. The dye adsorption amount can therefore be calculated from the difference in the concentration before and after soaking using an ultraviolet spectrophotometer (S4100, SCINCO, USA). In the release portion of the work, guest molecule-loaded hydrogels (1 g) were immersed in buffer solutions of different pHs (1 L) and were incubated in a shaking water-bath at room temperature. At designated specific intervals, 1 mL of the solution was withdrawn and an

equivalent volume of fresh buffer solution was added to maintain constant volume. The cumulative release of various guest molecules was determined by UV-vis spectrscopy. For each sample, experiments were performed in triplicate to reduce experimental error.

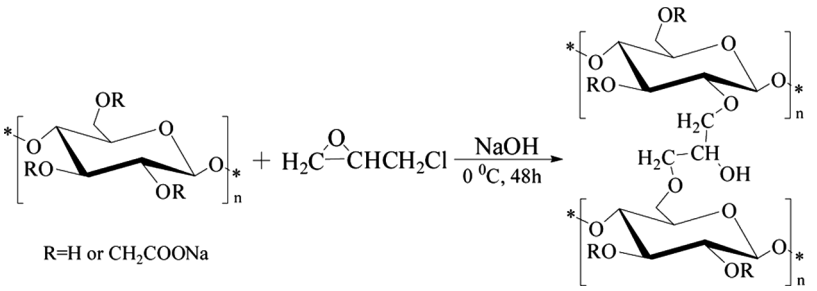
RESULTS AND DISCUSSION

Preparation of CMC/ECH Beads

CMC/ECH hydrogel beads were synthesized using a suspension crosslinking technique with epichlorohydrin as the crosslinking agent in aqueous alkaline conditions. The proposed reaction mechanism of ECH with CMC is shown in Scheme 1. ECH was widely used as a crosslinker to react with the hydroxyl groups of polysaccharide [20–25]. In alkaline conditions, the hydroxyl groups of CMC become alcoholate anion. The alcoholate anion attacks the epoxy groups of ECH to form a monoether of chloropropanediol [20, 21]. A new epoxy group will yield by chloride displacement rearranges of the chloropropanediol monoether [25]. When the new epoxy groups react with the hydroxyl groups of another CMC, the crosslinking reaction occurs between ECH and CMC. In the reaction, there may be some side reactions, for example, some ECH molecules may only react with one hydroxyl group of CMC and some unreacted ECH hydrolyzes to glycerol [22, 25].

Analysis of FTIR

FTIR spectra of the CMC and the CMC/ECH hydrogels were recorded in the range of 4000–500 cm^{-1} to verify the crosslinking in the CMC/ECH hydrogel. As shown in Figure 1, band differences can easily be observed between the spectra that support CMC/ECH crosslinking. Bands at 1422 cm^{-1}, 1608 cm^{-1}, 2931 cm^{-1} and 3420 cm^{-1} can be assigned to the stretching vibration of COO^{-}(symmetric), COO^{-}(asymmetric), C–H (aliphatic) and O-H, respectively



Scheme 1: Preparation of the CMC hydrogel particles with ECH as crosslinker.

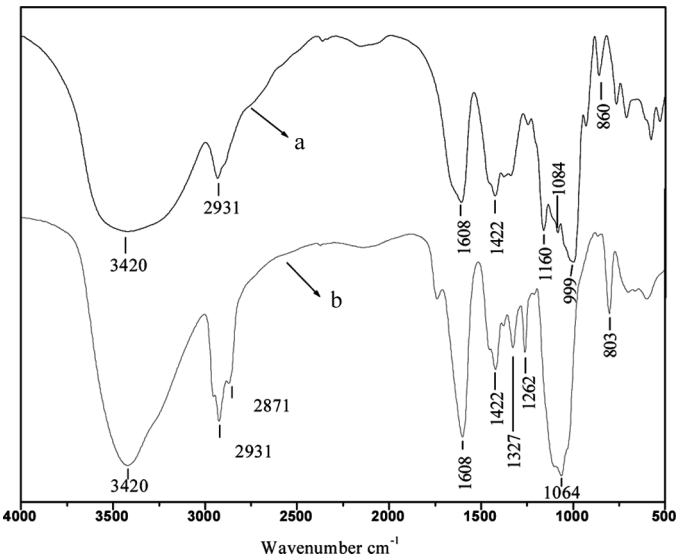


Figure 1: FTIR spectra of a) CMC, and b) CMC/ECH hydrogel.

[26]. The band observed at $1608\,cm^{-1}$ and $1422\,cm^{-1}$ in the spectrum of CMC/ECH hydrogel indicates that the carboxyl groups of CMC exists in the hydrogels after crosslinking. It can be seen from the spectrum of CMC/ECH hydrogels that some typical peaks appear at $1327\,cm^{-1}$, $1262\,cm^{-1}$ and $1064\,cm^{-1}$. The peaks at $1327\,cm^{-1}$ and $1262\,cm^{-1}$ belong to the stretching vibration of the new bond C–O–C and C–C stretching vibration from the components of the reacted ECH with CMC, respectively [27], while the band appearing at $1064\,cm^{-1}$ is characteristic for the bending vibration of the –OH group. The results show that a crosslinking reaction occurs between ECH and the hydroxyl groups of CMC.

Thermal Analysis of Hydrogels

Hydrogels can swell by the absorption of many times their weight of water and encompass a wide range of chemical compositions [28]. The state of water in the hydrogel networks can significantly affect the interaction between the hydrogel and other substances, which is critical to their applications in any drug release strategy [29]. It may affect, thus, the overall efficiency of absorption and/or release. In general, the bonding status of water in hydrogels can be analyzed with thermodynamic methods. DSC thermograms of CMC and ECH/CMC hydrogel are shown in Figure 2. The contents of different states of water in CMC/ECH hydrogel particles (free and bound water) were investigated by DSC melting thermograms. The DSC curve of CMC solution showed

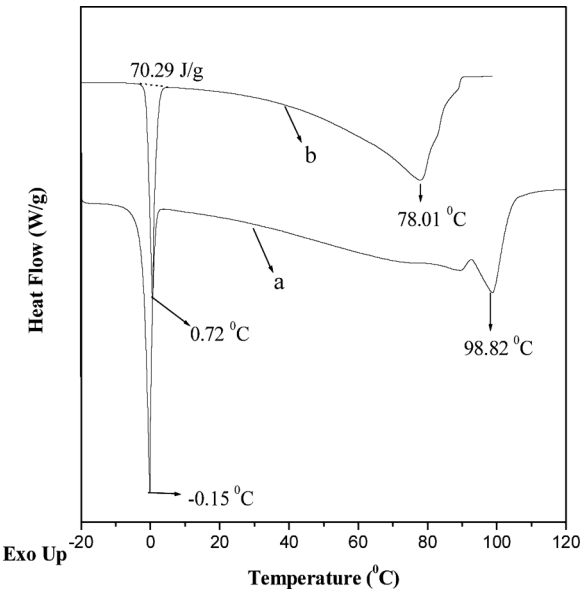


Figure 2: DSC curves of (a) CMC and (b) CMC/ ECH hydrogel.

two peaks at -0.15°C and 98.82°C. After it was crosslinked with ECH, the positions of the peaks shifted as a result of the new status of water. The first peak shifted to a slightly higher temperature of 0.72°C, but the second peak shifted to a lower temperature of 78.01°C, which can be ascribed to hydrophobic substitution of ECH and a reduction of the number of water binding sites as compared to CMC [30]. The ECH/CMC hydrogel showed an endothermic peak between −4 and 4°C which was assigned to free water. The fraction of free water to total water was approximated as the ratio of the endothermic peak area between −4 and 4°C for the water of the swollen hydrogel to the endothermic melting heat of pure water (334 J/g) [29]. By consequence, the content of free water and bound water were 21.04% and 78.46%, respectively, for the crosslinked hydrogel. The relatively high water content gives hydrogels a strong resemblance and biocompatibility exhibited by many soft living tissues, which make them ideal for drug release [31].

Morphology of Hydrogels

As shown in Figure 3, the hydrogel particles, with diameters of about 4 mm, are fully transparent and nearly spherical in shape. The SEM micrographs of the cross-section of CMC/ECH hydrogel particles before and after adsorbing MB were illustrated in Figures 4 and 5. We can see that the hydrogels have a porous internal structure (Figure 4). There are numerous

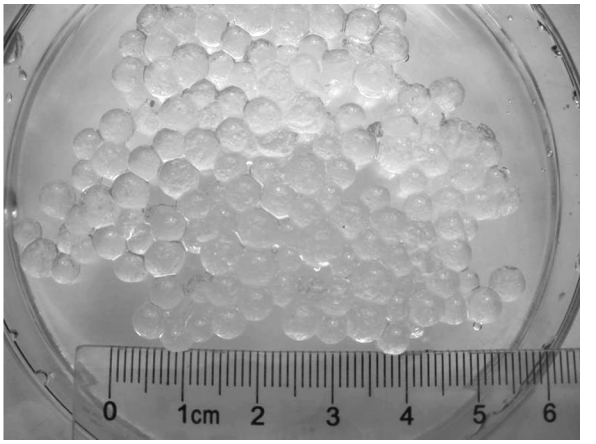


Figure 3: Photographs of hydrogel particles.

carboxylate anions (COO^-) in the network whose electrostatic repulsions result in an expansion of the network and the increase in the amount and size of the pores [32]. As a result of these numerous pores in the network, water molecules can easily diffuse in and out, resulting in a large swelling ratio and a fast response rate during the swelling and deswelling processes. After adsorbing MB, the SEM micrograph of the hydrogel is shown in Figure 5. The morphological difference is obviously observed between the unload hydrogel and the load hydrogel. The pore size of the load hydrogel decreases because the electrostatic repulsions decline in the network of hydrogels after the anion hydrogels absorbed the MB.

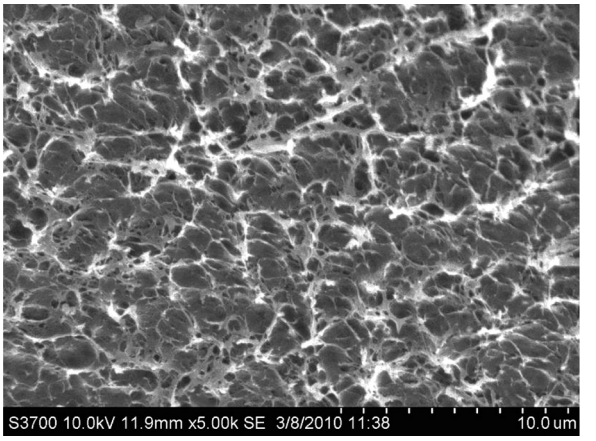


Figure 4: SEM image of the cross-section of the CMC/ECH hydrogel (magnification × 5000).

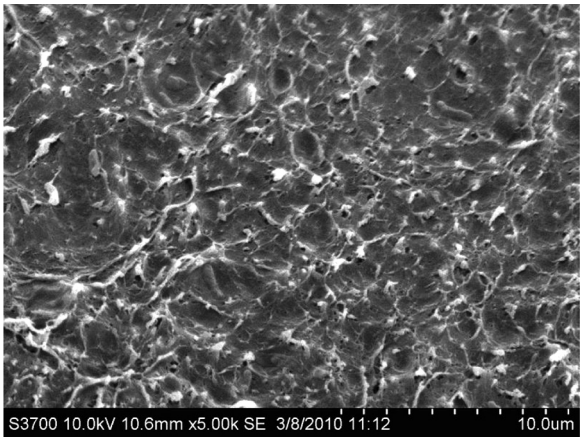


Figure 5: SEM image of hydrogel cross-sections after absorption MB (magnification × 5000).

Effect of pH on Swelling Ratio

The CMC/ECH hydrogels exhibit good pH sensitivity because of the many carboxylic groups. As shown in Figure 6, due to excellent hydrophilicity and a highly porous network, the particles quickly reached swelling equilibrium in 30 min. At pH 4, a screening effect of the counter ions ensues, shielding the charge of the carboxylate anions and, thus effectively preventing further repulsion. As a result, a remarkable lower equilibrium swelling is observed [33]. The CMC/ECH hydrogel attains a maximum swelling ratio at pH 7

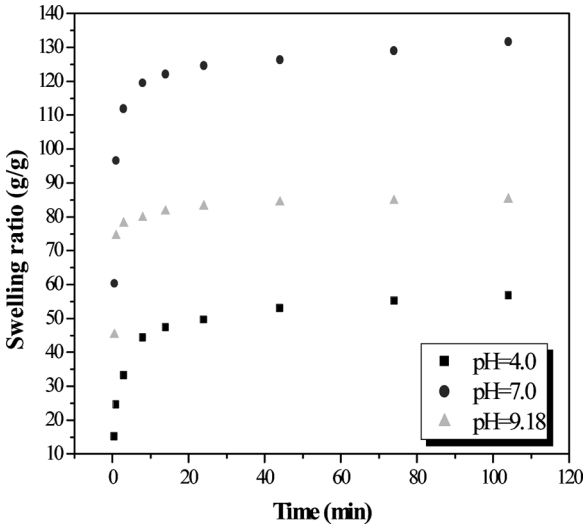


Figure 6: Swelling ratio of hydrogel particles with different pH as a function of time.

which is not surprising given that the pKa of the carboxylic groups is 4.6. Thus, the hydrogel expands as a result of the strong electrostatic repulsions among the developing polyelectrolyte chains [32]. Beyond this value, the hydrogel acid groups begins to undergo ionization screening, thus leading to decreased electrostatic repulsive forces among the molecular chains. Therefore, the swelling ratios of the hydrogels decrease at pH 9.18.

Adsorption and Release Behavior

MB was used as a model guest molecule to investigate adsorption-release behavior at pH 7. Figure 7 shows the MB absorption profiles of the crosslinked hydrogels (1 g dried gel) in different concentrations of aqueous MB (1 L MB solution) for 48 h at room temperature. It can observed that the MB uptake increased with increasing MB concentrations. The absorption ratio for MB is higher than 90% when the MB concentration is lower than 0.8 g/L. The maximum MB absorption exceeded 1350.6 mg/g with a 56.27% absorption ratio. A likely explanation is because the cationic MB had strong intermolecular interactions with the hydrogels because of the anionic nature of the CMC/ECH hydrogels.

MB release profiles from the CMC/ECH hydrogels at varying pHs are shown in Figure 8. As shown, the release rates of MB exhibited pH sensitivity, i.e., the MB release at pH 4 is much faster than that at pH 7 or pH 9.18. At pH 4, the hydrogel is relatively neutral. The very weak electrostatic attraction between cationic MB and the relatively neutral hydrogel allow MB to easily

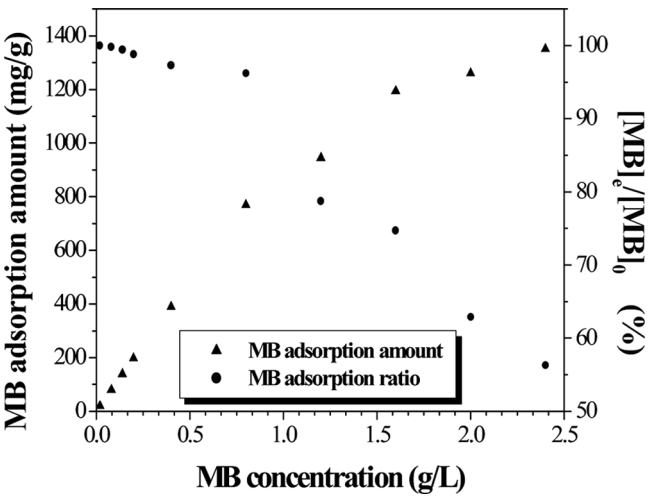


Figure 7: MB adsorption profiles of CMC/ECH hydrogels at room temperature. $(MB)_s$: MB adsorbed amount; $(MB)_0$: MB initial amount.

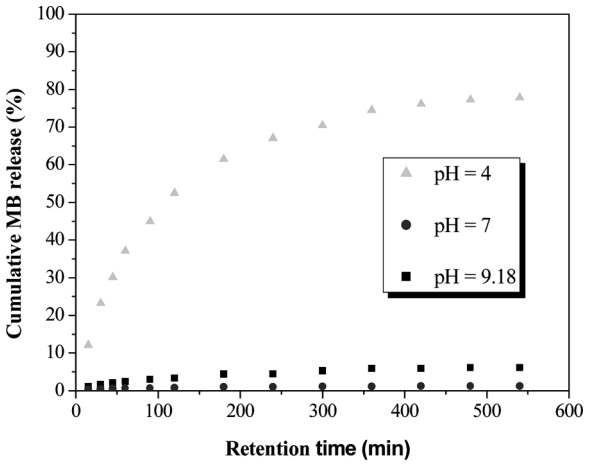


Figure 8: MB release profiles from CMC/ECH hydrogels at different pH values at 20°C.

diffuse from the hydrogels. Thus, the release amount and its associated rate are highest at pH 4 [17]. At pH 9.18, the hydrogel is highly ionized, and thus the electrostatic attraction between MB and the hydrogel is maximized; however, salt ions also play an important role in MB absorption capacity which can screen the attraction between MB and hydrogel particles. The result is that MB release at pH 9.18 is slightly faster than at pH 7 [34].

CONCLUSION

Novel pH-sensitive hydrogels were prepared from CMC crosslinked with ECH by using a suspension crosslinking technique. The hydrogel is highly crosslinked and has high porosity; therefore, a large amount of bond water is in the structure. Additionally, the external surface of hydrogel particles is compact and smooth, but the internal structure of the particles is very porous. The crosslinked hydrogel can display a rapid release response for guest molecules such as methylene blue (MB) and is pH-sensitive. Indeed, the hydrogel can absorb a high level of cationic MB (1350.6 mg/g hydrogel at pH 7). MB can be released at a high level (74.5% release ratio) from hydrogel particles at pH 4 because of weak electrostatic attractive forces which are maximized at pH = 7 and subsequently reduced because of screening by the common ion effect at higher pHs. The tunable electrostatic interaction between the hydrogel and guest molecule indicated in this report, i.e., pH-sensitive, absorption and release of the MB in and from the crosslinked hydrogels, respectively, points to a potential application in biomedical drug release schemes.

REFERENCES

[1] Kopecek, J., and Yang, J. *Polym. Int.* **56**, 1078 (2007).

[2] Cavalieri, F., Chiessi, E., Villa, R., Vigano, L., Zaffaroni, N., Telling, M. F., and Paradossi, G. *Biomacromol.* **9**, 1967 (2008).

[3] Hamidi, M., Azadi, A., and Rafiei, P. *Advan. Drug Deliv. Rev.* **60**, 1638 (2008).

[4] Dai, Y. N., Li, P., Zhang, J. P., Wang, A. Q., and Wei, Q. *Biopharma Drug Dispos.* **29**, 173 (2008).

[5] Chatterjee, S., Lee, D. S., Lee, M. W., and Woo, S. H. *Biores. Technol.* **100**, 2803 (2009).

[6] Hoare, T. R., and Kohane, D. S. *Polymer* **49**, 1993 (2008).

[7] Oh, J. K., Drumright, R., Siegwart, D. J., and Matyjaszewski, K. *Prog. Poly. Sci.* **33**, 448 (2008).

[8] Manal, F., and Taleb, A. *Poly. Bull.* **61**, 341 (2008).

[9] O'Connor, S. M., and Gehrke, S. H. *J. Appl. Poly. Sci.* **66**, 1279 (1997).

[10] Qiu, Y., and Park, K. *Adv. Drug Deliv. Rev.* **53**, 321 (2001).

[11] Shang, J., Shao, Z. Z., and Chen, X. *Biomacromol.* **9**, 1208 (2008).

[12] Bajpai, A. K., and Mishra, A. *Poly. Internat.* **54**, 1347 (2005).

[13] Popli, S. D., and Go, Z. O. US, 5563177-A. (1996)

[14] Kose, K. K. JP, 2004315463-A. (2004)

[15] Bayarri, S., Gonzalez,T. L., and Costell, E. *Food Hydrocoll.* **23**, 441 (2009).

[16] Xiao, C. M., Li, H. Q., and Gao, Y. K. *Poly. Internat.* **58**, 112 (2009).

[17] Bejenariu, A., Popa, M., Dulong, V., Picton, L., and Cerf, D. L. *Poly. Bull.* **62**, 525 (2009).

[18] Chunder, A., Sarkar, S., and Yu, Y. B. *Colloids Surf., B.* **58**, 172 (2007).

[19] Uraki, Y., Imura, T., Kishimoto, T., and Ubukata, M. *Cellulose* **13**, 225 (2006).

[20] Chang, C. Y., Duan, B., and Zhang, L. A. *Polymer* **50**, 5467 (2009).

[21] Chang, C. Y., Duan, B., Cai, J., and Zhang, L. A. *Eur. Polym. J.* **46**, 92 (2010).

[22] Bai, Y. X., and Li, Y. F. *Carbohydr. Polym.* **64**, 402 (2006).

[23] Silva, D. A., Feitosa, J. P. A., Maciel, J. S., Paula, H. C. B., and Paula, R. C. M. *Carbohydr. Polym.* **66**, 16 (2006).

[24] Chang, C. Y., Lue, A., and Zhang, L. A. *Macromol Chem. Phys.* **209**, 1266 (2008).

[25] Miguel, I. D., Rieumajou, V., and Betbeder, D. *Carbohydr. Res.* **139**, 17 (1999).

[26] Chiem, L. T. C., Huynh, L., Ralston, J., and Beattie, D. A. *Langmuir* **24**, 8036 (2008).

[27] Krol, P., Krol, B., and Dziwinski, E. *J. Appl. Polym. Sci.* **90**, 3122 (2003).

[28] Kopeček, J. D., and Yang, J. Y. *Poly. Internat.* **56**, 1078 (2007).

[29] Agrawal, A. M., Manek, R. V., Kolling, W. M., and Neau, S. H. *J. Pharm. Sci.* **93**, 1766 (2004).

[30] Su, J. C., Liu, S. Q., Joshi, S. C., and Lam, Y. C. *J. Therm. Analy. Calorim.* **93**, 495 (2008).

[31] Wang, T., and Gunasekaran, S. *J. Appl. Poly. Sci.* **101**, 3227 (2006).

[32] Zhao, Y., Kang, J., and Tan, T. W. *Polymer* **47**, 7702 (2006).

[33] Ma, J. H., Xu, Y. J., Fan, B., and Liang, B. R. *Euro. Poly. J.* **43**, 2221 (2007).

[34] Ma, J. H., Zhang, L., Fan, B., Xu, Y. J., and Liang, B. R. *J. Poly. Sci. B-Poly. Phys.* **46**, 1546 (2008).