Journal of Metals, Materials and Minerals, Vol.28 No.1 pp.77-86, 2018

Carboxymethylchitosan-based hydrogel film crosslinked with polydimethylsiloxane

Nantharak RODKATE, Nunthiya DEEPUPPHA, Boonjira RUTNAKORNPITUK, and Metha RUTNAKORNPITUK*

Department of Chemistry and Center of Excellence in Biomaterials, Faculty of Science, Naresuan University, Phitsanulok 65000, Thailand.

***Corresponding author e-mail:** methar@nu.ac.th

Received date:
28 May 2018
Accepted date:
7 June 2018

Keywords:
Carboxymethylchitosan
Polydimethylsiloxane
Hydrogel
Crosslinking

Abstract

Synthesis and properties of hydrophilic carboxymethylchitosan (CMC) hydrogels containing hydrophobic polydimethylsiloxane (PDMS) were herein presented. Fourier transform infrared spectroscopy indicated that PDMS can covalently bound to CMC chains with the use of hexamethylene-1,6-di-(aminocarboxysulfonate) (HDA), a water soluble crosslinker. Also, according to scanning electron microscopy, PDMS microphases with the size of 0.2-0.5 μm in diameter were thoroughly dispersed in CMC matrix. Addition of PDMS improved properties of the CMC hydrogels including increasing water vapor permeability and water swellability, improving tensile properties and increasing surface hydrophobicity. PDMS with different amounts (1-20 wt%) and molecular weights (2,000 and 8,000 $g \cdot mol^{-1}$) were added into CMC hydrogels in order to investigate the effect of its concentrations and chain lengths on these properties. It was found that increasing the concentrations and molecular weights of PDMS seemed to further improve these properties, indicating the feasibility in tuning these properties of CMC hydrogels for specific applications.

1. Introduction

Chitosan, a statistical copolymer of 2-amino-2-deoxy-D-glucopyranose (GlcN) and 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc) units, is typically prepared *via* a partial deacetylation reaction of chitin in an alkali solution [1-4]. As compared to chitin, it shows an improved solubility especially in acidic aqueous conditions owing to the presence of both hydroxyl and amino groups in chitosan structure [5,6]. In addition, these functional groups also allow for other chemical modification such as methylation [7], PEGylation [8,9], sulfonation [10,11], quaternization [12,13], acylation [14] and others [15]. However, the solubility of chitosan only in acidic aqueous condition is still the limitation for its chemical modifications and essentially for potential applications [16,17].

Carboxymethylchitosan (CMC), a water-soluble derivative of chitosan, is typically prepared *via* a carboxymethylation reaction of chitosan with monochloroacetic acid in an alkali solution [18]. Previous works have demonstrated potential applications of CMC especially in a wound healing application owing to its biocompatibility, antibacterial activity, and excellent water swellability [19,20]. Moreover, it has also been reported to have non-thrombogenicity properties making it appropriate for use as blood-contacting materials [21]. In recent years, incorporation of CMC with other functional polymer has been widely investigated. Grafting copolymerizations of CMC with other pH-responsive polymers such as poly(acrylic acid) [22-24] and poly(dialkyl aminoethyl methacrylate) [25-27], and/or thermo-responsive polymers such as poly(N-isopropyl acrylamide) [20,28,29], have been widely reported. In most cases, formation of network structure of CMC is necessary for use in most applications such as wound dressing materials; they must be chemically crosslinked to obtain water insoluble but highly swellable hydrogels. Additionally, formation of network structure can also promote miscibility of CMC with other functional polymers [30]. Glutaldehyde was mostly used as a crosslinking agent to form CMC-based hydrogels [20, 22, 31], while hexamethylene-1,6-di-(aminocarboxysulfonate) (HDA) were also effectively used for crosslinking CMC hydrogels in aqueous solutions [19,26,32].

In this research, preparation of CMC-based hydrogels containing flexible and highly hydrophobic polydimethylsiloxane (PDMS) is reported. The studies in the effect of flexible and

DOI: 10.14456/jmmm.2018.11

hydrophobic PDMS on the properties of CMC hydrogels are also presented (Figure 1). PDMS has been reported for use in many applications due to its high flexibility, high oxygen permeability, good oxidative and thermal stabilities [33,34]. The preparation of chitosan hydrogels modified with PDMS has been widely reported [35-37], while those of CMC-based hydrogels are very limited [35]. This was due to the insolubility of these two components, resulting in macrophase separation of these two components upon blending. Therefore, chemical crosslinking of PDMS-modified CMC-based hydrogels should enhance the miscibility of this two-phase mixture. In this report, a water-soluble HDA was used as a crosslinker to chemically lock PDMS chains into CMC structure. The effect of molecular weights and concentrations of PDMS in the network on the properties such as percent crosslinking, water swelling behavior, surface morphology, tensile strength, water contact angle, and water vapor permeability, were investigated.

2. Experimental

2.1 Material

Octamethylcyclotetrasiloxane (D_4), 99% (Fluka) was stirred in CaH_2 and distilled before used. Allyl alcohol, 99% (Acros) and 1,1,3,3-tetramethyldisiloxane, 97% (Acros) were distilled prior to used. Other reagents including chitosan from crabs (98% deacetylation) (Taming Enterprise, Co.), 1,6-hexamethylene diisocyanate (HDI), 99% (Acros), monochloroacetic acid ($ClCH_2COOH$), 99% (Acros), Karstedt's catalyst (Aldrich), trifluoromethanesulfonic acid, 98% (Aldrich), sodium metabisulphite, $Na_2S_2O_5$ (Carlo Erba reagent) were used as received.

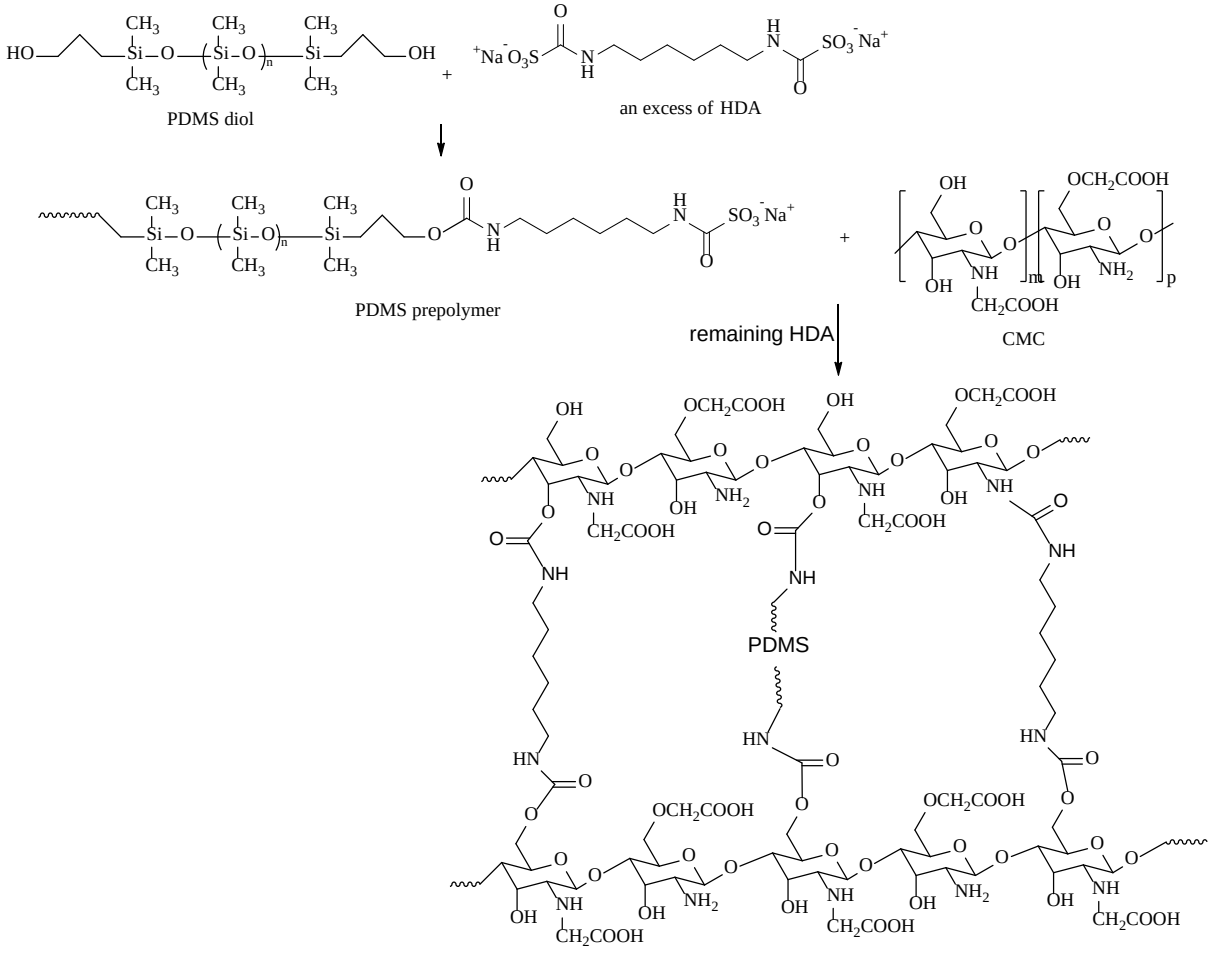

Figure 1. A scheme for the synthesis of CMC hydrogels containing hydrophobic PDMS.

2.2 Syntheses

2.2.1 Synthesis of carboxymethylchitosan (CMC)

CMC from crap (40 g) was first submerged into isopropyl alcohol (500 ml) overnight. The swollen CMC was then immersed in a saturated NaOH solution for 60 min. It was then reacted with monochloroacetic acid (48 g in 100 ml H_2O) at 60 °C for 5 h. The product was precipitated in an excess of methanol, washed with CH_3OH:H_2O solution (70:30 and 80:20 v/v, respectively), filtered and dried *in vacuo*. The final product appeared as a dried yellow powder with 87% yield.

2.2.2 Synthesis of polydimethylsiloxane diol (PDMS diol)

The synthesis of PDMS diol was previously reported [38]. Briefly, dihydro-terminated PDMS with the molecular weight of 2,000 (2K) and 8,000 $g \cdot mol^{-1}$ (8K) were first synthesized *via* a ring-opening polymerization of D_4 with 1,1,3,3-tetramethyl disiloxane as an endcapping agent to obtain PDMS with dihydro terminal (Si-H). The polymerization was set at 60°C for 72 h in the presence of triflic acid. After the workup process, dihydro-terminated PDMS appeared as yellowish liquid with 75% yield. Hydrosillylation between dihydro-terminated PDMS and allyl alcohol in the presence of Karstedt's catalyst was then set at 65°C for 2 h. After the workup process, PDMS diol appeared as yellowish liquid with 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 0.1 (*s*, 6H, 5×Si-C<u>H</u>$_3$) of 2K PDMS or 0.1 (*s*, 6H, 20×Si-C<u>H</u>$_3$) for 8K PDMS, 0.6 (*t*, 2H, 2×Si-C<u>H</u>$_2$-CH_2-CH_2-OH), 1.7 (*m*, 2H, 2×CH_2-C<u>H</u>$_2$-CH_2-OH), 3.7 (*t*, 2H, 2×CH_2-CH_2-C<u>H</u>$_2$-OH).

2.2.3 Synthesis of HDA crosslinker

Synthesis of HDA has been previous reported [19]. Briefly, an aqueous solution of HDI and $Na_2S_2O_5$ was stirred for 12 h at 30°C. After precipitation in acetone and then filtration, insoluble by-product was removed by dissolving HDA in water and then filtration. HDA was repeatedly precipitated in acetone, dried *in vacuo* to white powder with 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 1.3 (*m*, 2H, 2×C<u>H</u>$_2$-CH_2-CH_2-NH), 1.6 (*m*, 2H, 2×CH_2-C<u>H</u>$_2$-CH_2-NH), 3.3 (*t*, 2H, 2×CH_2-CH_2-C<u>H</u>$_2$-NH).

2.2.4 Synthesis of PDMS-containing CMC hydrogels

A given amount of PDMS diol solution (containing 1, 5, 10 or 20 wt% of PDMS based on weight of CMC in 50:50 v/v of THF: H_2O mixture) was slowly added into HDA solution (10 wt% based on weight of CMC in 50:50 v/v of THF: H_2O mixture). The mixture was stirred at 45 °C for 2 h to form PDMS prepolymer (PDMS having aminocarboxysulfonate chain terminals). The solution was subsequently added into an acidic solution of CMC in DI water and stirred for 10 min. The solution was poured into a mold and dried at 40 °C for 24 h to form PDMS-containing CMC hydrogels.

2.3 Measurement of percent crosslinking

The hydrogel films (1×1 cm^2) were immersed in water and stirred for 12 h to dissolve unreacted HDA and CMC. After dissolution, the remaining hydrogels were filtered and washed thoroughly with water and then acetone. They were then dried at 40 °C overnight. Percent crosslinking was estimated according to the following equation [32]:

$$\text{Percent crosslinking (\%)} = \left(\frac{W_2}{W_1}\right) \times 100 \quad (1)$$

where W_1 and W_2 are the weights of the dried films before and after dissolution, respectively. The reported values are the average of five tests.

2.4 Measurement of equilibrium water content

After immersing CMC films in water for 12 h to reach the swelling equilibrium, the swollen hydrogels were then weighed. Equilibrium water content was estimated using the following equation:

$$\text{Percentage of equilibrium water content (\%EWC)} = \frac{W_s - W_d}{W_d} \times 100 \quad (2)$$

where W_s and W_d are the weights of the swollen and dried samples, respectively. The reported values are the average of at least triplicate tests.

2.5 Measurement of tensile properties

Tensile properties were tested on a universal testing machine (model WDW-5E). The dried films

with a rectangular shape (1×5 cm^2) (ASTM D882) were performed at the 30 mm gage length with the crosshead rate of 10 $mm \cdot min^{-1}$ and 1 kN load cell. Tensile strength and percent elongation at break were estimated from the following equation:

$$\text{Tensile strength } (N \cdot mm^{-2}) = \frac{\text{Breaking force (N)}}{\text{Cross-section area of the sample } (mm^2)} \quad (3)$$

$$\text{Percent elongation at break (\%)} = \frac{\text{The increase in length at breaking point (mm)}}{\text{Original lenght (mm)}} \times 100 \quad (4)$$

The reported values are the average of eight samples.

2.6 Water contact angle measurement

Contact angles (θ) between water and dried CMC films were performed using a Ramé-hart model 200 standard contact angle goniometer. A drop of water was applied on dried CMC films and the contact angles were then recorded. The reported values are the average of five samples.

2.7 Determination of water vapor permeability

The sample films were cut and tightly attached onto the top of glass vials containing anhydrous $CaCl_2$. A glass vial containing glass beads with the same weight as those of the sample vials was used as a control. They were stored in a desiccator having a saturated NaCl solution at 35 ± 1 °C and 70 ± 3% RH for 14 days. Water vapor permeability was calculated from the following equation [34]:

$$\text{Water vapor permeability } (g \cdot d^{-1} \cdot L^{-1}) = \frac{[(S_f - S_i)-(C_f - C_i)]}{14\,v} \times 1000 \quad (5)$$

where S_i and S_f are initial and final weights (g) of the sample vials, C_i and C_f are initial and final weights (g) of the control vials and v is the volume (cm^3) of the vials. The reported values are the average of triplicate tests.

2.8 Characterization

Fourier transform infrared spectroscopy (FTIR) was conducted on a Perkin-Elmer model 1600 series FTIR spectrometer. Surface morphology was conducted on LEO 1455 VP scanning electron micrometer (SEM) using an accelerating voltage of 5 kV.

3. Results and discussion

3.1 Verification of the chemical coupling reaction between PDMS diol with HDA to form PDMS prepolymer

In a typical process of preparing the hydrogels, an excess of HDA was first introduced into a PDMS diol solution to form PDMS prepolymer (PDMS having aminocarboxysulfonate chain terminals), followed by an addition of CMC solution to eventually form a network structure. It was envisaged that PDMS prepolymer was interpenetrated into CMC networks having HDA as a crosslinker (Figure 1). It was interesting to know that PDMS chains were covalently crosslinked or just physically penetrated in the networks. Another experiment was performed with the use of an excess of HDA to react with PDMS diol (2K) in an absence of CMC. After the coupling reaction, excess HDA was extracted from the product to yield the PDMS prepolymer (Figure 2). From FTIR spectra shown in Figure 3, characteristic signals of a urethane linkage at 1,722 and 1,644 cm^{-1} were observed, signifying the formation of PDMS prepolymer owing to the coupling reaction between PDMS diol and HDA.

3.2 Properties of PDMS-modified CMC hydrogels

3.2.1 Surface morphology

It should be noted that PDMS/CMC blend exhibited a macroscopic phase separation of hydrophobic PDMS in hydrophilic CMC continuous phase due to the absence of HDA crosslinker. Once HDA crosslinking agent was used in the reaction between CMC and PDMS, no macrophase separation was observed. According to SEM images of CMC hydrogels containing 20 wt% of 8K PDMS, the film surface showed some roughness due to the microphase separation of these two phases (Figure 4a). After soxhlet extractions with acetone for 2 h, submicron phase owing to the removal of PDMS with the size of 0.2-0.5 μm in diameter was thoroughly observed (Figure 4b). These results signified the improved miscibility between CMC and PDMS phases due to the formation of network structure. Lowering PDMS molecular weights (from 8K to 2K) or decreasing the percentage of PDMS added (from 20 wt% to 1-10 wt%) also showed the improved miscibility of the hydrogels with less degree of microphase separation.

3.2.2 Percent crosslinking and water swelling properties

Percent crosslinking of PDMS-modified CMC hydrogels ranged between 46 to 65% (Figure 5a). It should be noted that percent crosslinking of CMC-HDA (the films without PDMS) was 60 ± 5%. Increasing the percentage of PDMS from 1 wt% to 10 wt% in CMC hydrogels exhibited no significant change in percent crosslinking. Nonetheless, addition of 20 wt% PDMS showed a slight decrease in percent crosslinking. It was rationalized that excessive PDMS incorporated might inhibit the interpenetrating efficiency to CMC structure due to the inherently poor solubility of hydrophobic PDMS in aqueous solutions. These hydrogels exhibited impressively high %EWC up to 3,980% (absorbing water 39.8 times of its original weight) (Figure 5b). This extremely high water swellability is quite typical for CMC-based hydrogels.

Percent EWC of PDMS-modified CMC hydrogels dropped from 1,600% (the films without PDMS) to 600-700% after addition of only 1 wt% PDMS into CMC hydrogels. The decrease in %EWC was attributed to hydrophobic characteristics of PDMS, which can express its nature in CMC hydrogels. Percent EWC gradually arose as increasing percent of PDMS (1-5 wt%) in the CMC hydrogel and drastically increased at high PDMS concentrations (10-20 wt%). It was rationalized that the microphase separation of hydrophobic PDMS in hydrophilic CMC matrix as shown in SEM (Figure 4) might result in the increase in polymer-polymer and polymer-air interfaces in the hydrogels and essentially absorbing large amount of water. In addition, EWC properties of the films were in good agreement with their crosslinking percentages. Namely, as increasing PDMS content, the hydrogels formed the lowered crosslinked structure (less network density), which essentially facilitated their water swellability and thus increased percent EWC. However, increasing the molecular weight of PDMS from 2K to 8K seemed to slightly decrease percent EWC. This was probably due to the hydrophobic characteristics of high molecular weight PDMS (8K) as opposed to the low molecular weight one (2K).

3.2.3 Tensile properties

Tensile strength and elongation properties were investigated to determine the effect of PDMS on tensile properties of the hydrogels (Figure 6). Tensile properties of non-crosslinked and HDA-crosslinked CMC hydrogels were also testified as control samples. After crosslinking with HDA, their tensile strength retained while percent elongation slightly dropped probably due to the formation of network structure in the hydrogels.

Addition of highly flexible PDMS into CMC hydrogels seemed to improve their tensile properties as compared to those without PDMS. The increases in the amounts (from 1 wt% to 20 wt%) and the molecular weights (from 2K to 8K) of PDMS tended to increase both tensile strength and elongation of the hydrogels. It was reasoned that PDMS chains were covalently bound to the crosslinked structure and essentially improved the tensile strength of the hydrogels. Interestingly, the increase in the percent elongation of the hydrogels indicated the improved toughness of the hydrogels. This was attributed to the presence of PDMS microphase serving as a toughener in the CMC continuous phase.

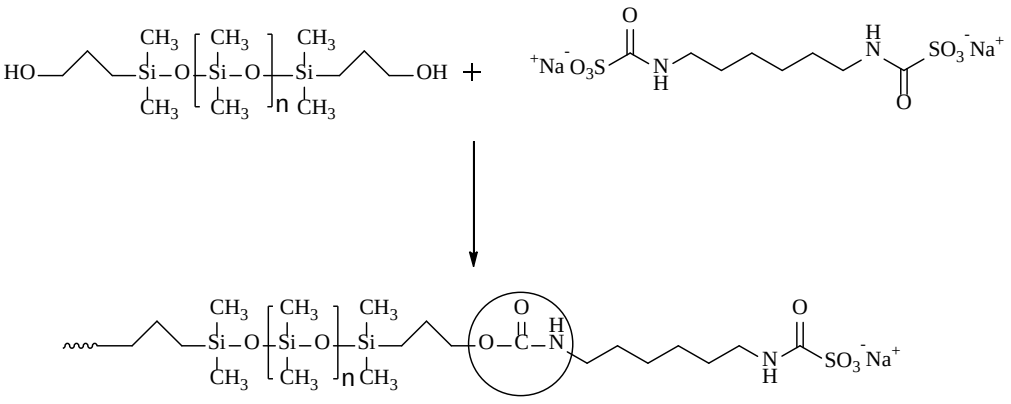

Figure 2. The coupling reaction between PDMS diol (2K) and HDA to form PDMS prepolymer (PDMS having aminocarboxysulfonate chain terminals).

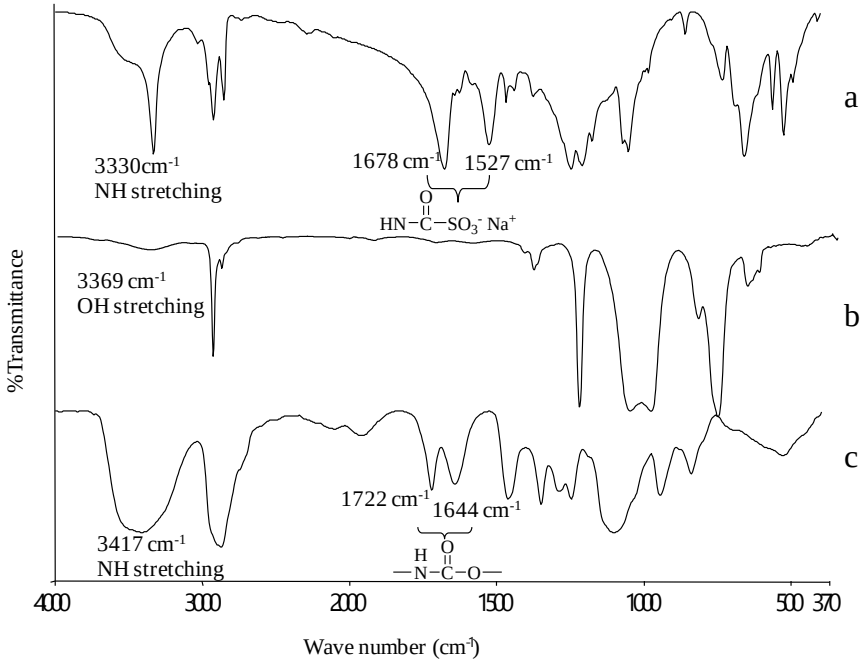

Figure 3. FTIR spectra of (a) HDA crosslinker, (b) PDMS diol and (c) PDMS prepolymer (PDMS having aminocarboxysulfonate chain terminals).

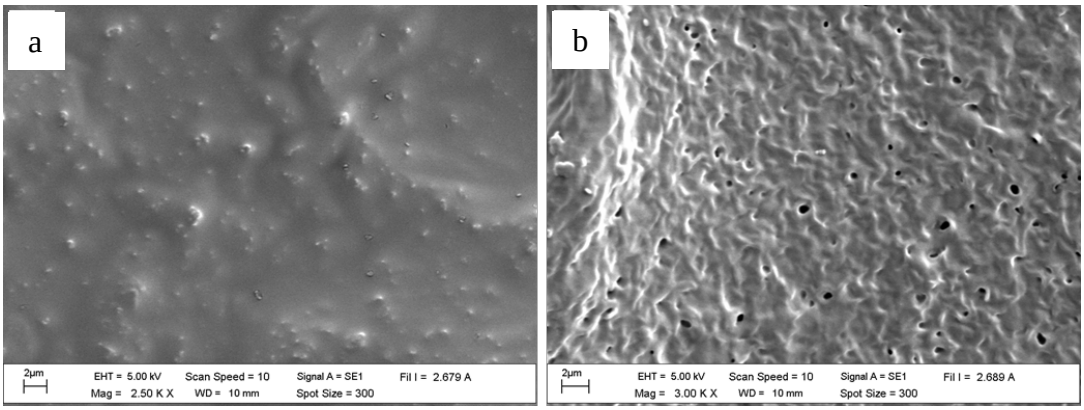

Figure 4. Surface morphology of dried CMC films containing 20 wt% of 8K PDMS; (a) before and (b) after soxhlet extractions with acetone.

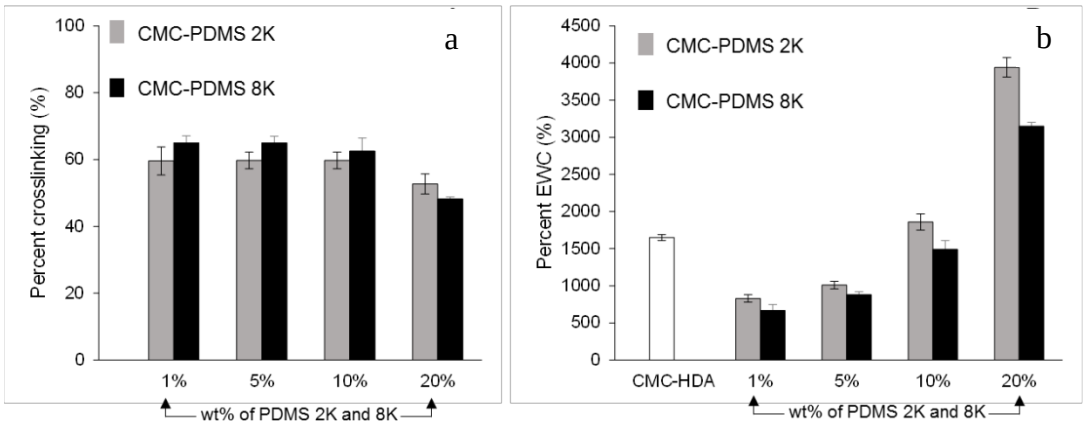

Figure 5. (a) Percent crosslinking and (b) percent EWC of PDMS-containing CMC hydrogels crosslinked with 10 wt% HDA as a crosslinker.

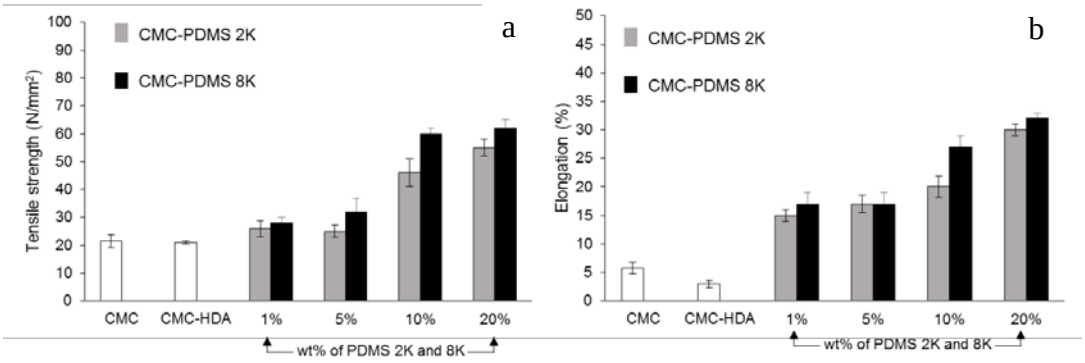

Figure 6. (a) Tensile strength and (b) elongation properties of CMC hydrogels with and without PDMS**.**

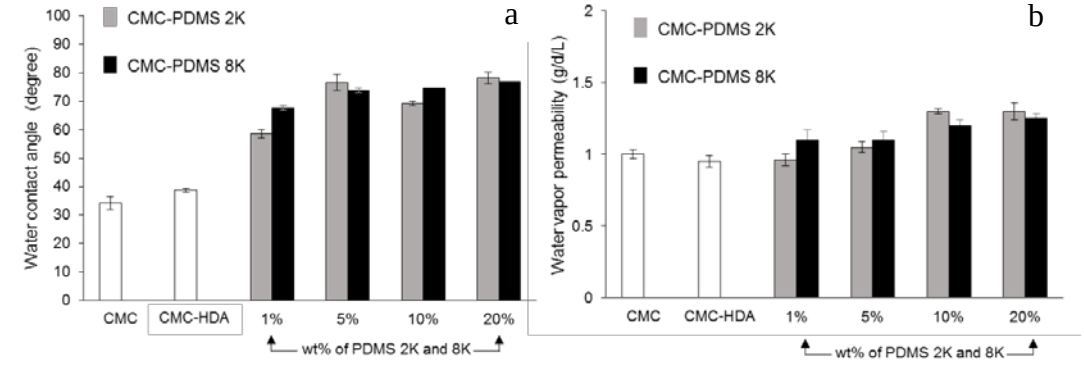

Figure 7. (a) Water contact angles and (b) water vapor permeabilities of CMC hydrogels with and without PDMS**.**

3.2.4 Water contact angles

Water contact angle measurements were performed on CMC hydrogels modified with 1-20wt% PDMS having two different molecular weights (2K and 8K) and those of unmodified CMC and HDA-crosslinked CMC hydrogels were also tested as control samples. According to the results in Figure 7a, addition of PDMS to the CMC hydrogels can apparently increase their surface hydrophobicity as indicated by the increase in water contact angles. Interestingly, increasing PDMS concentrations in CMC hydrogels seemed to increase their surface hydrophobicity. This was probably owing to the inherently hydrophobic characteristics of PDMS that was covalently bound in CMC continuous phase (indicated by FTIR results in Figure 3) and in the separated microphases (indicated by SEM results in Figure 4). However, increasing the molecular weights of PDMS from 2K to 8K did not show an obvious influence to their surface hydrophobicity.

3.2.5 Water vapor permeability

The study of water vapor permeability enables us to know the rate of moisture permeating through membranes. In this report, water vapor permeability of CMC hydrogels containing 1-20 wt% PDMS (2K and 8K) were investigated to compare with those of unmodified CMC and HDA-crosslinked CMC hydrogels as control samples. Water vapor permeability of unmodified CMC (0.99 ± 0.02 $g \cdot d^{-1} \cdot L^{-1}$) did not show a significant difference to that of HDA-crosslinked CMC (0.97 ± 0.01 $g \cdot d^{-1} \cdot L^{-1}$) (Figure 7b). Addition of PDMS to the CMC hydrogels seemed to slightly improve their water permeability. Increasing PDMS concentrations from 1 wt% to 20 wt% gradually improved the water vapor permeability of CMC hydrogels. However, increasing the molecular weights of PDMS from 2K to 8K did not exhibit some trend in the increase in water vapor permeability of the hydrogels.

4. Conclusions

This work presented the synthesis of hydrophilic CMC hydrogels containing hydrophobic PDMS with the use of HDA crosslinker to prevent macrophase separation. FTIR results indicated the covalent bonding of PDMS to CMC chains with HDA as a linker. SEM images exhibited some

microphase separation of PDMS thoroughly dispersed in CMC matrix. This microphase separation of PDMS rendered many advantages properties to the CMC hydrogels. For instance, water vapor permeability and water swellability of the hydrogels were improved when PDMS microphase occurred because of the formation of polymer-polymer and polymer-air interfaces and thus enhancing these properties. Tensile strength and elongation were also improved after the addition of highly flexible PDMS into the hydrogels. The modified CMC hydrogels possessed PDMS-enriched surface as indicated by their higher water contact angles than the unmodified CMC hydrogels. These properties can also be tuned by varying the amounts and molecular weights of PDMS incorporated into CMC hydrogels. These novel hydrogels might be a good candidate in advanced applications such as artificial skin, packaging and wound healing materials.

5. Acknowledgements

The authors thank the National Research Council of Thailand (NRCT) (R2560B090) for financial support.

References

[1] J. Cai, Q. Dang, C. Liu, B. Fan, J. Yan, Y. Xu, and J. Li, "Preparation and characterization of *N*-benzoyl-*O*-acetyl-chitosan," *International Journal of Biological Macromolecules*, 2015, vol. 77, pp. 52-58, 2015.

[2] M. Khemkhao, B. Nuntakumjorn, S. Techkarnjanaruk, and C. Phalakornkule, Bioresour Technol, "Effect of chitosan on UASB treating POME during a transition from mesophilic to thermophilic conditions," *Bioresource Technology*, vol. 102, pp. 4674-4681, 2011.

[3] J. Cai, Q. Dang, C. Liu, T. Wang, B. Fan, J. Yan, and Y. Xu, "Preparation, characterization and antibacterial activity of *O*-acetyl-chitosan-*N*-2-hydroxypropyl trimethyl ammonium chloride," International Journal of Biological Macromolecules, vol. 80, pp. 8-15, 2015.

[4] P. K. Dutta, S. Tripathi, G.K. Mehrotra, and J. Dutta, "Perspectives for chitosan based antimicrobial films in food applications," *Food Chemistry*, vol. 114, pp. 1173-1182, 2009.

[5] T. G. Liu, B. Li, W. Huang, B. Lv, J. Chen, J.X. Zhang, and L.P. Zhu, "Effects and kinetics of a novel temperature cycling treatment on the *N*-deacetylation of chitin in alkaline solution," *Carbohydrate Polymers*, vol. 77, pp. 110-117, 2009.

[6] R. Mahjub, T. Heidari Shayesteh, M. Radmehr, S. Y. Vafaei, M. Amini, R. Dinarvand, and F. A. Dorkoosh, "Preparation and optimization of *N*-trimethyl-*O*-carboxymethyl chitosan nanoparticles for delivery of low-molecular-weight heparin," *Pharmaceutical Development and Technology*, vol. 21, pp.14-25, 2016.

[7] T. D. A. Senra, D. M. Santos, J. Desbrières, and S. P. Campana-Filho, "Extensive *N*-methylation of chitosan: evaluating the effects of the reaction conditions by using response surface methodology," *Polymer International*, vol. 64, pp. 1617-1626, 2015.

[8] K. Wang, J. Zhuang, Y. Liu, M. Xu, J. Zhuang, Z. Chen, Y. Wei, and Y. Zhang, "PEGylated chitosan nanoparticles with embedded bismuth sulfide for dual-wavelength fluorescent imaging and photothermal therapy," *Carbohydrate Polymers*, vol. 184, pp. 445-452, 2018.

[9] T. Ouchi, H. Nishizawa, and Y. Ohya, "Aggregation phenomenon of PEG-grafted chitosan in aqueous solution," *Polymer*, vol. 39, pp. 5171-5175, 1998.

[10] A. Shirdast, A. Sharif, and M. Abdollahi, "Effect of the incorporation of sulfonated chitosan/sulfonated graphene oxide on the proton conductivity of chitosan membranes," *Journal of Power Sources*, vol. 306, pp. 541-551, 2016.

[11] K. R. Holme and A. S. Perlin, "Chitosan *N*-sulfate. A water-soluble polyelectrolyte," *Carbohydrate Research*, vol. 302, pp. 7-12, 1997.

[12] M. Wu, Z. Long, H. Xiao, and C. Dong, "Preparation of *N*, *N*, *N*-trimethyl chitosan *via* a novel approach using dimethyl carbonate," *Carbohydrate Polymers*, vol. 169, pp. 83-91, 2017.

[13] Z. Jia, D. shen and W. Xu, "Synthesis and antibacterial activities of quaternary ammonium salt of chitosan," *Carbohydrate Research*, vol. 333, pp. 1-6, 2001.

[14] Z. Zhang, F. Jin, Z. Wu, J. Jin, F. Li, Y. Wang, Z. Wang, S. Tang, C. Wu, and Y. Wang, "*O*-acylation of chitosan nanofibers

by short-chain and long-chain fatty acids," *Carbohydrate Polymers*, vol. 177, pp. 203-209, 2017.

[15] Y. Machida, T. Nagai, M. Abe, and T. Sannan, "Use of chitosan and hydroxypropylchitosan in drug formulations to effect sustained release," *Drug Design and Delivery*, vol. 1, pp. 119-130, 1986.

[16] A. Fiamingo and S. P. Campana-Filho, "Structure, morphology and properties of genipin-crosslinked carboxymethylchitosan porous membranes," *Carbohydrate Polymers*, vol. 143, pp. 155-163, 2016.

[17] X. G. Chen and H.-J. Park, "Chemical characteristics of *O*-carboxymethyl chitosans related to the preparation conditions," *Carbohydrate Polymers*, vol. 53, pp. 355-359, 2003.

[18] D. Lv, M. Zhang, J. Cui, J. Lu, and W. Li, "Grafting of edible colorants onto *O*-carboxymethyl chitosan: preparation, characterization and anti-reduction property evaluation," *New Journal of Chemistry*, vol. 40, pp. 3363-3369, 2016.

[19] R. Jankaew, N. Rodkate, S. Lamlertthon, B. Rutnakornpituk, U. Wichai, G. Ross, and M. Rutnakornpituk, ""Smart" carboxymethyl chitosan hydrogels crosslinked with poly(*N*-isopropylacrylamide) and poly(acrylic acid) for controlled drug release," *Polymer Testing*, vol. 42, pp. 26-36, 2015.

[20] N. Rodkate and M. Rutnakornpituk, "Multi-responsive magnetic microsphere of poly(*N*-isopropylacrylamide)/ carboxymethylchitosan hydrogel for drug controlled release," *Carbohydrate Polymers*, vol. 151, pp. 251-259, 2016.

[21] L. Fan, Y. Du, B. Zhang, J. Yang, J. Zhou, and J. F. Kennedy, "Preparation and properties of alginate/carboxymethyl chitosan blend fibers," *Carbohydrate Polymers*, vol. 65, pp. 447-452, 2006.

[22] S. Yu, F. Mi, S. Shyu, C. Tsai, C. Peng, and J. Lai, "Miscibility, mechanical characteristic and platelet adhesion of 6-*O*-carboxymethylchitosan/polyurethane semi-IPN membranes," *Journal of Membrane Science*, vol. 276, pp. 68-80, 2006.

[23] Y. Chen, Y. Zhang, F. Wang, W. Meng, X. Yang, P. Li, J. Jiang, H. Tan, and Y. Zheng, "Preparation of porous carboxymethyl chitosan grafted poly(acrylic acid) superabsorbent by solvent precipitation and its application as a hemostatic wound dressing," *Materials Science & Engineering. C, Materials for Biological Applications*, vol. 63, pp. 18-29, 2016.

[24] Q.B. Wei, F. Fu, Y.-Q. Zhang, and L. Tang, "Synthesis and characterization of pH-responsive carboxymethyl chitosan-g-polyacrylic acid hydrogels," *Journal of Polymer Research*, vol. 22, pp. 1-8, 2015.

[25] Y. Chen, W. Liu, G. Zeng and Y. Liu, "Microporous PDMAEMA-based stimuli-responsive hydrogel and its application in drug release," *Journal of Applied Polymer Science*, vol. 134, p. 45326, 2017.

[26] N. Rodkate, B. Rutnakornpituk, U. Wichai, G. Ross, and M. Rutnakornpituk, "Smart carboxymethylchitosan hydrogels that have thermo- and pH-responsive properties," *Journal of Applied Polymer Science*, vol. 132, p. 41505, 2015.

[27] Y. Chen, C. Peng, Y. Lu, W. Liu and W. Xu, "Responsiveness and release characteristic of semi-IPN hydrogels consisting of nano-Sized clay crosslinked poly(dimethylaminoethyl methacrylate) and linear carboxymethyl chitosan," *Journal of Nanoscience and Nanotechnology*, vol. 15, pp.164-171, 2015.

[28] M. G. Antoniraj, C. S. Kumar, and R. Kandasamy, "Synthesis and characterization of poly(*N*-isopropylacrylamide)-g-carboxymethyl chitosan copolymer-based doxorubicin-loaded polymeric nanoparticles for thermoresponsive drug release," *Colloid and Polymer Science*, vol. 294, pp. 527-535, 2015.

[29] B. L. Guo and Q. Y. Gao, "Preparation and properties of a pH/temperature-responsive carboxymethyl chitosan/poly(*N*-isopropyl acrylamide)semi-IPN hydrogel for oral delivery of drugs," *Carbohydrate Research*, vol. 342, pp. 2416-2422, 2007.

[30] F. Yoshii, L. Zhao, R. A. Wach, N. Nagasawa, H. Mitomo, and T. Kume, "Hydrogels of polysaccharide derivatives crosslinked with irradiation at paste-like condition," *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, vol. 208, pp. 320-324, 2003.

[31] Y. F. Liu, K. L. Huang, D. M. Peng, P. Ding, and G.Y. Li, "Preparation and characterization of

glutaraldehyde cross-linked *O*-carboxymethyl chitosan microspheres for controlled delivery of pazufloxacin mesilate," *International Journal of Biological Macromolecules*, vol. 41, pp. 87-93, 2007.

[32] A. Kadnaim, W. Janvikul, U. Wichai, and M. Rutnakornpituk, "Synthesis and properties of carboxymethylchitosan hydrogels modified with poly(ester-urethane)," *Carbohydrate Polymers*, vol. 74, pp. 257-267, 2008.

[33] M. Rutnakornpituk, P. Ngamdee, and P. Phinyocheep, "Synthesis, characterization and properties of chitosan modified with poly(ethylene glycol)-polydimethylsiloxane amphiphilic block copolymers," *Polymer*, vol. 46, pp. 9742-9752, 2005.

[34] M. Rutnakornpituk and P. Ngamdee, "Surface and mechanical properties of microporous membranes of poly(ethylene glycol)-polydimethylsiloxane copolymer/ chitosan," *Polymer*, vol. 47, pp. 7909-7917, 2006.

[35] W. C. Huang, K. H. Liu, T. C. Liu, D. M. Liu, and S.Y. Chen, "Synergistic hierarchical silicone-modified polysaccharide hybrid as a soft scaffold to control cell adhesion and proliferation," *Acta Biomaterialia*, vol. 10, pp. 3546-3556, 2014.

[36] M. Bračič, T. Mohan, T. Griesser, K. Stana-Kleinschek, S. Strnad, and L. Fras-Zemljič, "One-Step noncovalent surface functionalization of PDMS with chitosan-based bioparticles and their protein-repellent properties," *Advanced Materials Interfaces*, vol. 4, pp. 1700416, 2017.

[37] W. C. Huang, S. Y. Chen, and D. M. Liu, "An amphiphilic silicone-modified polysaccharide molecular hybrid with in situ forming of hierarchical superporous architecture upon swelling," *Soft Matter*, vol. 8, pp. 10868, 2012.

[38] N. Rodkate, U. Wichai, B. Boontha, and M. Rutnakornpituk "Semi-interpenetrating polymer network hydrogels between polydimethyl siloxane/polyethylene glycol and chitosan", *Carbohydrate Polymer*, vol. 81, pp. 617-625, 2010.