Carbohydrate Polymers 82 (2010) 412–418

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

# Photo-crosslinked glucose-sensitive hydrogels based on methacrylate modified dextran–concanavalin A and PEG dimethacrylate

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ARTICLE INFO

*Article history:*
Received 26 March 2010
Received in revised form 26 April 2010
Accepted 27 April 2010
Available online 26 May 2010

*Keywords:*
Photo-crosslinking
Hydrogels
Glucose-sensitive
Dextran
Concanavalin A

ABSTRACT

A series of glucose-sensitive hydrogels based on glycidyl methacrylate modified dextran (Dex-G), ethylene glycol acrylate methacrylate modified concanavalin A (Con A–E) and poly (ethylene glycol) dimethacrylate (PEGDMA) were synthesized by photopolymerization. The Dex-G precursor was prepared through ring-opening reaction, while Con A–E was obtained from Michael addition reaction. FT-IR was used to characterize the structures of pre-polymers and hydrogels. The degree of substitution (DS) of Dex-G was confirmed by $^1$H NMR and the activity of modified Con A was approved by fluorescence spectroscopy. Swelling test, component loss measurement and SEM observation demonstrated that the size of hydrogels changed differently in the medium of different glucose concentrations and the glucose sensitivity was influenced by the content of component, especially PEGDMA. SEM image also displayed that hydrogels had microporous structures. All the results indicated that the hydrogels had glucose-sensitive property and good biocompatibility, which could be prospectively applied as glucose biosensor and intelligent insulin delivery carrier.

## 1. Introduction

Stimuli-sensitive hydrogels, also known as “smart” or “intelligent” materials, which can sense environmental changes and induce structural changes by themselves, have attracted considerable attention in the biomedical and biochemical areas (Miyata, Uragami, & Nakamae, 2002). Glucose-responsive hydrogels, which exhibit swelling changes in response to glucose concentration, are very useful for applications such as biosensing, microfluidics and bio-microelectromechanical systems, as well as implantable drug delivery systems for diabetes management applications (Kost & Langer, 2001; Qiu & Park, 2001; Robert & Nicholas, 2003). Four types of glucose-sensitive hydrogels have been intensively investigated, which are on the basis of glucose oxidase (Qi et al., 2009), concanavalin A (Che, Liu, Huang, Wang, & Xu, 2008; Kim & Park, 2001), phenylboronic acid (Jin et al., 2009; Matsumoto, Ikeda, Harada, & Kataoka, 2003) and glucose binding protein (Jason et al., 2009).

Concanavalin A (Con A), a sugar-binding lectin from jack bean, shows reversible strong affinity for non-reducing α-D-mannose, α-D-glucose, N-acetyl-D-glucosamine and polysaccharide as dextran with unmodified hydroxyl groups at C-3, C-4 and C-6, and the competitiveness of these substrates decrease following the sequence mentioned above, which makes it useful for fabricating glucose-sensitive systems (Kim & Park, 2001). Many researches, such as Obaidat and Park (1997), Ballerstadt and Schultz (1998), and You, Lu, Li, Zhang and Li (2002), have reported Con A reacted with polymers containing terminal or pendant glucose moieties to form glucose-sensitive hydrogels. However, these hydrogels are vulnerable to component loss, especially Con A loss, which could lead to weak glucose sensitivity and undesirable biocompatibility. Therefore, it is necessary to develop efficient crosslinking hydrogels and covalently immobilize Con A to polymer matrix. Some investigations have developed Con A covalent-binding gels by using carbodiimide reaction, ring-opening reaction and Schiff base reaction (Ladmiral et al., 2006; Tanna, Joan Taylor, Sahota, & Sawicka, 2006; Tanna, Sahota, Clark, & Taylor, 2002; Tanna, Sahota, Sawicka, & Taylor, 2006; Zhang, Tang, Bowyer, Eisenthal, & Hubble, 2006). Hydrogels obtained from these approaches have been shown to resist component loss and maintained glucose sensitivity to a certain extent. But available modification of protein calls for mild synthetic condition and high reaction efficiency. More efficient way to modify Con A and crosslink hydrogel components should be investigated.

Hence, here we introduced Michael addition reaction of Con A and ethylene glycol acrylate methacrylate (EGAMA) at room temperature to covalently bind Con A efficiently, then form hydrogel matrix with glycidyl methacrylate modified dextran (Dex-G) and the crosslinker poly (ethylene glycol) dimethacrylate (PEGDMA)

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doi:10.1016/j.carbpol.2010.04.075

by using photopolymerization. Dextran, composed of α-D-glucose residues, is polysaccharide with favorable biocompatibility and has been used in various biomedical applications (Sarmento, Ribeiro, Veiga, & Ferreira, 2006). Glycidyl methacrylate modification of dextran has been a complimentary method to develop immobilized dextran hydrogels with the objective of biomaterial applications (Lee, Boettiger, & Composto, 2008). PEGDMA is an unsaturated linear polyether with methacrylate double bonds that can be crosslinked by photopolymerization. Cross-linked PEGDMA, which have been successfully used by several groups both in vitro and in vivo, have been shown to be biocompatible (Lin-Gibson et al., 2004; Zhou, Yang, Nie, Ren, & Cui, 2009).

In this study, hydrogels with glucose-sensitive property and improved biocompatibility on the basis of methacrylate derivatives of dextran and Con A were fabricated. We first prepared the precursors of Dex-G and Con A–E, followed by cross-linking hydrogels through UV-polymerization. FT-IR was recorded to assess the structures of pre-polymers and hydrogels. The degree of substitution (DS) of Dex-G was confirmed by $^1$H NMR and the activity of modified Con A was approved by fluorescence spectroscopy. Swelling test, component loss measurement and SEM were used to study the glucose sensitivity, the effect of hydrogel compositions, the advantage of Con A modification, and the microstructures of different hydrogels.

## 2. Methods

### 2.1. Materials

Dextran ($\bar{M}_w$ 40 kDa) was obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Concanavalin A (Con A; type IV, extracted from Jack Bean, $\bar{M}_w$ 102 kDa, BR) and D-glucose anhydrouse (AR) were purchased from Yuanju Bio-Tech Co., Ltd (Shanghai, China). Acryloyl chloride was supplied by Shanghai Chemical Reagents Company (China). 2-Hydroxyethyl methacrylate (HEMA) was purchased from Beijing Chemical Reagents Company (China), distilled under reduced pressure and stored at 4 °C until use. Chloroform and triethylamine were also obtained from Beijing Chemical Reagent Company (China). 4-(N,N-dimethylamino) pyridine (DMAP, 99%) was purchased from J&K chemical, Ltd., Beijing, China. Glycidyl methacrylate (GMA) and polyethylene glycol (600) diamethacrylate (PEGDMA) were donated by Sartomer Company, Inc., USA, and used without further purification. The photoinitiator 2-hydroxy-1-[4-(hydroxyethoxy) phenyl]-2-methyl-1-propanone (Irgacures 2959) was offered by Ciba-Geigy Chemical Co. (Switzerland). Other reagents were all obtained from Beijing Chemical Agent Co. (Beijing, China) and used as received.

### 2.2. Synthesis of methacrylated dextran

Methacrylated dextran (Dex-G), was synthesized according to the literature (van Dijk-Wolthuis et al., 1995) with slight modification. Dextran (5.0 g) was dissolved in DMSO (50 mL) in a round bottom flask under nitrogen purge, followed by adding DMAP (1.0 g) and GMA (1.0 g) to get a clear solution. The reaction took place at 33 °C under stirring for 48 h, after which it was stopped by adding HCl to neutralize the DMAP. Subsequently, the solution was poured into 200 mL of ethanol to remove the unreacted reactant, filtrated to collect solid, then dialyzed against distilled water at 4 °C for 4 days. The product Dex-G was freeze-dried and stored at −20 °C before use with yield of 80%.

### 2.3. Synthesis of methacrylated Con A

Ethylene glycol acrylate methacrylate (EGAMA) was first prepared according to the previously reported method (Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004). Briefly, 105 mL of triethylamine and 83.81 g of HEMA were dissolved in 250 mL of toluene in a three-necked flack equipped with stirrer, thermometer and dropping funnel, under cooling. 79.79 g of acryloyl chloride dissolved in 50 mL of toluene was dropped into the mixture within 4 h. After dropping, the mixture was allowed to stir for another 4 h and then stand overnight. The obtained solution was filtered and then the filtered liquid was extracted three times with 1 mol/L HCl, 1 mol/L $NaHCO_3$ solution and deionized water, respectively, then anhydrous $Na_2SO_4$ was added overnight to get rid of residual water. In the end, toluene was removed by rotary evaporation and the obtained yellow liquid was dried under vacuum at room temperature, then purified by silica gel column chromatography. The yield was up to 70%.

Methacrylated Con A (Con A–E), was then synthesized through Michael addition reaction. 0.5 g of Con A was dissolved in 200 mL phosphate buffer solution (PBS, pH 7.4). 0.15 g of EGAMA dissolved in 1 mL ethanol was then dropped into the solution and stirred for 36 h at room temperature. After that, the solution was extensively dialyzed against distilled water at 4 °C for 5 days and freeze-dried to get pure Con A–E with yield of 66%. The product was stored at −20 °C before use.

### 2.4. Preparation of photo-crosslinked hydrogel

The hydrogel was prepared by first mixing Dex-G with Con A–E solution (PBS, pH 7.0, 0.1 M KCl, 0.1 mM $CaCl_2$, 0.1 mM $MnCl_2$, 6 h before utilization to allow the reactivation of the denatured lectin by $Ca^{2+}$ and $Mn^{2+}$) for 3 h, then adding PEGDMA and photoinitiator I 2959 (0.1 wt%) to get a final mixture. After mild stir and ultrasonication, the mixture was transferred into a flat mold consisting of two glass plates (25 mm × 25 mm) separated by a 2-mm thick spacer (diameter 12 mm), and then exposed to ultraviolet light (365 nm, EXFO lite, EFOS Corporation, Mississauga, Canada) at intensity of 30 mW/cm$^2$ for 3 min. Subsequently, the resultant hydrogels were washed with distilled water to remove the unreacted components, then freeze dried and stored at 4 °C prior to use.

The final concentration of reactant in the mixtures was about 12 wt% for all polymerized mixtures, and hydrogels with different weight ratio of Dex-G, Con A–E and PEGDMA were synthesized here, which was listed in Table 1. The hydrogel using unmodified

**Table 1**
Weight ratio of reactant and glucose-sensitive swelling behaviors of hydrogels.

| Sample code | Dex-G/Con A–E (weight ratio) | PEGDMA/(Dex-G + Con A–E) (weight ratio) | ESR[b] (in glucose 0 mg/mL) | ESR[b] (in glucose 4 mg/mL) | $T_{ESR}$ (min) | RI |
|---|---|---|---|---|---|---|
| Hydrogel-1 | 10/3 | 1/10 | 4.22 | 3.64 | 3 | −0.58 |
| Hydrogel-2 | 10/10 | 1/10 | 4.56 | 3.83 | 2 | −0.73 |
| Hydrogel-3 | 10/1 | 2.5/10 | 3.51 | 3.56 | 15 | 0.05 |
| Hydrogel-4 | 10/5 | 2.5/10 | 4.58 | 4.79 | 20 | 0.21 |
| Hydrogel-5 | 10/10 | 2.5/10 | 4.36 | 4.67 | 25 | 0.31 |
| Control sample[a] | 10/10 | 2.5/10 | 4.23 | 4.58 | 7 | 0.35 |

[a] Control sample used unmodified Con A instead of Con A–E.

[b] ESR of hydrogel-1, hydrogel-2 and control sample were maximum swelling ratio, since these three could not achieve equilibrium owing to component loss.

Con A, with a composition as the same with hydrogel-5, was also prepared as control (named control sample).

### 2.5. Structural characterization of Dex-G, Con A–E and the obtained hydrogels

Fourier transform infrared (FT-IR) spectra, recorded on the Nicolet 5700 instrument, were used to confirm the structure of Dex-G, Con A–E, and various hydrogels. Samples were prepared as KBr pellet and scanned against a blank KBr pellet background at wavenumber ranging from 4000 to 650 $cm^{-1}$ with resolution of 4.0 $cm^{-1}$.

The structure and DS of Dex-G were investigated by $^1H$ nuclear magnetic resonance (NMR) with a BrukerAV600 unity spectrometer operated at 600 MHz, with $D_2O$ as solvent and tetramethysilane (TMS) as the internal standard.

The activity of Con A–E was determined by analysis of the structure stability of Con A–E by using a Hitachi F-4500 Fluorescence spectrophotometer at an excitation wavelength of 278 nm and emission wavelength of 337 nm. The resulting spectrum was compared to unmodified Con A.

### 2.6. Swelling behaviors of hydrogels

The swelling ratio (SR) of hydrogel samples was analyzed by keeping immersed the hydrogels at 37 °C (±0.5 °C) in PBS (pH 7.4) with different glucose concentrations (0 and 4 mg/mL) while shaking (100 r/min). At appropriate time intervals, samples were taken out and the surplus surface water was removed by filter paper. The humid weight was then measured carefully. SR of a sample was calculated as follows:

$$\mathrm{SR} = \frac{W_t - W_0}{W_0} \tag{1}$$

where $W_0$ is the initial dry weight and $W_t$ is the wet weight at time $t$, respectively.

When a hydrogel reaches its swelling equilibrium state for a fixed period of time, the swelling ratio is called equilibrium swelling ratio (ESR). According to the previous article (Wang et al., 2010), we defined responsive index (RI) here to personify glucose sensitivity of the hydrogel:

$$\mathrm{RI} = \mathrm{ESR}_{(\text{in glucose 4 mg/mL})} - \mathrm{ESR}_{(\text{in glucose 0 mg/mL})} \tag{2}$$

where $\mathrm{ESR}_{(\text{in glucose 4 mg/mL})}$ and $\mathrm{ESR}_{(\text{in glucose 0 mg/mL})}$ are the equilibrium swelling ratio of hydrogels in different medium of PBS (pH 7.4) with glucose concentrations of 4 and 0 mg/mL, respectively. The time to reach equilibrium swelling was named $T_{\mathrm{ESR}}$. The results were also listed in Table 1. All measurements were replicated three times.

RI was defined as the difference between equilibrium swelling at different glucose concentrations. Increasing in RI indicated that the difference enhanced and the glucose sensitivity of the hydrogels increased accordingly.

### 2.7. Characterization of Con A (or Con A–E) loss

Concanavalin A (or Con A–E) was apt to leach out from the hydrogels during swelling process. Leached Con A from different hydrogels was measured by the fluorescence spectrophotometer at an emission wavelength of 337 nm. The ratio of Con A loss was calculated as the ratio of fluorescence intensity at 337 nm in the medium of PBS (pH 7.4) with glucose concentrations of 4 and 0 mg/mL.

### 2.8. Characterization of morphology and porosity

The morphologies and pore structures of different hydrogels were observed by a Hitachi S-4700 scanning electron microscopy (SEM) at an accelerating voltage of 10 kV. Prior to the observation, specimen were fixed on stubs with sputter coated with gold.

## 3. Results and discussion

### 3.1. FT-IR and $^1H$ NMR characterization of Dex-G

Dex-G was achieved by ring-opening reaction of glycidyl methacrylate with dextran (see Fig. 1a). The efficient method to obtain dextran with polymerizable groups has been described by van Dijk-Wolthuis et al. (1995). FT-IR spectra confirmed the structure of Dex-G (see Fig. 2a). The increase of peaks at 1714 and 810 $cm^{-1}$ in the spectrum of Dex-G corresponded to the methacrylate carbonyl and vinyl groups (C=O stretch and C—H stretch of $—C{=}CH_2$) respectively, which was similar to the character peaks of GMA (1725 and 810 $cm^{-1}$). The result indicated that the methacrylate double bonds of GMA were introduced to the side-chain of dextran (Lee, Boettiger, & Composto, 2008).

The $^1H$ NMR spectra of dextran and Dex-G in $D_2O$ were shown in Fig. 2b. In the spectrum of dextran, the signal from the anomeric proton of the glucopyranosyl ring, also known as the proton at the anomeric carbon of the α-1,6 linkages ($H^a$, at 4.9 ppm) was well separated from the multiplet peaks from 3.3 to 4.0 ppm. The low-intensity signal at 5.3 ppm was assigned to the proton at the anomeric carbon of the α-1, 3 linkages ($H^{a'}$). From the ratio of the integrals of 5.3 and 4.9 ppm, on the average 4.0% of α-1,3 linkages was calculated, which was common for the dextran used in this study. In the spectrum of Dex-G, the signals from the methacryloyl group were observed at 1.95 ppm (methyl protons, $H^b$) as well as at 5.75 and 6.2 ppm (protons at the double bond, $H^c$), having an inte-

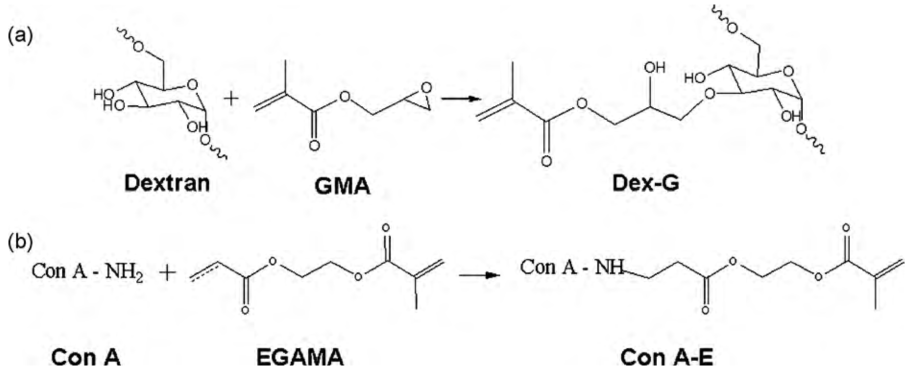

**Fig. 1.** Reaction process of Dex-G (a) and Con A–E (b).

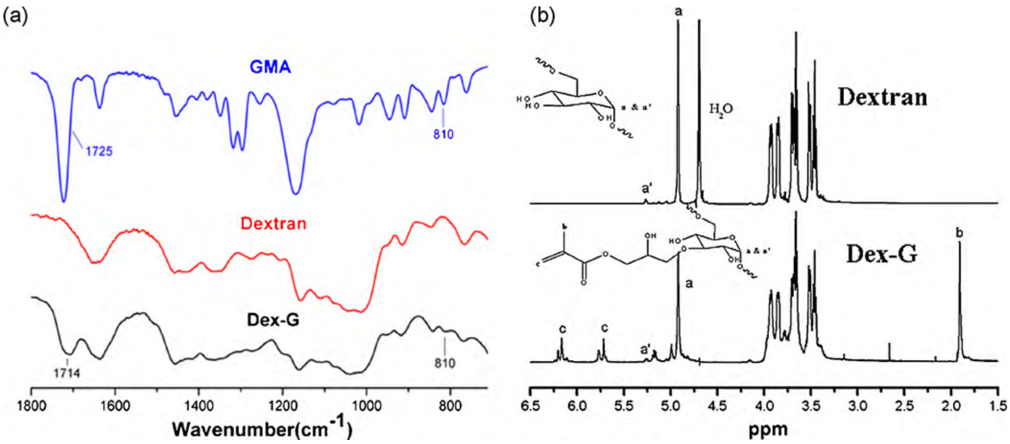

**Fig. 2.** (a) FT-IR spectra of GMA, dextran, Dex-G and (b) $^1$H NMR spectra of dextan and Dex-G with $D_2O$ as solvent.

gral ratio of 3:2 as expected. According to the assignment of the $^1$H NMR spectra, the DS of Dex-G was calculated as $100X/Y$ (van Dijk-Wolthuis et al., 1995), in which $X$ was the average peak area of the protons at the double bond, and $Y$ was the integral of the anomeric proton at 4.9 ppm with addition of 4.0% of α-1,3 linkages. The DS here was about 19.

### 3.2. Structure and activity of Con A–E

Modification of protein calls for mild conditions to inhibit the denaturation during the process. Here, Michael addition reaction was used to obtain methacrylated Con A (Con A–E), making the amino groups of protein react with the acrylate double bonds of EGAMA (see Fig. 1b). The whole process was taken place under room temperature in PBS (pH 7.4), therefore the activity of Con A could be protected.

FT-IR was used to analyze the structure of unmodified and modified Con A (Tanna et al., 2006a,b). Fig. 3a demonstrated the FT-IR spectra of EGAMA, Con A and Con A–E. Comparing to Con A, Con A–E showed two new character peaks similar to EGAMA, one at 1720 cm$^{-1}$ which could be attributed to ester bond formation, the other at 810 cm$^{-1}$ which was due to the wagging of the vinylidene (C=CH) deformation. The result indicated that the acrylate double bond of EGAMA had reacted with $-NH_2$ group of Con A. However, the Con A–E had a very small peak area at 810 cm$^{-1}$ and this could be owing to the derivatised lectin having a low DS.

Fluorescence spectrophotometer was used to evaluate the conformational changes of protein (Amidi et al., 2008; Murali & Jayakumar, 2005). Fig. 3b showed the fluorescence spectra of unmodified and modified Con A, which revealed the tertiary structure. Con A–E and Con A displayed similar peaks with an emission maximum at 337 nm, indicating that the tertiary structure of Con A was not distorted. It could be inferred that the methacrylated Con A stayed active.

### 3.3. FT-IR spectra of hydrogels

The obtained hydrogels were analyzed by FT-IR (Fig. 4). The peak originating from the methacylate double bond (810 cm$^{-1}$) disappeared after polymerization, indicating that the hydrogels were successfully cross-linked by UV light. A more prominent carbonyl peak (1720 cm$^{-1}$) was observed in hydrogel-5 compared to control sample, which could be attributed to the generated methacrylate substitute of Con A–E. From the spectra of hydrogel-1 to hydrogel-5, there were no novel peaks and no significant peak shifts occurred in these hydrogels, but slightly increase in carbonyl peak area with the increscent of Con A–E and PEGDMA content.

### 3.4. Glucose-sensitive swelling behaviors

According to present research (Zhang et al., 2006), hydrogels obtained from dextran and Con A have the ability to change in response to different glucose concentrations in the environment, which is due to the reversible specific lectin–saccharide binding property. In this study, the swelling property of various hydrogels in the medium of different glucose concentrations (0 and 4 mg/mL) has been investigated (Table 1). The effect of Con A–E content on swelling behavior could be observed. For hydrogels with the same

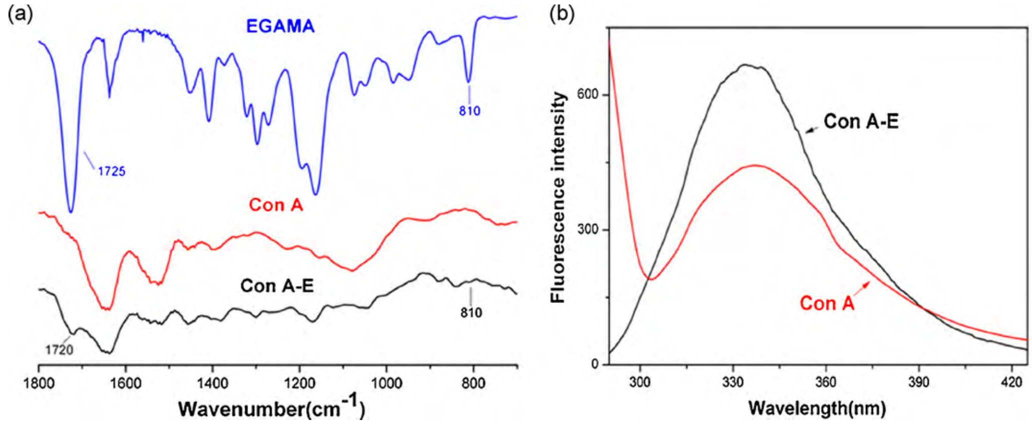

**Fig. 3.** (a) FT-IR spectra of EGAMA, Con A, Con A–E and (b) fluorescence spectra of Con A and Con A–E.

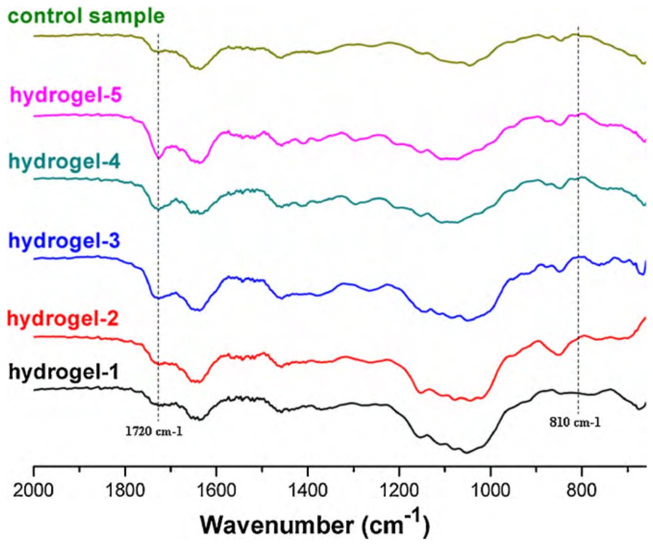

**Fig. 4.** FT-IR spectra of different hydrogels obtained from photopolymerization.

compositions of Dex-G and PEGDMA (hydrogel-3 to hydrogel-5), RI increased with the increase of Con A–E content, thus the glucose sensitivity of the hydrogels increased accordingly, demonstrating that the glucose sensitivity of the hydrogels was strongly associated with the content of Con A–E.

Moreover, from Table 1 it could be seen that the swelling behavior was also influenced by the content of PEGDMA, which was used as the cross-linking agent. In hydrogel-1 and hydrogel-2, the hydrogels reached a maximum swelling ratio very fast, within only a few minutes, then the swelling ratio decreased, even could not achieve equilibrium and the phenomenon was much more apparent in the presence of glucose. This was probably caused by the leakage of uncoupled components, especially the Con A–E with low DS. With the increase of PEGDMA (hydrogel-3 to hydrogel-5), the cross-linking density increased, resulting in more opportunities of Con A–E binding in the hydrogel and thereby much more obvious glucose sensitivity.

Fig. 5 depicted the dynamic swelling behavior of control sample and hydrogel-5 in PBS (pH 7.4) with glucose concentrations of 0 and 4 mg/mL. For both hydrogels, water-absorbing was performed dramatically at the very beginning of swelling process, no matter glucose existed or not, on account of the high hydrophilic components of the hydrogels. But the swelling ratios in glucose solution were much higher than that in PBS (pH 7.4) solution, which could be attributed to that glucose competed with dextran for the binding site of Con A protein, resulting in the disconnection of lectin–saccharide crosslinking in the hydrogels. However, compared to control sample (Fig. 5a), the swelling ratio of which in glucose 4 mg/mL stayed increase for only less than 10 min and then decreased significantly, hydrogel-5 (Fig. 5b) showed stable glucose-sensitive swelling behavior, which might be mainly owing to the photo-crosslinking of Con A–E prevented the leakage of lectin. The result indicated that hydrogel made from Con A–E maintained sensitivity to glucose and developed better swelling ability than that made from unmodified Con A.

### 3.5. Comparison of component loss

Component loss, mainly Con A loss, was the primary problem which restricted the glucose sensitivity of the hydrogels obtained from dextran and Con A. In the present researches, dextran–Con A hydrogels showed component loss in the receptor fluid, as monitored at 276 nm in the in vitro diffusion experiments, and

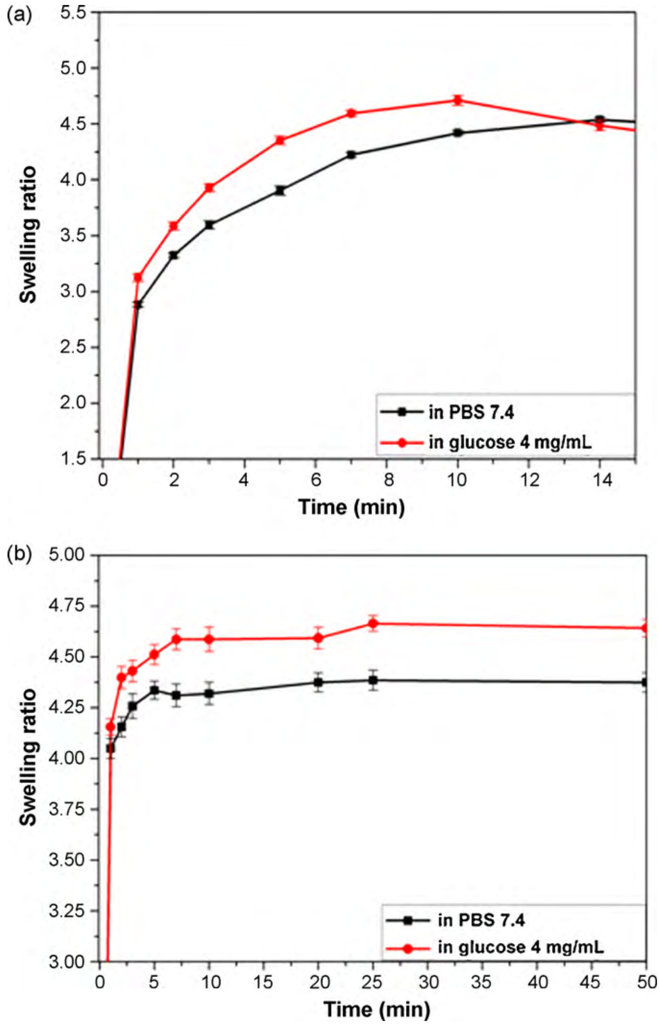

**Fig. 5.** Dynamic swelling behavior of control sample (a) and hydrogel-5 (b) in PBS (pH 7.4) with glucose concentrations of 0 and 4 mg/mL.

crosslinking to prevent component loss was the main purpose in the study of polymerizing dextran and Con A (Tanna, Taylor, & Adams, 1999; Taylor, Tanna, & Sahota, 2008). Fig. 6 displayed the comparison of Con A (or Con A–E) loss from different hydrogels. It could be observed that the ratio of Con A loss from hydrogels contained Con A–E was much lower than that from control

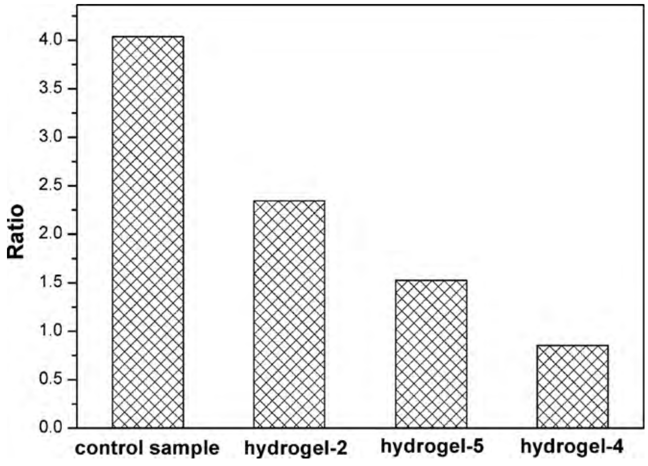

**Fig. 6.** Comparison of the ratio of Con A loss from different hydrogels.

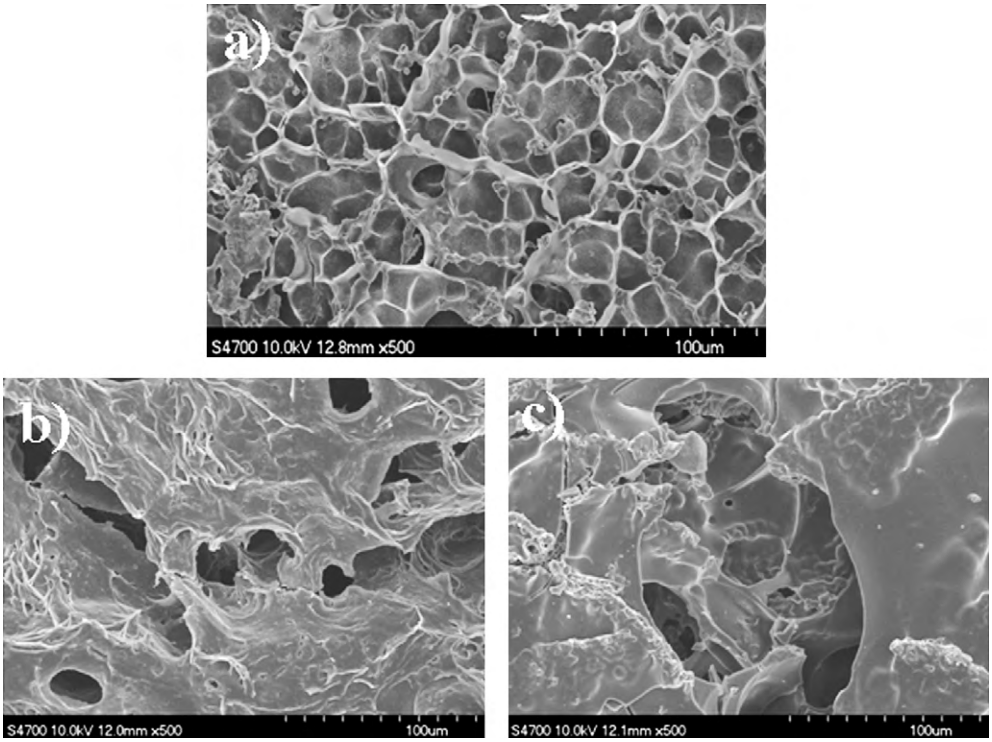

**Fig. 7.** SEM images of freeze drying hydrogels after just photo-crosslinking (a), swelling in PBS (pH 7.4) with glucose concentrations of 0 mg/mL (b) and 4 mg/mL (c).

sample and the ratio decreased with the increscent content of PEGDMA. This could be ascribed to the covalent binding of Con A–E to the hydrogels and more bonding opportunities with the increase of double-bond density. The result demonstrated that bonding Con A–E into hydrogels could efficiently reduce the leakage thus improved the biocompatibility and retained preferable glucose sensitivity.

### *3.6. Hydrogel morphology and porosity*

The morphologies and pore structures of freeze drying hydrogels after just photo-crosslinking and swelling in PBS (pH 7.4) with glucose concentrations of 0 and 4 mg/mL, were observed by a scanning electron microscopy. Using hydrogel-4 as an example, the images were shown in Fig. 7. From Fig. 7a, it could be found that the photo-crosslinking hydrogel had a microporous surface and a co-continuous open porous structure, leading to high internal surface areas. Moreover, the hydrogel network became looser and less compact from Fig. 7a–c, indicating that glucose in the medium could accelerate the shape change of hydrogel, which was also in good agreement with the swelling experiment.

## 4. Conclusions

Photo-crosslinked glucose-sensitive hydrogels based on Dex-G, Con A–E and crosslinking agent, PEGDMA, were synthesized and characterized. The results of swelling test, component loss measurement and SEM observation showed that the size of hydrogels changed differently in the medium of different glucose concentrations and the glucose sensitivity was influenced by the content of component, especially PEGDMA. Methacrylated Con A here kept the activity of reversible binding to saccharide and could reduce the leakage of lectin, therefore improved the glucose-sensitive property and biocompatibility of hydrogels. SEM image also displayed that hydrogels had microporous structures. These glucose-sensitive hydrogels have the potential to be used as glucose biosensor and intelligent insulin delivery carrier.

## Acknowledgments

The authors are grateful to the Program for Changjiang Scholars and Innovative Research Team in University. We also appreciate Changzhou scientific and technological project (CE20090021).

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