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Solution blowing of chitosan/PVA hydrogel nanofiber mats

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ABSTRACT

Both nanofiber mats and hydrogel have their own advantages in wound healing. In this study, a novel hydrogel nanofiber mats were fabricated via solution blowing of chitosan and PVA solution, with various content of ethylene glycol diglycidyl ether (EGDE) as cross-linker. SEM observation showed that the fibers were several hundred nanometers in diameter with smooth surface and distributed randomly forming three-dimensional mats. The structure of the chitosan/PVA nanofibers was examined by FTIR and XPS, and the results showed that the cross-linking reaction occurred between EGDE and the hydroxyl groups. The mats could quickly hydrate in an aqueous environment to form hydrogel. Their value of equilibrate water absorption varied from 680 to 459% various content of EGDE. The nanofiber mats showed good bactericidal activity against *Escherichia coli*. The chitosan/PVA hydrogel nanofiber mats showed the combination advantages of nanofibrous mats and hydrogel dressing, and were suggested as potential application in wound healing.

1. Introduction

Solution blowing process is an attractive approach for fabrication of fibers with diameters ranging from a few nanometers to several micrometers by blowing of polymer solution streams using the high-velocity gas flow (Zhuang, Li, Y., Fan, L., Lin, J., & Hu, 2012; Zhuang, Shi, Jia, Cheng, & Kang, 2013; Zhuang, Yang et al., 2012). A wide range of natural and synthetic polymers, such as polyvinylpyrrolidone (PVP) (Zhang, Kopperstad, West, Hedin, & Fong, 2009), polyacrylonitrile (PAN) (Zhuang, Jia et al., 2013; Zhuang, Shi, Jia et al., 2013; Zhuang, Shi, Zhang, Cheng, & Kang, 2013), polylactic acid (PLA) (Medeiros, Glenn, Klamczynski, Orts, & Mattoso, 2009), and cellulose (Zhuang, Li et al., 2012; Zhuang, Yang et al., 2012) has been solution blown into nanofibers. The process is similar to electrospinning but with different fiber formation driving forces. During solution blowing process, high-velocity gas flow deforms the solution streams, evaporates the solvent, and solidifies them into fibers; while electric force performs in electrospinning (Ellison, Phatak, & Giles, 2007; Yan, Zhuang, Tao, & Cheng, 2013). In solution blowing process, high-voltage equipment is not required and it is easy to use a die assembly with many nozzles without considering of electric field interference. Therefore, solution blowing process is expected to be developed as a secure and energy saving method for mass production of nanofibers (Sinha-Ray, Zhang, Yarin, Davis, & Pourdeyhimi, 2011; Zhuang, Shi, Zhang et al., 2013). By far, nanofiber mats have been widely used in industrial applications (e.g., multifunctional membranes, filters, textiles and templates for hollow fibers) and biomedical applications (e.g., tissue engineering scaffolds, wound dressing, vascular grafts, and drug delivery systems) (Ji et al., 2006; Kim, Akada, Kai, Kim, & Kim, 2011; Loh, Peh, Liao, Sng, & Li, 2010; Nakagawa, Hara, Maeda, & Hasimoto, 2011; Tan et al., 2008).

Wound healing is a very complex process and affected by a number of factors including blood coagulation, inflammation, fibroplasia, collagen deposition, wound contraction, etc. (Busilacchi, Gigante, Mattioli-Belmonte, Manzotti, & Muzzarelli, 2013; Gurtner, Werner, Barrandon, & Longaker, 2008; Lee, Chang, Yang, Chien, & Lai, 2012; Muzzarelli, Greco, Busilacchi, Sollazzo, & Gigante, 2012). Bacterial infection is also one of the factors and one of the treating approaches is using antibacterial agents with a broad-spectrum of activity and high killing rates (Jones, Bowler, Walker, & Parsons, 2004; Unnithan et al., 2012). Compared with most of the synthetic antibacterial agents, natural polysaccharide chitosan possesses high intrinsic activity against bacteria and fungi, low toxicity, biodegradability and ability to affect macrophage function which make it effective to faster wound healing process and used widely for wound dressing applications in several kind forms, such as hydrogel, membrane, sponge and fibers (Denkbas, Ozturk, Ozdem, Kecec, & Agalar, 2004; Kossovich, Salkovskiy, & Kirillova, 2010; Li et al., 2007; Murakami et al., 2010; Sudheesh Kumar et al., 2010; Wang, Zhu, Xue, & Wu, 2012). Nowadays, chitosan based nanofibers are attracting more and more attention being used as wound dressing. With its huge surface area and microporous

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structure, chitosan nanofiber mats wound dressing are very favorable for the adsorption of liquids, preventing bacteria penetration and attracting fibroblasts to the derma layer to repair damaged tissue (Uppal, Ramaswamy, Arnold, Goodband, & Wang, 2011; Wang, Zhang, Zhang, & Li, 2011). Various studies have suggested that chitosan based nanofibers mats seem to be an excellent dressing material for wound healing (Cai et al., 2010; Kang et al., 2010).

On the other hand, it is well known that wet dressing has better effect on healing due to the fact that renewed skin, no formation of eschar, which takes place during healing in a wet environment (Eaglstein, 2001). Hydrogel, as a kind of effective and convenient moist dressing for rapid wound healing, is capable of absorbing the surplus contaminated exudates and safely retaining them within the get structure, and possesses the advantages of good biocompatibility, water absorption ability, moisture retention and ventilating ability (Dumville, O'Meara, Deshpande, & Speak, 2011). PVA is widely used in preparation of hydrogel with chitosan in various ratios either by physical linking or by chemical linking, because of its biocompatible, nontoxic and cell adhesion properties.

In this study, chitosan/PVA blended hydrogel nanofibers mats (HNMs) were fabricated via solution blowing process, with various content of ethylene glycol diglycidyl ether (EGDE) as cross-linker. The fabrication of hydrogel nanofibers was analyzed by FT-IR and XPS. The morphological properties, swelling properties and antimicrobial properties of the mats were investigated to evaluate the application in the medical field.

2. Experimental

2.1. Materials

Chitosan, with viscosity-average molecular weight of 5.1×10^4 and deacetylation degree of 0.92, was provided by Zhejiang Ao-Xing Biotechnology Co. Ltd. (Zhejiang, China). Poly(vinyl alcohol) (PVA, an average degree of polymerization of 2000–2100) was purchased from Shanghai Chemical Reagent Co. (Shanghai, China). Ethylene glycol diglycidyl ether (EGDE, medical grade) was purchased from Shanghai YiBo Bio-Ppharmaceutical Tech Co., Ltd. (Shanghai, China) and used as a water soluble cross-linker. Formic acid (92 wt.%) was analytical grade and used as received.

2.2. Preparation of spinning solutions

The polymer solutions were obtained by dissolving chitosan (8.0 g) and PVA (8.0 g) in 200 mL formic acid at ambient temperature. Then, EGDE was added into the solutions with stirring to obtain homogeneous solutions. To obtain nanofibers with different degree of cross-linking, several spinning solutions were prepared with different EGDE content (7, 5, 4, 3 and 2% in weight to whole polymer content).

2.3. Solution blowing of CS/PVA hydrogel nanofibrous membranes

A purpose-built solution blowing setup, schematically shown in Fig. 1, was used for the experiments. The spinning programs were described briefly as follows: The spinning solution was feed to the orifices and the compressed air was supplied to the slots, respectively. The diameter of the orifices was 0.38 mm and the width of air slot was 0.5 mm. The solution feeding rate was 16 mL/h per orifice and the air was supplied to at the pressure of 0.5 MPa. After the solution streams were pressed out of the orifices, they were stretched to the extreme by the high-velocity gas flows. Then the nanofibers formed accompanying with solvent evaporation and deposited on a porous collector (the collector distance was 60 cm) to form a fibrous mat. Finally, the produced nanofiber mats were heat-treated in a vacuum oven at 60 °C for 3 h to enhance the cross-linking reaction and to remove the residual formic acid.

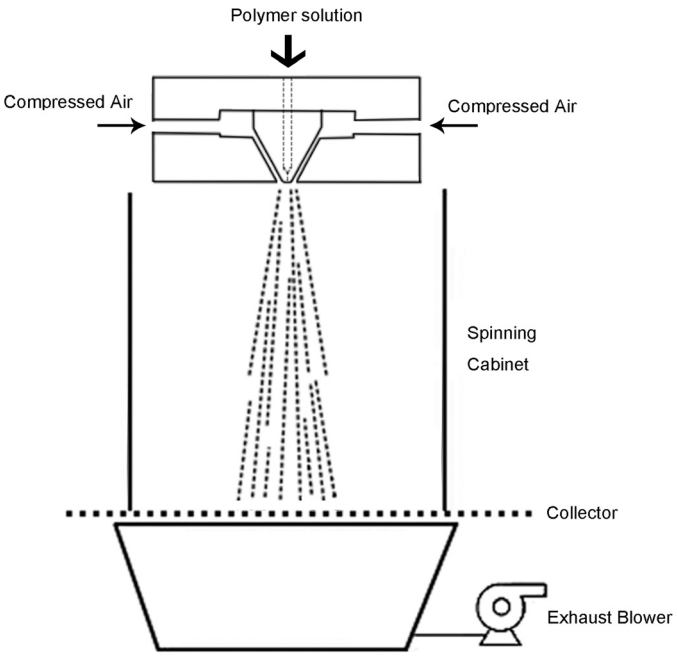

Fig. 1. Schematic of the solution blowing apparatus.

2.4. Characterization of hydrogel nanofibrous membranes

The morphology of the nanofibers mats was observed using a Hitachi S-4800 FE-SEM. All specimens were coated with a conductive layer of sputtered gold. The fiber diameters were determined as mean values of 50 measurements on the SEM images. The cross-linking reaction of CS/PVA with EGDE was confirmed by Fourier transform infrared spectroscopy (FT-IR, Nicolet 6700, USA) and X-ray photoelectron spectroscopy (XPS, Thermo-VG Scientific Ltd., UK).

2.5. Swelling measurements

The hydrogel nanofibers mats were cut into $1 \times 1\ cm^2$ and dried in a vacuum oven at 50 °C for 24 h to determine their dry weight (W_d). The dried specimens were soaked in normal saline solution at 37 °C for 10 h. The mats were taken out and the free water on the surface was absorbed by filter paper. Then the mats were immediately weighed to obtain their wet weights (W_t). This procedure was repeated three times to gain the average water content. The water content was calculated from the following formula:

$$\text{Water content } (\%) = \frac{Wt - Wd}{Wd} \times 100 \quad (1)$$

2.6. Antimicrobial activity

Antimicrobial activity was evaluated from examining the killing rate by the viable cell counting technique against *Escherichia coli*. Briefly, one loopful of *E. coli* was inoculated in 50 mL of nutrient broth at 37 °C for 10 h in a conical flask. After this, 1 mL of the bacteria/nutrient solution was added to 9 mL of phosphate-buffered saline (PBS) solution. Several decimal dilutions were performed until the bacterial concentration increased from 1×10^6 to 2×10^6 CFU/mL. To perform the antibacterial testing, the respective mats (150 mg in dry weight and 0.5 cm in diameter) were put into 15 mL of the bacteria/PBS solution and incubated in a shaker at

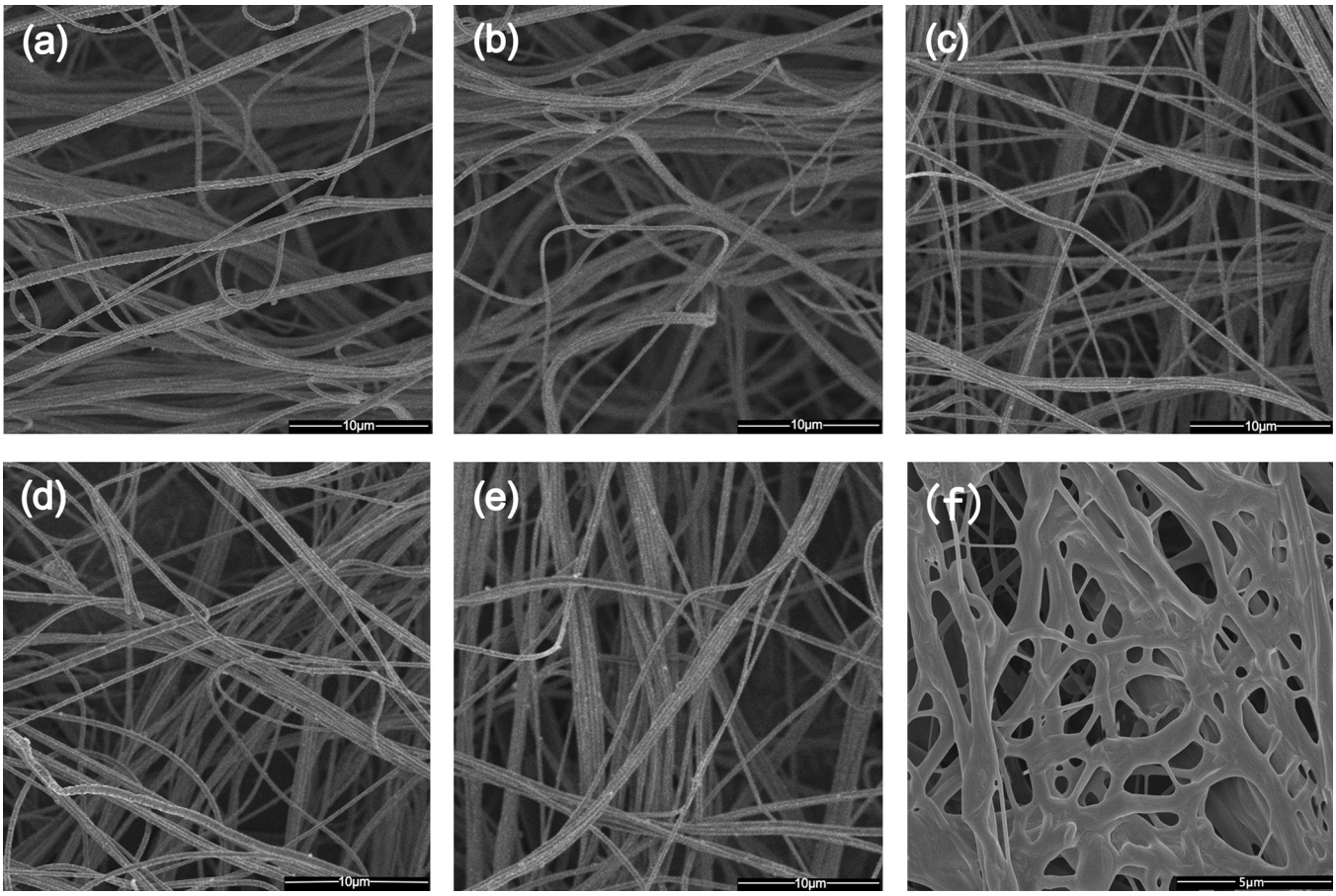

Fig. 2. SEM images of solution blown CS/PVA nanofibers with different EDGE content: (a) 7%, (b) 5%, (c) 4%, (d) 3%, (e) 2% and (f) the swollen CS/PVA-E7.

37 °C for 18 h. After the exposure of the bacteria to fiber mats, several decimal solutions were repeated. From every diluted solution, 200 μL of the bacterial solution was taken out and quickly spread on a plate containing nutrient agar. Plates containing bacteria were incubated at 37 °C for 24 h, and then the numbers of the surviving colonies were counted. These results were compared to the number of bacteria colonies of the untreated control that had not been exposed to the fiber mats. Then bacteriostatic rate can be obtained from the following equation:

$$\text{Bacteriostatic rate } (\%) = \frac{Wt - Qt}{Wt} \times 100 \quad (2)$$

where W_t is the number of colonies counted for the control and Q_t is the number of colonies obtained from each tested sample.

3. Results and discussion

3.1. Fabrication of CS/PVA hydrogel nanofiber mats

In solution blowing process, spinning solutions are blown and attenuated into ultrafine fibers by high-velocity airflow, accompanied with the evaporation of the solvent. It was found that it was difficult to do solution blowing of chitosan nanofibers because of the high viscosity of chitosan solution (Zhuang, Li et al., 2012; Zhuang, Yang et al., 2012). In this study, poly(vinyl alcohol) was blended with chitosan as assistant polymer to obtain nanofibers considering of its excellent spinnability. To study the effect of cross-linking degree on the properties of nanofibers, we spun several chitosan/PVA blend nanofibers with fixed ratio of PVA and chitosan but with different content of cross-linker. With co-dissolving of PVA and EGDE in solutions, the chitosan/PVA blended nanofibers were easily spun. After hot-treated in vacuum oven, they were observed with SEM, as shown in Fig. 2(a–e). The images show that the solution blown nanofibers are smooth in surface and distributed randomly to form three-dimensional mats. With different content of cross-linker (degree of cross-linking), the nanofibers were slightly different in diameter. For the nanofibers with 7%, 5%, 4%,

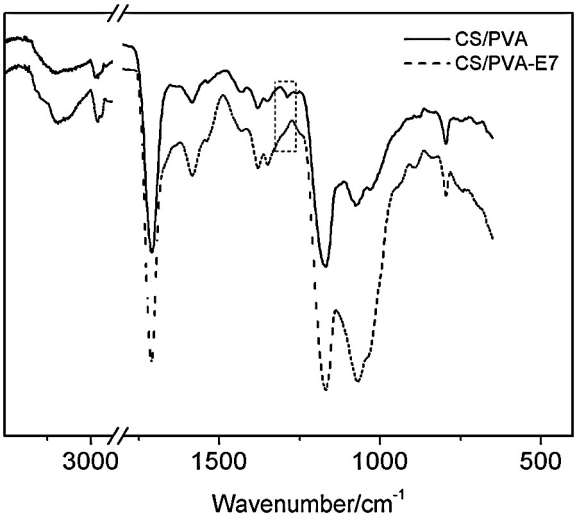

Fig. 3. FT-IR spectra of CS/PVA-E7 and CS/PVA.

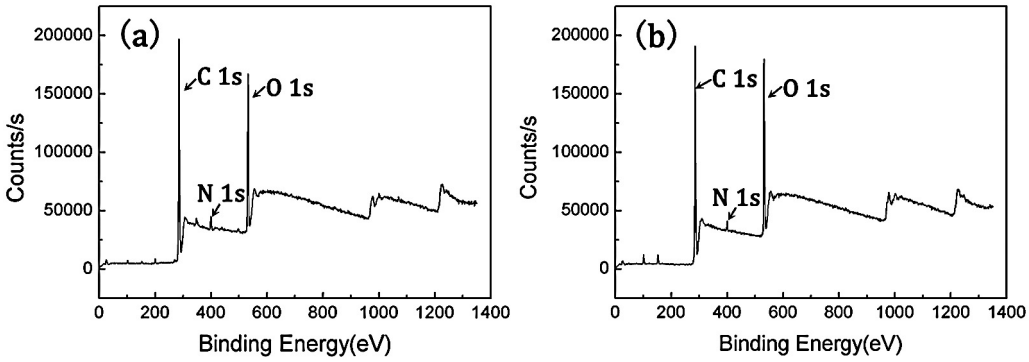

Fig. 4. XPS wide scan spectra in the C 1s, O 1s, and N 1s region of the nanofiber mats (a) CS/PVA and (b) CS/PVA-E7.

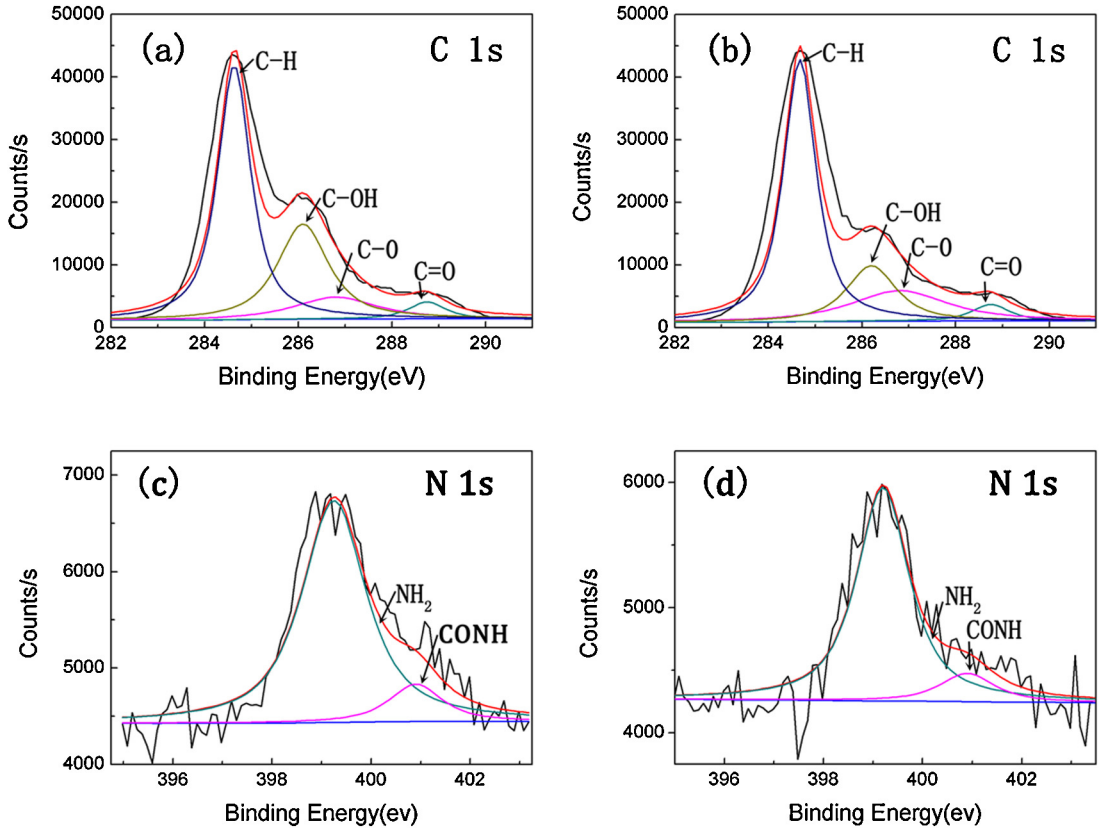

Fig. 5. Narrow scans of C 1s and N 1s spectra of CS/PVA (a, c) and CS/PVA-E7 (b, d) and their fitting curves.

3%, 2% content of EGDE, their average diameters were 475, 462, 459, 441 and 437 nm, respectively.

After immersed in saline solution for 8 h, the nanofibers with 7% EGDE (CS/PVA-E7) changed much in morphology. As shown in Fig. 2(f) the nanofibers were swollen to 400–600 nm in diameter and still maintained their fibrous appearance well. That is to say, hydration obviously occurred and the hydrogel nanofiber mat was formed because of the hydrophilic groups and domains involved in the cross-linked polymeric network. Compared with hydrogel films, this kind of hydrogel nanofiber mat allows gaseous exchange, which is helpful for wound healing.

To study the chemical structure of the nanofibers, CS/PVA-E7 was examined by FT-IR and XPS, compared with the one without cross-linker (CS/PVA). As shown in Fig. 3, there is a significant change in the adsorption intensity at wave numbers of 1073 cm^{-1}, which is attributed to C—O—C stretching vibration. This implies that the cross-linking reaction occurred between EGDE and CS/PVA (Liu et al., 2010). The FT-IR spectra of CS/PVA show a remarkable absorption band at about 1286 cm^{-1} that is assigned to the characteristic vibration of —OH on the chitosan, but it disappeared in the spectrum of CS/PVA-E7. This obvious disappearance demonstrates that hydroxyl group participated in the reaction (Zheng, Du, Yu, & Xiao, 2000). Moreover, the adsorption intensity of 1650 cm^{-1}(—NH stretching vibration) had no significant change, indicating that the amino groups of chitosan not involved in cross-linking reaction (Zhuang, Li et al., 2012).

Table 1
The carbon, oxygen and nitrogen atomic concentrations of CS/PVA and CS/PVA-E7.

Samples	Atomic concentrations (%)		
	C	O	N
CS/PVA	73.54	21.98	4.47
CS/PVA-E7	75.36	22.78	1.85

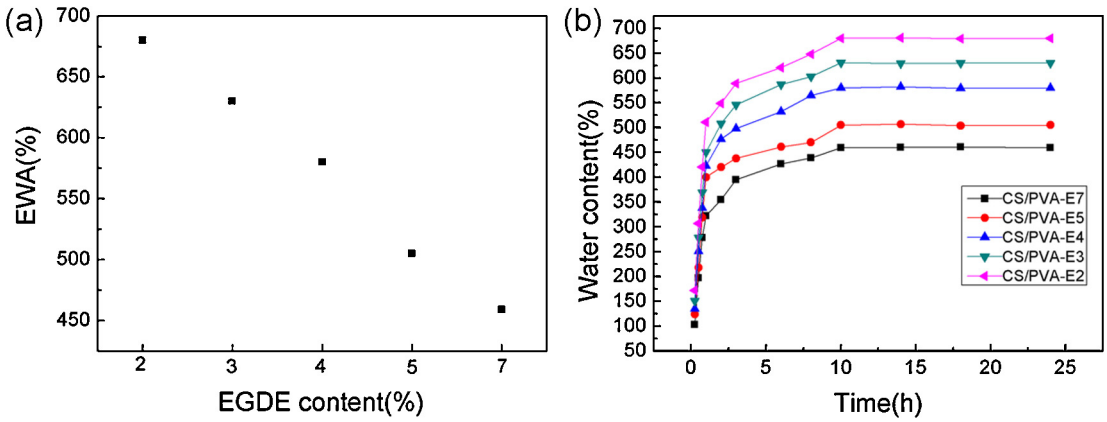

Fig. 6. Equilibrate water absorption (a) and water absorption dynamics (b) of nanofiber hydrogel mats with various EGDE content.

Table 2
The antibacterial activity of hydrogel nanofibers mats.

Samples	CS/PVA-E2	CS/PVA-E3	CA/PVA-E4	CA/PVA-E5	CS/PVA-E7
Bacteriostatic rate (%)	84.56	82.88	83.56	84.23	81.88

The XPS wide scan spectra of CS/PVA and CS/PVA-E7 are shown in Fig. 4. The peaks corresponding to C 1s (binding energy of 285 eV), O 1s (binding energy of 532 eV) and N 1s (binding energy of 400 eV) are presented in both spectra. Table 1 lists the content of calculated elemental ratios according to their peak areas and sensitivity factors. Compared with CS/PVA, the content of nitrogen decreased from 4.47 to 1.85%, while carbon and oxygen content increased. The reason was attributed to the addition of EDGE which is rich of the carbon and oxygen elements.

In order to further illustrate the cross-linking reaction, XPS-peak-differentiation-imitating analysis was applied to study the variation of the chemical shifts of C 1s, N 1s and O 1s. Fig. 5 presents the fitted XPS spectra of the C 1s region (a, c) and N 1s region (b, d). Four components at 284.65, 286.15, 286.80 and 288.75 eV in the C 1s region were observed for CS/PVA and CS/PVA-E7, which was corresponded to C—H, C—O, C—OH and C=O, respectively (Ma, Su, Sun, Wang, & Jiang, 2007). Their corresponding proportions are 53.3, 30.8, 11.6 and 4.3% for CS/PVA and 57.5, 18.5, 19.8 and 4.2% for CS/PVA-E7. After cross-linking using EGDE, C—H content increased slightly because of the introduction of EGDE, and there was barely change for C=O, which belonged to the acetamido groups of chitosan (Li et al., 2007). The most obvious changes were that the C—OH content decreased while the C—O content increased drastically, indicating part of C—OH groups changed into C—O after cross-linking reaction. On the other hand, N 1s peak was fitted into two peaks of $-NH_2$ (binding energy of 399.25 eV) and —CONH (binding energy of 400.90 eV) (Lawrie et al., 2007), and their proportions did not change much. Considering that EGDE is a kind of epoxide containing two epoxide groups at the ends of molecule chain, the results indicated the cross-linking reacted in —OH positions, and $-NH_2$ groups were not involved, and the cross-linking reaction could be identified as the opening the epoxy groups and hydroxyl groups of chitosan and PVA.

3.2. Properties of CS/PVA hydrogel nanofiber mats

3.2.1. Swelling behavior

In this study, PVA is used as assistant polymer for the spinning of chitosan. Meantime, it offers hydrophilic part for hydration. We know that the swelling behavior of hydrogel is affected by its degree of cross-linking. To study the effect of degree of cross-linking (DCL) on swelling behaviors, cross-linked CS/PVA mats with different EGDE content were prepared to examine their equilibrate water absorption and absorption kinetics.

Fig. 6(a) gives the results of the equilibrate water absorption (EWA) of samples with 7, 5, 4, 3 and 2% EGDE content in weight (marked as CS/PVA-E7, CS/PVA-E5, CS/PVA-E4, CS/PVA-E3 and CS/PVA-E2, respectively). With EGDE content increasing from 2 to 7%, EWA of the hydrogel nanofiber mats gradually decreased from 680 to 459%. The equilibrate water absorption decreased along with DCL increasing. But it does not affect the absorption kinetics intensively. As shown in Fig. 6(b), all the mats with different DCL absorb water rapidly in the first stage, get over half of the total water content in 2 h, almost reach equilibrate water absorption in 10 h. The quick absorption kinetics and high equilibrate water absorption make the mats could absorb excess exudate and create a moist wound healing environment.

3.2.2. Antibacterial activity

An open wound is highly susceptible to infectious bacteria. Once the wound becomes infected, it requires additional treatments that are painful and result in delayed healing. The use of antimicrobial materials in wound dressings provides enhanced protection.

The antibacterial activities of hydrogel nanofiber mats against *E. coli* were shown in Table 2. The results showed that all mats showed good antibacterial activities with bacteriostatic rate over 81%. It can be discerned from the antibacterial rate values that there was no significant change between nanofiber hydrogels of different DCL, because that the cationic amine group of chitosan is responsible for its antibacterial activity (Paul and Sharma, 2004) and the amino group was not involved in the cross-linking reaction.

4. Conclusions

The results indicated that CS/PVA hydrogel nanofiber mats possess the advantages of both hydrogel and fibrous mat, such as absorbing excess exudate, creating a moist wound healing environment, allowing gaseous exchange and possessing good antibacterial activity. This CS/PVA hydrogel nanofiber mats would be suggested as an ideal moist dressing.

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