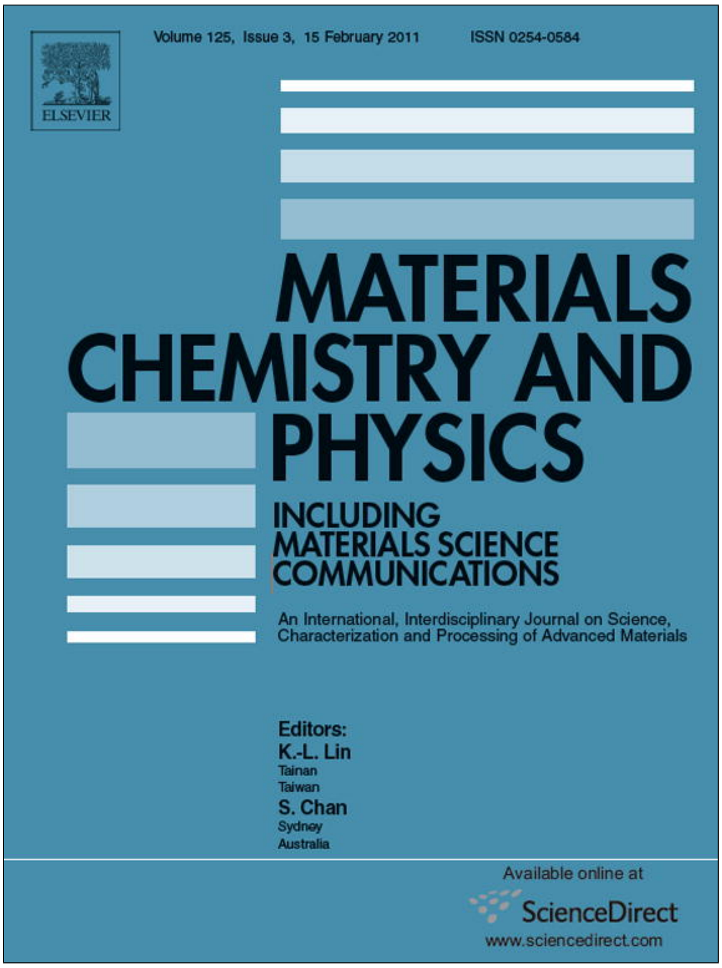
Volume 125, Issue 3, 15 February 2011
ISSN 0254-0584
ELSEVIER
MATERIALS CHEMISTRY AND PHYSICS
INCLUDING MATERIALS SCIENCE COMMUNICATIONS
An International, Interdisciplinary Journal on Science, Characterization and Processing of Advanced Materials
Editors:
K.-L. Lin
Tainan
Taiwan
S. Chan
Sydney
Australia
Available online at
ScienceDirect
www.sciencedirect.com

Materials Chemistry and Physics 125 (2011) 606–611

Contents lists available at ScienceDirect

Materials Chemistry and Physics

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

Fabrication, characterization and in vitro drug release behavior of electrospun PLGA/chitosan nanofibrous scaffold

Z.X. Meng[a], W. Zheng[a], L. Li[a], Y.F. Zheng[a,b,*]

[a] Center for Biomedical Materials and Engineering, Harbin Engineering University, Harbin 150001, China
[b] Department of Advanced Materials and Nanotechnology, College of Engineering, Peking University, Beijing 100871, China

ARTICLE INFO

Article history:
Received 5 July 2010
Received in revised form
30 September 2010
Accepted 8 October 2010

Keywords:
Biomaterials
Composite materials
Nanostructures
Polymers

ABSTRACT

In this study both aligned and randomly oriented poly(D,L-lactide-co-glycolide) (PLGA)/chitosan nanofibrous scaffold have been prepared by electrospinning. The ratio of PLGA to chitosan was adjusted to get smooth nanofiber surface. Morphological characterization using scanning electron microscopy showed that the aligned nanofiber diameter distribution obtained by electrospinning of polymer blend increased with the increase of chitosan content which was similar to that of randomly oriented nanofibers. The release characteristic of model drug fenbufen (FBF) from the FBF-loaded aligned and randomly oriented PLGA and PLGA/chitosan nanofibrous scaffolds was investigated. The drug release rate increased with the increase of chitosan content because the addition of chitosan enhanced the hydrophilicity of the PLGA/chitosan composite scaffold. Moreover, for the aligned PLGA/chitosan nanofibrous scaffold the release rate was lower than that of randomly oriented PLGA/chitosan nanofibrous scaffold, which indicated that the nanofiber arrangement would influence the release behavior. In addition, crosslinking in glutaraldehyde vapor would decrease the burst release of FBF from FBF-loaded PLGA/chitosan nanofibrous scaffold with a PLGA/chitosan ratio less than 9/1, which would be beneficial for drug release.

1. Introduction

Electrospinning is a simple and convenient method to produce non-woven ultrafine fibers with fiber diameters ranging from tens of nanometer to micron scales. The electrospun fiber morphology can be controlled by many parameters [1]. During the process of electrospinning, the droplet of the polymer solution at the nozzle would be affected by two competitive forces: the electrostatic force and the surface tension. When the applied electric voltage overcame the surface tension, one or several jets of the solution were ejected from the tip and then underwent a stretching and whipping process, leading to the formation of a long and thin thread, and finally fell onto the collector. Thus the increasing voltages applied to the solution increased the electrostatic force which improved stretching and whipping of the jet, resulting in the thinner fiber diameter, meanwhile the longer distance between spinneret and collector would increase the stretching time which also attributed to the thinner fiber diameter. On the contrary, higher viscosity of solution would improve the surface tension thus increase the fiber diameter. The temperature and humidity of the experimental environment directly influenced the solvent evaporation of the jet, as to some solvent with high volatility, high temperature or low humidity would enhance the solvent evaporation resulting in the porous surface of the fiber. The electrospun nanofibrous scaffolds possess high specific surface area, high porosity, and three-dimensional reticular structure, which is similar to the natural extracellular matrix (ECM) and can enhance the adhesion, proliferation and growth of cells [2]. Therefore, the electrospun nanofiber has received increasing attentions in the past few years. So far, many kinds of polymers, such as poly(ε-caprolactone) (PCL), poly(lactic-co-glycolic acid) (PLGA), poly(ethylene oxide) (PEO) and mixtures of collagen with chitosan [3–6] have been electrospun into nanofibers for tissue engineering scaffold and drug delivery [7–10] in biomedical field.

In recent years, because the drug controlled release systems have great benefits for patients such as improved therapeutic effect, reduced toxicity, lessened drugs given times, a lot of polymeric materials have been synthesized for drug controlled release systems. Chitosan, a natural macromolecule widely used as biomaterials in the pharmaceutical and medical fields [11,12], possesses many useful properties such as good biocompatibility, wound healing property and bioactivity because of its chemical similarity to glycosaminoglycan, the main component of proteoglycans [13]. Chitosan has been successfully electrospun into fibers when

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[*] Corresponding author at: Department of Advanced Materials and Nanotechnology, College of Engineering, Peking University, Beijing 100871, China. Tel.: +86 10 6276 7411; fax: +86 10 6276 7411.
E-mail address: yfzheng@pku.edu.cn (Y.F. Zheng).

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doi:10.1016/j.matchemphys.2010.10.010

using concentrated organic acid as the solvent [14,15]. However, it has a poor mechanical property for supporting cell culture [16]. Therefore the synthetic polymer/natural macromolecules such as composite chitosan/PEO [17,18], chitosan/PVA [19,20] were widely investigated. Unfortunately, PEO and PVA were soluble polymers which may dissolve and form gel in the aqueous solution, not only decreasing the mechanical properties sharply but also leading to large initial burst release of drug. Alicyclic polymers such as PLA and PGA were FDA-approved biodegradable polymers with excellent biocompatibility and mechanical property, which have attracted increasing interest in many areas. However, up to date only a few research works reported the electrospun composite of alicyclic polyester/chitosan (PGA/chitin, PLA/chitosan) [21,22]. Park et al. fabricated the PGA/chitin ($M_w = 91{,}000$) electrospun composite nanofibers with 1,1,1,3,3,3-hexafluoro-2-propanol as solvent [21]. It showed that PGA/chitin 25/75 with bovine serum albumin coating has an excellent cell attachment and spreading for normal human fibroblasts which would be a good candidate for tissue engineering scaffold. Xu et al. chose trifluoroacetic acid as solvent to prepare chitosan/PLA blend nanofiber through electrospinning, and the results indicated that chitosan and PLA were blended in at molecular level [22]. However, the low molecular weight of PLA ($M_w = 5000$) and chitosan ($M_w = 8000$–$20{,}000$) would not fit for the mechanical property in the application. In the present study we attempt to use PLGA and high molecular weight chitosan ($M_w = 1{,}000{,}000$) to prepare both randomly oriented and aligned electrospun PLGA/chitosan composite fibrous membranes because PLGA has moderate biodegradation rate and eximious mechanical property compared to PGA and PLA, and chitosan with high molecular weight would not degrade soon, which would sustain bioactive for a longer time. Moreover we chose fenbufen (FBF) as a model drug to investigate the optimization of release profile for drug delivery based on the PLGA/chitosan nanofibrous scaffold, because fenbufen is a non-steroidal anti-inflammatory drug used to treat acute and chronic painful symptoms such as rheumatoid arthritis, osteoarthritis, backaches and sprains [23], which may be potential as a kind of drug delivery systems as effective painkillers.

2. Materials and methods

2.1. Materials

Poly(D,L-lactide-co-glycolide) (PLGA, LA/GA 85/15, $M_w = 200{,}000$)was purchased from Jinan Daigang Biomaterial Co. Ltd. (China). Chitosan ($M_w = 1{,}000{,}000$) was purchased from Golden-shell Biochemical Co. Ltd. (China). Trifluoroacetic acid (TFA) was purchased from Shanghai Jingchun Chemical Regent Co. Ltd. (China). Fenbufen (FBF) was purchased from Group Sanjing Pharmaceutical Co. Ltd. (China).

2.2. Electrospinning

A 10% (w/v) PLGA solution and 1% (w/v) chitosan solution were at first prepared separately by dissolving PLGA and chitosan in trifluoroacetic acid as solvent. The composite solutions of PLGA/chitosan were prepared by mixing 10% (w/v) PLGA/TFA and 1% (w/v) chitosan/TFA in different volume ratios (PLGA/chitosan: 10/0, 9.375/0.625, 9/1 and 7/3) by gentle stirring for 24 h at room temperature. For electrospinning, the polymer solution was loaded in a 5 mL glass syringe and injected through a stainless-steel blunt needle using an infusion pump (TS2-60, Baoding Longer Precision Pump Co. Ltd., China) at an injection rate of 0.5 mL h^{-1} with an applied voltage of 7–12 kV (HB-F303-1-AC, China). Randomly oriented fibers were collected on a flat collector wrapped with aluminum foil which was kept at a distance of 10–15 cm from the needle tip. Aligned fibers were formed using a rotating drum with the same parameters at a speed of 3000 rpm for obtaining well-aligned nanofibers. For spinning with fenbufen doping, fenbufen was dissolved in PLGA/chitosan solution at final concentration of 2 mg mL^{-1}. The scaffolds were dried overnight under vacuum at room temperature.

2.3. Morphologies of electrospun nanofibers

The morphologies of the electrospun PLGA/chitosan nanofibers were observed by scanning electron microscope (CamScan MX2600FE, UK) at an accelerating voltage of 20 kV. All samples were coated with a thin layer of platinum in two 30 s consecutive cycles at 45 mA to reduce charging and produce a conductive surface. The diameters of resulting nanofibers were analyzed using software Image J.

2.4. Fourier transform infrared (FT-IR) analysis

FT-IR spectra were recorded for PLGA/chitosan nanofibrous scaffolds in the attenuated total reflection (ATR) mode using an IR spectrophotometer (PE Company, USA). The spectra were obtained in the range 650–4000 cm^{-1} with a resolution of 4.0 cm^{-1} and 16 scans.

2.5. Swelling studies

The water adsorption capacity was determined by swelling ratio. The samples with weight W_0 were immersed in doubly distilled water for 24 h, and then removed the water from surface with filter paper and were weighed W. The swelling ratio (Q) was calculated according to the following equation [24]:

$$Q = \left(\frac{W - W_0}{W_0}\right) \times 100\% \qquad (1\text{-}1)$$

2.6. Water contact angle measurement

Water contact angles of nanofibrous scaffolds were measured by water contact angle analyzer (CAM200, KSV Co., Finland). The samples were cut into 1 cm^2 square and then placed on the testing plate, after that distilled water was carefully dropped on the surface of samples. The contact angles were measured by a video monitor, and for each sample group the measurements were carried out five times.

2.7. Release behavior study

The drug-loaded nanofiber sample was incubated in 10 mL of phosphate buffer solution (pH = 7.4) at 37 °C. At various time points, 2 mL of the release medium was removed and followed by diluting them to 10 mL using fresh buffer solution. The amount of released fenbufen was determined using the UV–vis spectrophotometer at the wavelength of 280 nm. All the release experiments on these electrospun nanofibers were carried out five times, and the average values are shown in this study.

3. Results and discussion

Fig. 1 shows the SEM micrographs of randomly oriented and aligned electrospun PLGA and PLGA/chitosan nanofibers formed under controlled parameters. As can be seen, randomly oriented PLGA and PLGA/chitosan nanofibers were obtained exhibiting beadless and smooth surface with average diameter of 146 ± 35 nm, 189 ± 51 nm, 246 ± 44 nm and 229 ± 71 nm corresponding to the blending ratios of 10/0, 9.375/0.625, 9/1 and 7/3, respectively. The fiber diameter was found to increase with the increase of chitosan content which may be because that the increasing chitosan content enhanced the viscosity of the composite solution. When the ratio of PLGA/chitosan was up to 7/3, the nanofiber diameter decreased and the fiber diameter distribution broadened (Table 1). Similar result was reported by Jia et al. [19], who found that the fiber diameter became smaller and distribution increased when the weight ratio of PVA/chitosan changed from 90/10 to 70/30. This observation could be attributed to the ionization of chitosan under acidic pH condition [25]. The increasing chitosan content increased charge density on the surface of the jet during electrospinning, not only improving the stretching force but also enhancing self-repulsion of the jet under the electrical field, which resulted in the smaller fiber diameter and broader distribution.

For electrospinning research, aligned nanofibrous scaffold was also an important part because alignment fibers would guide cell growth which is necessary for special tissue such as bone or nerve [21,26]. In this study, we also want to investigate the influence of fiber orientation on drug release characteristic, which had not been considered in previous reports. As can be seen in Fig. 1, the aligned nanofibers showed smooth surface with the angular deviations of ±30°. The alignment degree of nanofibers decreased with the increase of chitosan concentration which may be because the increasing charge increased instability of whipping, resulting in the uneven splitting of the jet. The diameters of the aligned nanofibers were 135 ± 26 nm, 147 ± 46 nm, 222 ± 84 nm

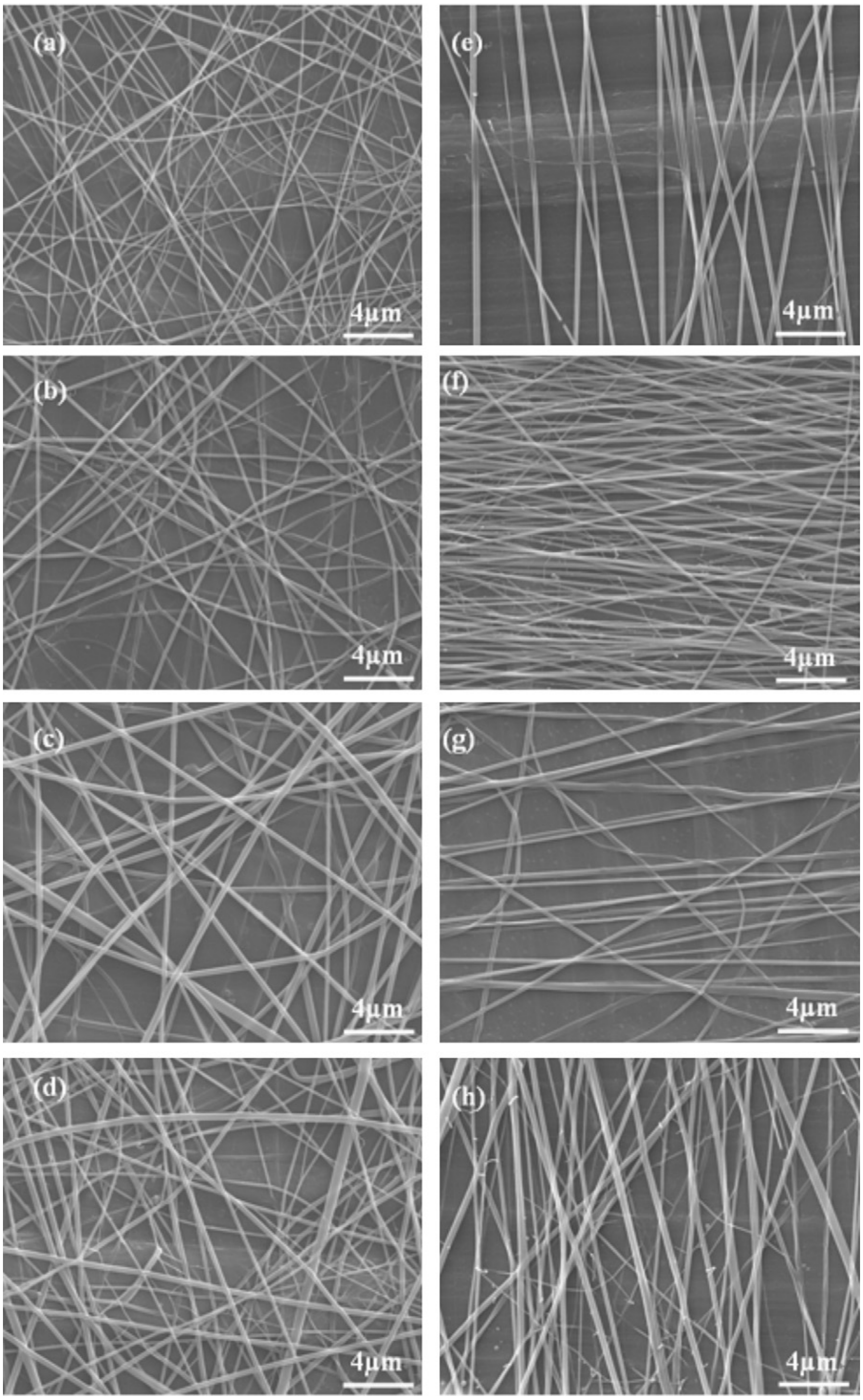

Fig. 1. SEM images showing the morphology of randomly oriented (a–d) and aligned (e–h) electrospun PLGA/chitosan nanofibers at various PLGA/chitosan ratios: (a and e) 10/0, (b and f) 9.375/0.625, (c and g) 9/1 and (d and h) 7/3.

Table 1
Diameter and distribution of electrospun PLGA/chitosan nanofibers.

Sample of PLGA/chitosan	Randomly oriented fiber		Aligned fiber	
	Average diameter (nm)	Diameter distribution (nm)	Average diameter (nm)	Diameter distribution (nm)
10/0	146 ± 35	78–217	135 ± 26	95–183
9.375/0.625	189 ± 51	60–297	147 ± 46	83–253
9/1	246 ± 44	165–342	222 ± 84	125–375
7/3	229 ± 71	70–345	198 ± 73	63–363

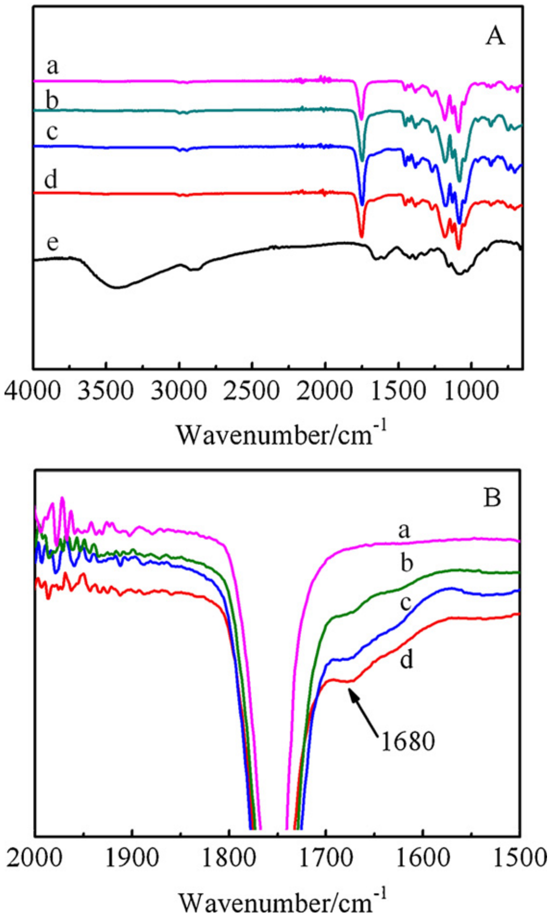

Fig. 2. FT-IR of electrospun nanofibers from (a) PLGA, (b) PLGA/chitosan 9.375/0.625, (c) PLGA/chitosan 9/1, (d) PLGA/chitosan 7/3 and (e) chitosan.

and 198 ± 73 nm corresponding to the ratio of 10/0, 9.375/0.625, 9/1 and 7/3, respectively (see Table 1), which were smaller than that of randomly oriented nanofibers because the jet was drawn by rotating drum during fabrication. The aligned nanofiber diameter distribution increased with the increase of chitosan content which was similar to that of randomly oriented nanofiber (see Table 1).

The FT-IR spectra of the electrospun PLGA/chitosan nanofibers with different ratios are shown in Fig. 2. For pure PLGA nanofibers (curve a), the strong characteristic absorption bands at about 1752 cm^{-1} attributed to the stretching vibration of C=O bond, the bands at 1182 cm^{-1} could be assigned to the C–O–C ether group stretching, the bands at 1130 cm^{-1} and 1452 cm^{-1} arose from C–O bond and methyl group C–H bond of PLGA, respectively [27]. These characteristic absorption bands, along with chitosan characteristic bands of 1680 cm^{-1} and 1540 cm^{-1} which attributed to the stretching of C=O and N–H bend coupled with C–N [13], were all observed in the FT-IR spectra of PLGA/chitosan nanofibers. The main characteristic peaks of both PLGA and chitosan appeared on PLGA/chitosan composite nanofibers (curves b–d) and the peak position did not change with different PLGA/chitosan ratios, which demonstrated the weak interaction between PLGA and chitosan. Moreover, it was obvious that with the increase of chitosan, the relative strength of peak at 1680 cm^{-1} which represented the amide I absorption band of chitosan was increased (Fig. 2B).

The characteristic of hydrophilicity plays an important role for scaffold material, because it not only enhances the cell viability and proliferation [28], but also changes the drug release from matrix. Fig. 3 depicts the swelling ratio of neat PLGA and PLGA/chitosan nanofibrous scaffolds. Compared with neat PLGA nanofibers, the PLGA/chitosan composite nanofibers showed higher swelling ratio. The swelling ratio increased from 121% to 285% when the PLGA/chitosan ratio increased from 9.375/0.625 to 7/3, which indicated the addition of chitosan could improve the hydrophilicity of the nanofibrous scaffold. In order to test the changing of hydrophilicity exactly, the water contact angle technique was used in the study. Fig. 4 shows the varied water contact angles after the water droplets were placed on the surface of different PLGA/chitosan nanofibrous scaffolds. It can be seen that the water contact angle of samples decreased from 116.59° to 71.09° (Table 2) when the PLGA/chitosan ratio increased from 10/0 to 7/3, which indicated the chitosan enhanced the hydrophilicity of PLGA/chitosan nanofibers again.

In this work, a model drug fenbufen was added into the PLGA and PLGA/chitosan solution with the concentration of 2 mg mL^{-1} to prepare nanofibers through electrospinning in order to investigate its feasibility as carrier in drug delivery. No significant difference on morphology could be found between the neat and drug-loaded

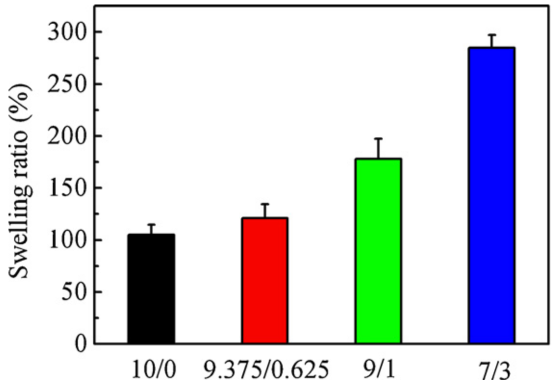

Fig. 3. Swelling ratio of electrospun nanofibers at ratios of PLGA/chitosan of 10/0, 9.375/0.625, 9/1and 7/3.

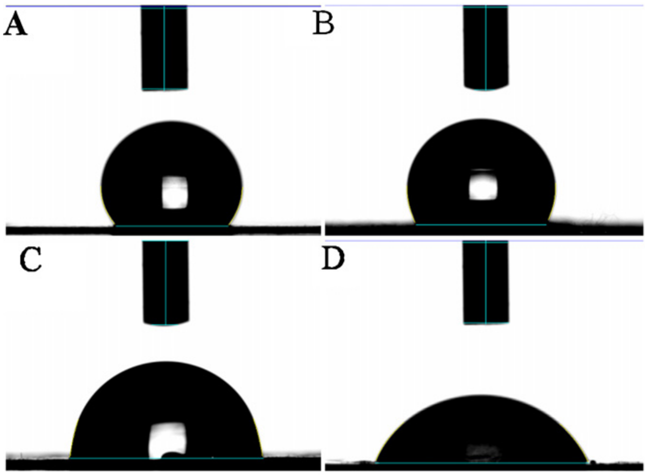

Fig. 4. Water contact angle of electrospun nanofibers at ratios of PLGA/chitosan of 10/0 (A), 9.375/0.625 (B), 9/1 (C) and 7/3 (D).

Table 2
Water contact angle of electrospun PLGA/chitosan nanofibers.

Sample of PLGA/chitosan	Water contact angle (°)
10/0	116.59 ± 10.18
9.375/0.625	108.87 ± 4.42
9/1	81.36 ± 0.92
7/3	71.09 ± 2.62

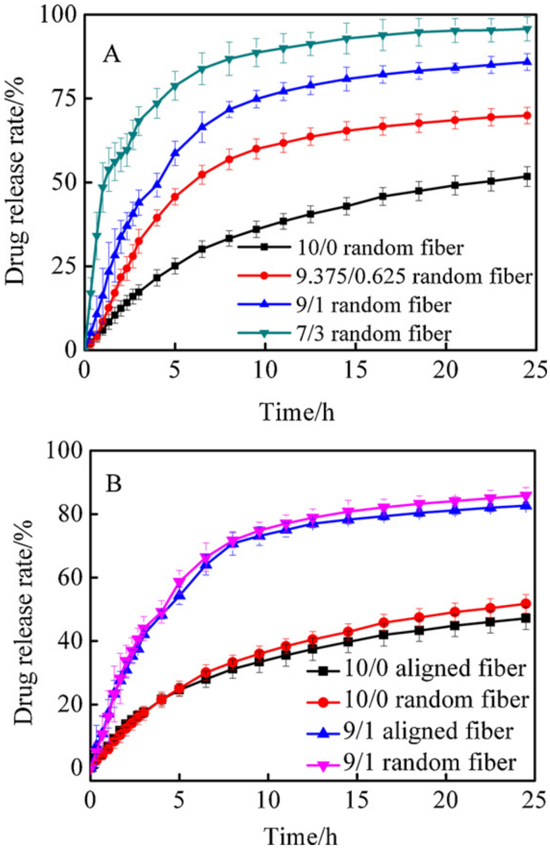

Fig. 5. Release curves of FBF from FBF-loaded PLGA and PLGA/chitosan electrospun nanofibers (A), aligned and randomly oriented PLGA and PLGA/chitosan (9/1) electrospun nanofibers (B).

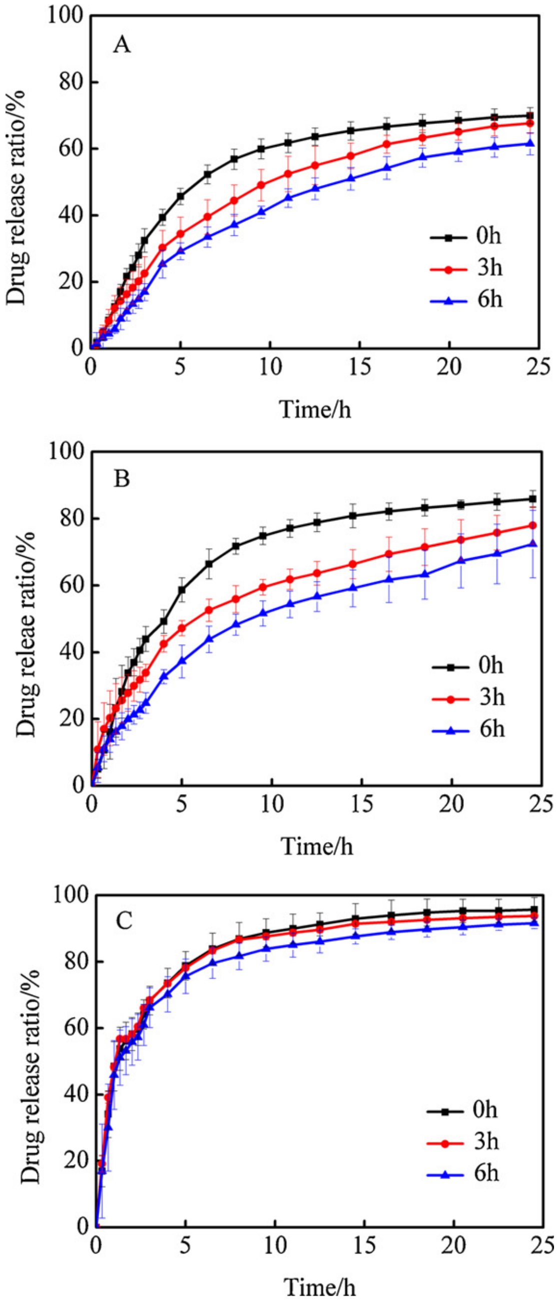

Fig. 6. Release behaviors of FBF from FBF-loaded PLGA/chitosan (9.375/0.625) nanofibrous scaffold (A), PLGA/chitosan (9/1) nanofibrous scaffold (B) and PLGA/chitosan (7/3) nanofibrous scaffold (C) with different crosslinking time for 0 h, 3 h and 6 h.

PLGA and PLGA/chitosan nanofibers, and no obvious drug aggregates were found on the surface of drug-loaded nanofibers, which indicated that the drug was under amorphous condition within the fibers. After crosslinking, the contours of some nanofibers were indistinct under SEM and this phenomenon became more obvious with the chitosan content increasing.

Fig. 5A shows the release characteristics of FBF from the FBF-loaded randomly oriented PLGA and PLGA/chitosan nanofibrous scaffolds. It can be seen that the FBF released from the PLGA scaffold showed gradual increase with time increasing. Compared with PLGA scaffold, the release rate and maximum amount of FBF released from the electrospun PLGA/chitosan scaffold increased with the increase of chitosan content, and FBF released from the PLGA/chitosan scaffold showed two release stages: a burst release stage and followed gradually increased stage. The increasing chitosan concentration resulted in the higher swelling of scaffold (Fig. 3), which allowed drug molecules to diffuse from the matrix into the medium more easily [29]. Thus, the burst release stage was mainly dependent on the water transport in the chitosan phase. In order to investigate the influence of fiber orientation on drug release characteristic, aligned FBF-loaded PLGA and PLGA/chitosan with ratio of 9/1 nanofibrous scaffolds were fabricated by rotating drum under the same parameters and were chosen as a representative for comparing to the randomly oriented counterpart. As can be seen from Fig. 5B, the drug release behaviors from aligned scaffold showed a similar trend with that of the randomly oriented scaffold, but the drug release rate was a little different. At the initial 5 h, the drug release rate of aligned scaffold was almost equal to that of random scaffold, but after that the difference became larger with the release time increasing. The difference of drug release amount was 3–4% after 5 h immersion, which indicated that scaffold structure changed by nanofibrous arrangement would influence the drug release in certain extent. At the initial stage of 5 h, large amount of drugs near the surface of fiber rapidly released from the fiber and diffuse from the scaffold to the outer surrounding driven by the large drug concentration difference. With the time increasing after 5 h, the drug concentration difference became lower because the drug near the surface of fiber almost released out and the drug diffused from inner to the surface of the fiber was relatively slower. At the moment the diffusion rate of drug from scaffold to the outer surrounding became more important. Because the aligned nanofibers enhanced the density and decreased the pore size of scaffold compared with the randomly oriented nanofibers, the drug diffused outwards from the aligned scaffold was less than that of random scaffold. Therefore, under the same condition, the drug release rate of aligned scaffold was lower than that of randomly oriented scaffold.

Fig. 6 shows the drug release behavior of FBF-loaded PLGA/chitosan randomly oriented nanofibrous scaffolds with different crosslinking time. When the chitosan content was lower in PLGA/chitosan (9.375/0.625 and 9/1) nanofibrous scaffold (Fig. 6A and B), the increasing crosslinking time significantly decreased both the release rate and the maximum amount of FBF released from FBF-loaded electrospun nanofibrous scaffold. The FBF-loaded PLGA/chitosan scaffold contained a burst release stage and followed by gradually increased stage and the burst release stage was mainly dependent on the water transportation in the chitosan phase. After the crosslinking treatment, the linear chain of chitosan changed to network chain which had a lower swelling ratio and thus decrease the diffusion of the drug from the fiber. Therefore the diffusion of drug decreased with the increase of crosslinking time and inhibited the initial burst release of drug. Moreover, different drug release rates would be obtained with different crosslinking time which would be used as drug controlled release system. However, as for PLGA/chitosan (7/3) nanofibrous scaffold which is shown in Fig. 6C, the drug release was not changed significantly as that of PLGA/chitosan (9.375/0.625 and 9/1) nanofibrous scaffold, which may because crosslinking could not decrease the swelling when a large amount of chitosan existed in the scaffold.

4. Conclusions

In this study, we produced randomly oriented and aligned PLGA/chitosan nanofibers by electrospinning. The average diameter increased with the increase of chitosan content and then decreased due to stretching and self-repulsion force by high charge density. The result of FT-IR indicated a weak molecular force between PLGA and chitosan. The release rate of fenbufen increased with the increase of chitosan because the addition of chitosan enhanced hydrophilicity of the electrospun PLGA/chitosan scaffold. The drug release rate of aligned PLGA/chitosan nanofibrous scaffold was lower than that of randomly oriented scaffold, where the nanofibers arrangement direction might influence the release behavior to a certain extent. Moreover, the FBF released from PLGA/chitosan scaffold with low chitosan content would be controlled through crosslinking in glutaraldehyde vapor, which seems to be feasible for future application in biomedicine.

Acknowledgements

This work is supported by the Research Fund for the Doctoral Program of Higher Education (No. 20060217012) and the Fundamental Research Funds for the Central Universities (No. HEUCF101003).

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