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ScienceDirect
Journal of Bionic Engineering 13 (2016) 143–149

Electrospinning and Crosslinking of COL/PVA Nanofiber-microsphere Containing Salicylic Acid for Drug Delivery

Xiaoli Zhang[1,2], Keyong Tang[1], Xuejing Zheng[1]

1. *College of Materials Science and Engineering*, *Zhengzhou University*, *Zhengzhou* 450001, *China*
2. *Henan Key Laboratory of Functional Textile Materials*, *College of Textiles*, *Zhongyuan University of Technology*, *Zhengzhou* 450007, *China*

Abstract

Porous nanofiber-microsphere mats of collagen (COL)/polyvinyl alcohol (PVA) containing salicylic acid (SA) as model drug were prepared by electrospinning for the assessment of drug delivery system. The electrospun fibrous mats were crosslinked by UV-radiation or glutaraldehyde to weaken the degree of drug burst release and morphology damage when meeting water. The morphology and chemical structures of COL/PVA-SA electrospun fibers were characterized by SEM and FTIR. The crosslinking of UV-radiation did not destroy the morphology of COL/PVA-SA electrospun fibers in the crosslinking process, however, the crosslinking of glutaraldehyde did it. *In vitro* release studies showed that COL/PVA-SA electrospun fibers efficiently controlled the release of drugs by the crosslinking of UV-radiation for 4 h. The transport mechanism that controlled the release of drugs from electrospun mats was Fickian diffusion.

Keywords: electrospinning, collagen, polyvinyl alcohol, nanofibers, drug delivery

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doi: 10.1016/S1672-6529(14)60168-2

1 Introduction

Electrospinning has gained increasing interest and attention in recent years due to its versatility and potential for applications in diverse fields[1,2]. Various polymers including synthetic, natural, and hybrid materials have been successfully electrospun into ultrafine fibers[3].The development of nanofibers has led to resurgence in interest regarding the electrospinning process due to its potential applications in filtration, protective clothing, and biological applications such as tissue engineering scaffolds and drug delivery devices[3,4]. Among the various potential applications, drug delivery is one of the most promising applications. The high loading capacity, high encapsulation efficiency, simultaneous delivery of diverse therapies, ease of operation, and cost-effectiveness are appealing features for electrospinning used in drug delivery[5]. Taepaiboon *et al*. found that the molecular weight of the model drugs played a major role in both the rate and total amount of drug released from the drug-loaded electrospun PVA mats[6]. Eranka *et al*. fabricated fast dissolving paracetamol/caffeine nanofibers by electrospinning for children and patients with swallowing difficulties[7]. He *et al*. investigated the effects of drug loading capacity on polyvinylidene fluoride fibrous membranes containing enrofloxacin drugs for wound dressing by electrospinning[8].

Nowadays, collagen has been found various applications in drug delivery and tissue engineering[9,10]. The electrospinning process of collagen, a major component of native extracellular matrix (ECM) and related bio-derived polymers into porous scaffolds, has thus attracted great interests[11,12]. However, collagen usually was denatured into gelatin during electrospinning, due to the solvents choice of electrospinning[13,14]. The most widely used solvents for electrospinning of collagen are highly volatile organic solvents such as 1,1,1,3,3,3 hexafluoroisopropanol (HFP)[12,15,16], trifluoroacetic acid (TFA)[15,17] or 2,2,2-trifluoroethanol (TFE)[18]. These fluoroalcohols not only lead to collagen denaturation, but also lower its denaturation temperature[14]. To overcome this, Dong *et al*. investigated the electrospinning of type I collagen scaffolds from a benign solvent system comprised of ethanol and phosphate buffered

Corresponding author: Keyong Tang
E-mail: keyongtangzzu@yahoo.com

saline[19]. Liu *et al*. fabricated collagen nanofibers from 40% acetic acid[14]. However, electrospun collagen scaffolds had poor mechanical strength, especially in hydrated state[20]. Various approaches have been developed to reinforce and improve the mechanical properties of collagen materials, *e.g*. preparing collagen-based polymer blends or composites by incorporation with synthesized or natural materials[21].

Polyvinyl alcohol (PVA) has gained a great attention as a scaffold supporter for tissue engineering applications and biomedical applications. In recent years, PVA was usually added into some natural polymer solutions to prepare nanofibers by electrospinning process, such as electrospinning of polysaccharides/PVA[22] and agar/PVA[23]. The drug-loaded electrospun PVA mats were studied, which exhibited much better release characteristics of model drugs than that of drug-loaded as-cast films[6]. The gelatin/PVA bicomponent nanofibers were prepared *via* electrospinning to investigate its control release of raspberry ketone[24]. But there were few reports on the application of collagen and PVA blending nanofibers by electrospinning in drug release system. In this work, PVA solution was added to collagen acetic acid solution in the process of electrospinning to reinforce the mechanical ability and spinning performance of collagen nanofiber.

Both collagen and PVA are hydrophilic materials, when meeting water, the morphology of COL/PVA nanofibers will be destroyed by the swelling of water absorption. A degree of post treatment is needed after generating the electrospun fiber so that nanofibers can not be destroyed in aqueous media. Crosslinking of electrospun collagen is often carried out to preserve scaffold fibrous architecture, which is an important feature of electrospun constructs[14]. In addition, crosslinking is another method to prevent burst release of drug from nanofibers[5]. Chemical crosslinking by glutaraldehyde (GTA) vapor treatment is the most extensively-used method[25,26]. However, chemical crosslinking requires crosslinking agent which could potentially pose negative impact from remaining trace amount of chemicals especially in medical application. Unfortunately, the induction of cytotoxicity and calcification in host tissues are among the most commonly associated problems. So physical crosslinking achieved by UV-irradiation has also been used[14,27].

The purpose of this study is to obtain the COL/PVA nanofibers containing salicylic acid (SA) by electrospinning. The model drug is a nonsteroidal anti-inflammatory drug used to treat inflammation and pain[28]. Therefore, the use of composite nanofibers for implants or localized treatment of wound areas may not only provide anti-inflammatory effects, but also localize pain relief for a long period of time through sustained SA release. The electrospun fibrous mats were crosslinked by post treatment of UV-radiation or glutaraldehyde. The influence of post treatment on fiber morphology is characterized by SEM. Further, salicylic acid release kinetics from electrospun fibrous mats are evaluated and quantified.

2 Experimental

2.1 Materials

PVA with average molecular weight from 85,000 $g \cdot mol^{-1}$ to 124,000 $g \cdot mol^{-1}$ and hydrolysis degree from 87% to 89% was purchased from Sigma-Aldrich and used without further treatment or purification. Pigskin type I collagen was extracted from pigskin by pepsin hydrolysis, and freeze-dried to yield collagen sponge for subsequent use.

2.2 Preparation of electrospinning solutions

To obtain the COL/PVA electrospinning solutions containing SA, the solutions of PVA containing SA, and collagen were prepared separately and then mixed. The solution of 8 wt% PVA containing SA (3 wt%) was prepared in de-ionized water. After being stirred at 80 ˚C for 1.5 h, the solutions were cooled to room temperature. Collagen of 1.64 g was dissolved in 100 mL of 0.5 M acetic acid solution to make collagen acid solution. In other studies, we found that the electrospinning ability of collagen/PVA mixtures was adverse with the increase in collagen amount. To develop the biological advantage of collagen we choose the collagen content as much as possible, but little effect of the collagen content on electrospinning performance. Then the collagen acid solution was blended with 8 wt% PVA solution containing SA at the COL/PVA ratios (w/w) of 5/5, and stirred for 2 h at room temperature to obtain electrospinning solutions containing embedded drug.

2.3 Electrospinning of the COL/PVA blended solutions containing SA

The blended solution was poured into a 20 mL

plastic syringe equipped with a blunt metallic needle with inner diameter of 0.8 mm. A board covered with aluminum foil was placed 15 cm away from the needle tip as counter electrode. Electrospinning was carried out at room temperature in a horizontal electrospinning configuration as shown in Fig. 1 and the applied voltages driven by a high voltage generator was 18 kV. A syringe pump was used to feed at the flow rate of 0.4 mL·h^{-1}. The electrospun fibers were collected directly on the aluminum foil.

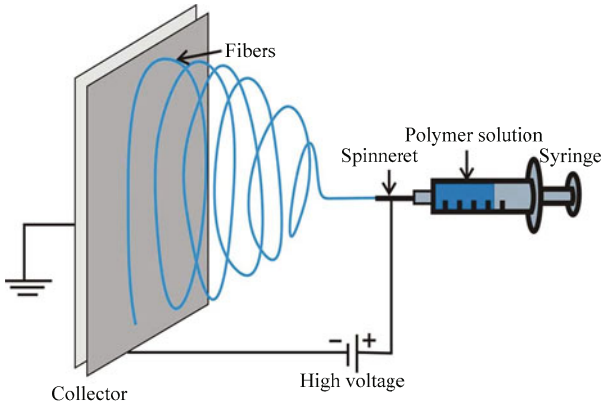

Fig. 1 Schematic diagram of the set for electrospinning.

2.4 Crosslinking of electrospun COL/PVA nanofibers containing SA

The ultraviolet crosslinking process was carried out by placing the air-dried nanofibrous membrane together with a supporting aluminum foil in a QUV accelerated weathering tester. UV light intensity using UV-340 lamp and temperature were respectively set as 0.89 w·m^{-2} and 50 ˚C. The irradiation time was designated as 4 h and 8 h. The corresponding samples were UV-4h and UV-8h, respectively.

The glutaraldehyde crosslinking process was carried out by placing the air-dried nanofibrous membrane together with a supporting aluminum foil in a sealed jar containing aqueous glutaraldehyde solution of 20 mL. The membranes were hung in the jar and crosslinked in the glutaraldehyde vapor at room temperature for 5 h.

After crosslinking, all samples including non-crosslinking sample were exposed in an oven for 2 h at 50˚C to remove residual glutaraldehyde and water.

2.5 Morphology

Samples were prepared by directly electrospinning the solutions of COL/PVA blended solutions containing SA on the aluminium foil and followed by Au sputtering for better conductivity during image. The morphology of the electrospun nanofibers was investigated by scanning electron microscope (JSM-6360LV).

2.6 FTIR analysis

FTIR spectra of the electrospun COL/PVA nanofibers containing SA were obtained by infrared spectroscopy instrument (NICOLET, USA), with the wavenumber range of 650 cm^{-1} – 4000 cm^{-1}.

2.7 *In vitro* drug release

The electrospun nanofiber membranes of COL/PVA containing SA were dried, and the initial weight was measured. For the drugs release behavior study, each specimen was placed in a tube containing phosphate-buffered saline solution of 30 mL (PBS, pH 7.4, 19.00 g NaH_2PO_4 and 2.52 g Na_2HPO_4 in 500 mL pure water, 37˚C). At various time intervals, supernatant of 5 mL was taken from the tube on magnetic rotation speed of 60 r·min^{-1} (EYELA ChemiStation PPS-CTRL1, Japan), and an equal volume of fresh medium was added again. The amount of salicylic acid released from the nanofibers to the PBS solution was measured using a UV-Vis spectrophotometer (SDPTOP UV2400, China) by measuring the absorbance at 296 nm. A 50 ppm stock solution of salicylic acid in PBS was used to prepare standard solutions with different concentrations from 0 ppm to 10 ppm in order to obtain the calibration curve $y = 0.0238x+0.0162$ (x is the absorbance at 296 nm, y is the concentration of salicylic acid) and R^2 =0.9996. Drug cumulative release amount was calculated as

$$E_r = \frac{V_e \sum_{i=n-1}^{n-1} C_i + V_0 C_n}{m_{\text{drug}}}, \quad (1)$$

where E_r is the drug cumulative release amount (%), V_e is the PBS displacement volume (mL), V_0 is the release fluid volume (mL), C_i is release drug concentration at time replacement i. So E_r is a function of time.

3 Results and discussion

3.1 Morphology of the electrospun fibers

The SEM images of the electrospun PVA/COL nanofibers containing SA with different crosslinking methods are shown in Fig. 2. The nanofibers of non-crosslinking reveal a surface with some formation

of beads in the fibers. UV irradiation did not exhibit a dramatic effect on the diameter of PVA/COL blended electrospun nanofibers containing SA. There are no changes between UV-irradiation crosslinking and non-crosslinking of the nanofibers in the morphology. However, glutaraldehyde vapor crosslinking induces adhesion between the electrospun fibers. This may be the result that the fibers tend to swell in the glutaraldehyde vapor and adhere with each other. It was seen from Fig. 3 that when meeting water the non-crosslinking sample without any crosslinking lost the morphology of nanomfiber for moisture absorption and swelling, and for the samples treated with different time of ultraviolet irradiation, although the nanofibers's morphology is not well preserved, but a bit better than that of the non-crosslinking sample. Samples after crosslinking with glutaraldehyde vapor kept a little better fiber morphology than that of ultraviolet light, while humidity in glutaraldehyde crosslinking is too big to lose the original morphology of nanofibers before crosslinking from Fig. 2.

3.2 FTIR analysis

The FTIR spectrum is suitable to study the spectral changes caused by polymer-polymer interactions by comparing the vibration bands of the blended matters with those of the pure component. The FTIR spectra of PVA/COL blended solutions containing SA with different crosslinking methods were shown in Fig. 4. The FTIR spectroscopy was used to elucidate the presence of collagen in the blended electrospun nanofibers and to analyze any structural changes that might have occurred after being crosslinked. In the spectra of PVA/COL blended nanofibers containing salicylic acid, the one at 3336 cm^{-1} was the stretching of N-H and O-H, the one at 1733cm^{-1} was the stretching of C=O, the one at 1434cm^{-1} was the bending of O-H, the one at 1093cm^{-1} was the stretching vibration of C-O-H, the one at 1660 cm^{-1} was the stretching of C-O (amide I), the one at 1556 cm^{-1} was the bending of and stretching of C-N (amide II). There were no changes among the FTIR curve of all samples.

3.3 *In vitro* release study

From the data of Fig. 5a, SA-loaded nanofiber mats fabricated by electrospinning a blended solution of drug and polymer showed an initial burst release. The drug was not released completely because the drug was

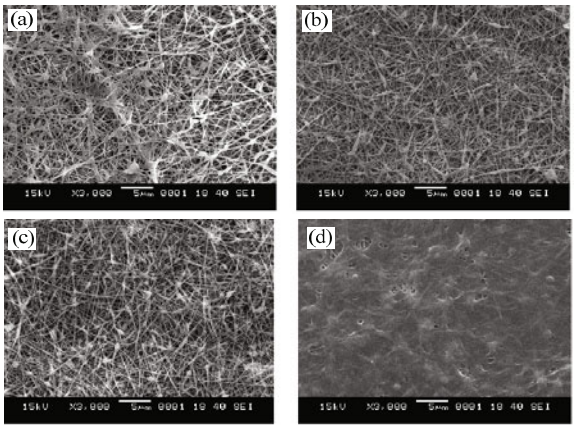

Fig. 2 SEM images of electrospun nanofiber mats made of PVA/COL blended solutions containing SA with different crosslinking method. (a) Non-crosslinking sample; (b) sample treated with UV-4h; (c) sample treated with UV-8h; (d) sample treated with glutaraldehyde-5h.

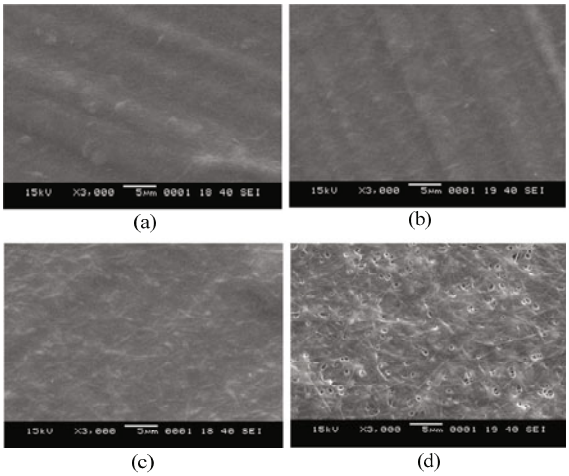

Fig. 3 SEM images of electrospun nanofiber mats made of PVA/COL blended solutions containing SA with different crosslinking method after meeting water. (a) Non-crosslinking sample; (b) sample treated with UV-4h; (c) sample treated with UV-8h; (d) sample treated with glutaraldehyde-5h.

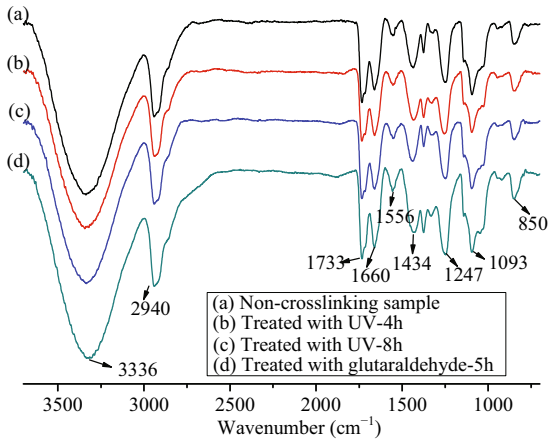

Fig. 4 FTIR of the electrospun PVA/COL fibers.

dispersed in the carrier and had intermolecular forces with the carrier such as the H-bond between the –OH or –COOH of the SA drug and the –OH of the PVA[28]. Crosslinking of fiber surface can regulate the rate of drug release. In this paper the chemical method of glutaraldehyde vapor and physical method of ultraviolet light were used to crosslink the fiber surface and to control the drug release. Drug release profiles from nanofibers mats treated with different crosslinking method can obviously decrease the rate of drug release. The effect of ultraviolet light crosslinking is better than that of the glutaraldehyde crosslinking. However, the release percentage of SA from electrospun COL/PVA nanofibers treated with UV-4h is lower than that of sample treated with UV-8h. Because there is UV-induced cross-linking in short time and UV-induced fragmentation of the collagen chains in long time[29].

The release kinetics of drug from the developed matrices was analyzed using Korsmeyer Peppas kinetic model. The release data were thus fitted according to the following Korsmeyer Peppas equation[30,31]:

$$\frac{M_t}{M_\infty} \times 100\% = kt^n, \qquad (2)$$

where M_t is the mass of the drug released at time t, M_∞ is the mass of the drug released when time approaches infinity, k is a release rate constant and n is the diffusion exponent. The constant value of k is usually related to the characteristics of the delivery system and the drug. The diffusion exponent of n characterizes the transport mechanism of the drug and is dependent on the type of transport, geometry and polydispersity. If $n \leq 0.5$ the releasing mechanism is Fickian diffusion, if $0.5 \leq n \leq 1.0$ the releasing mechanism is anomalous transport, if $n \geq 1.0$ the releasing mechanism is case-II transport[32,33]. From the slope and intercept of the plot of $\ln(M_t/M_\infty)$ versus $\ln(t)$ for the release of SA from nanofibers fabricated by electrospinning, the constant value of release rate, k, and the diffusion exponent n was calculated, which are shown in Table 1. All the n values from different crosslinking methods are less than 0.5, so the mechanism belongs to Fickian diffusion. The k values of SA-loaded nanofibers after crosslinking were reduced, and the k values of ultraviolet light crosslinking sample were lower than those of the glutaraldehyde crosslinking sample. The k value of UV-4h sample was reduced to 1.7. So *in vitro* release study showed that

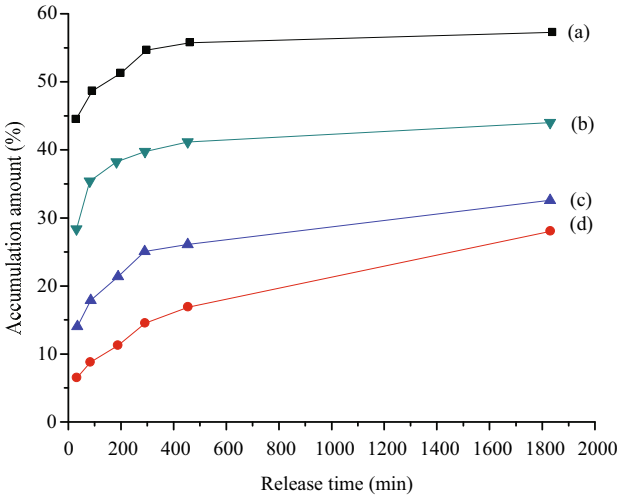

Fig. 5 Release percentage of SA from electrospun COL/PVA nanofibers with different crosslinking method: (a) Original sample; (b) sample treated with glutaraldehyde-5h; (c) sample treated with UV-8h; (d) sample treated with UV-4h.

Table 1 The constant value of release rate k and the diffusion exponent n obtained by the Korsmeyer-peppas model

Samples	k (min^{-n})	n	R^2
Non-crosslinking sample	36.5	0.0645	0.919
UV-4h	1.7	0.3697	0.995
UV-8h	6.9	0.2138	0.975
Glutaraldehyde-5h	21.5	0.1028	0.882

COL/PVA-SA electrospun fibers efficiently control the release of drugs by the crosslinking of UV-radiation for 4 h.

4 Conclusion

In this study, the COL/PVA nanofibers containing SA were obtained by electrospinning for assessment as drug delivery system. The morphology of COL/PVA-SA electrospun fibers treated with UV-radiation was not change before meeting water, but the surface of electrospun fibers treated with glutaraldehyde was swelled and adhesived. The FTIR curves of all samples were not obviously changed. The results showed that COL/PVA-SA efficiently controlled the release of drugs by the crosslinking of UV-radiation, but the morphology was destroyed when meeting water. The mechanism of SA release from electrospun fibers belongs to Fickian diffusion.

Acknowledgment

The financial supports from the National Natural Science Foundation Commission of China (Nos.

21076199, 51373158 and 51473150) and Department of Science and Technology of Henan Province (No. 124300510) are gratefully acknowledged.

References

[1] Nandana Bhardwaj, Kundu S C. Electrospinning: A fascinating fiber fabrication technique. *Biotechnology Advances*, 2010, **28**, 325–347.

[2] Agarwal S, Greiner A, Wendorff J H. Functional materials by electrospinning of polymers. *Progress in Polymer Science*, 2013, **38**, 963–991.

[3] Huang Z M, Zhang Y Z, Kotaki M, Ramakrishna S. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. *Composites Science and Technology*, 2003, **63**, 2223–2253.

[4] Sill T J, von Recum H A. Electrospinning: Applications in drug delivery and tissue engineering. *Biomaterials*, 2008, **29**, 1989–2006.

[5] Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X. Electrospinning of polymeric nanofibers for drug delivery applications. *Journal of Controlled Release*, 2014, **185**, 12–21.

[6] Taepaiboon P, Rungsardthong U, Supaphol P. Drug-loaded electrospun mats of poly(vinyl alcohol) fibres and their release characteristics of four model drugs. *Nanotechnology*, 2006, **17**, 2317–2329.

[7] Illangakoon U E, Gill H, Shearman G C, Parhizkar M, Mahalingam S, Chatterton N P, Williams G R. Fast dissolving paracetamol/caffeine nanofibers prepared by electrospinning. *International Journal of Pharmaceutics*, 2014, **477**, 369–379.

[8] He T, Wang J N, Huang P L, Zeng B Z, Li H H, Cao Q Y, Zhang S Y, Luo Z, Deng D B, Zhang H W, Zhou W Y. Electrospinning polyvinylidene fluoride fibrous membranes containing anti-bacterial drugs used as wound dressing. *Colloids and Surfaces B*: *Biointerfaces*, 2015, **130**, 278–286.

[9] Ottania V, Raspantib M, Ruggeria A. Collagen structure and functional implications. *Micron*, 2001, **32**, 251–260.

[10] Friess W. Collagen-biomaterial for drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 1998, **45**, 113–136.

[11] Sell S A, McClure M J, Garg K, Wolfe P S, Bowlin G L. Electrospinning of collagen/biopolymers for regenerative medicine and cardiovascular tissue engineering. *Advanced Drug Delivery Reviews*, 2009, **61**, 1007–1019.

[12] Matthews J A, Wnek G E, Simpson D G, Bowlin G L. Electrospinning of Collagen Nanofibers. *Biomacromolecules*, 2002, **3**, 232–238.

[13] Zeugolis D I, Khew S T, Yew E S Y, Ekaputra A K, Tong Y W, Yung L Y L, Hutmacher D W, Sheppard C, Raghunath M. Electro-spinning of pure collagen nano-fibres-Just an expensive way to make gelatin? *Biomaterials*, 2008, **29**, 2293–2305.

[14] Liu T, Teng W K, Chan B P, Chew S Y. Photochemical crosslinked electrospun collagen nanofibers: Synthesis, characterization and neural stem cell interactions. *Journal of Biomedical Materials Research Part A*, 2010, **95A**, 276–282.

[15] Chen Z, Mo X, Qing F. Electrospinning of collagen-chitosan complex. *Materials Letters*, 2007, **61**, 3490–3494.

[16] Huang C, Chen R, Ke Q, Morsi Y, Zhang K, Mo X. Electrospun collagen-chitosan-TPU nanofibrous scaffolds for tissue engineered tubular grafts. *Colloids and Surfaces B*: *Biointerfaces*, 2011, **82**, 307–315.

[17] Chen Z, Wei B, Mo X M, Cui F Z. Diameter control of electrospun chitosan-collagen fibers. *Journal of Polymer Science Part B*: *Polymer Physics*, 2009, **47**, 1949–1955.

[18] Zhong S P, Teo W E, Zhu X, Beuerman R, Ramakrishna S, Yung L Y L. Development of a novel collagen-GAG nanofibrous scaffold via electrospinning. *Materials Science and Engineering*: *C*, 2007, **27**, 262–266.

[19] Dong B, Arnoult O, Smith M E, Wnek G E. Electrospinning of collagen nanofiber scaffolds from benign solvents. *Macromolecular Rapid Communications*, 2009, **30**, 539–542.

[20] Yang L, Fitié C F C, van der Werf K O, Bennink M L, Dijkstra P J, Feijen J. Mechanical properties of single electrospun collagen type I fibers. *Biomaterials*, 2008, **29**, 955–962.

[21] Fullana M J, Wnek G E. Electrospun collagen and its applications in regenerative medicine. *Drug Delivery and Translational Research*, 2012, **2**, 313–322.

[22] Santos C, Silva C J, Büttel Z, Guimarães R, Pereira S B, Tamagnini P, Zille A. Preparation and characterization of polysaccharides/PVA blend nanofibrous membranes by electrospinning method. *Carbohydrate Polymers*, 2014, **99**, 584–592.

[23] Sousa A M M, Souza H K S, Uknalis J, Liu S C, Gonçalves M P, Liu L. Electrospinning of agar/PVA aqueous solutions and its relation with rheological properties. *Carbohydrate Polymers*, 2015, **115**, 348–355.

[24] Yang D, Li Y, Nie J. Preparation of gelatin/PVA nanofibers and their potential application in controlled release of drugs. *Carbohydrate Polymers*, 2007, **69**, 538–543.

[25] Zhong S, Teo W E, Zhu X. An aligned nanofibrous collagen scaffold by electrospinning and its effects on in vitro fibroblast culture. *Journal of Biomedical Materials Research*. *Part A*, 2006, **79A**, 456–463.

[26] Zhang Y Z, Venugopal J, Huang Z M, Lim C T, Ramakrishna S. Crosslinking of the electrospun gelatin nanofibers. *Polymer*, 2006, **47**, 2911–2917.

[27] Zhou C, Wang Q, Wu Q. UV-initiated crosslinking of electrospun poly(ethylene oxide) nanofibers with pentaerythritol triacrylate: Effect of irradiation time and incorporated cellulose nanocrystals. *Carbohydrate Polymers*, 2012, **87**, 1779–1786.

[28] Nguyen T T T, Ghosh C, Hwang S G, Chanunpanich N, Park J S. Porous core/sheath composite nanofibers fabricated by coaxial electrospinning as a potential mat for drug release system. *International Journal of Pharmaceutics*, 2012, **439**, 296–306.

[29] Sionkowska A. Thermal denaturation of UV-irradiated wet rat tail tendon collagen. *International Journal of Biological Macromolecules*, 2005, **35**, 145–149.

[30] Sohrabi A, Shaibani P M, Etayash H, Kaur K, Thundat T. Sustained drug release and antibacterial activity of ampicillin incorporated poly(methyl methacrylate)-nylon6 core/shell nanofibers. *Polymer*, 2013, **54**, 2699–2705.

[31] Cao T, Tang W, Zhao J, Qin L, Lan C. A novel drug delivery carrier based on α-eleostearic acid grafted hydroxyapatite composite. *Journal of Bionic Engineering*, 2014, **11**, 125–133.

[32] Li X, Kanjwal M A, Lin L, Chronakis I S. Electrospun polyvinyl-alcohol nanofibers as oral fast-dissolving delivery system of caffeine and riboflavin. *Colloids and Surfaces B*: *Biointerfaces*, 2013, **103**, 182–188.

[33] Immich A P S, Arias M L, Carreras N, Boemo R L, Tornero J A. Drug delivery systems using sandwich configurations of electrospun poly(lactic acid) nanofiber membranes and ibuprofen. *Materials Science and Engineering*: *C*, 2013, **33**, 4002–4008.