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Fabrication and characterization of biodegradable nanofibrous mats by mix and coaxial electrospinning

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Abstract The aim of this study is to investigate an innovative tissue engineering scaffold with a controllable drug-releasing capability. The hypothesis is that the nanofibers fabricated by coaxial electrospinning could encapsulate and release sustainedly Tetracycline Hydrochloride (TCH). To testify the hypothesis, nanofibers were prepared by coaxial electrospinning from Poly(L-lactid-co-ε-caprolactone) [PLLACL]/2,2,2-Frifluoroethanol (TFE) solutions (as the shell solutions) and TCH/TFE solutions (as the core solutions). In addition, nanofibers of PLLACL-blend-TCH were also prepared as the control by mix electrospinning. The relationship between fibers morphologies and processed conditions in electrospinning were investigated. TCH release behaviors from the nanofibrous mats were studied. The antibacterial properties of aforementioned nanofibers were detected by the *Escherichia coli* growth-inhibiting tests. The results indicated that the nanofibers prepared by coaxial-electrospinning had the desired and controllable TCH encapsulation/release profile; thus, it could be utilized as both a drug encapsulation/release vehicle and a tissue engineering scaffold.

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1 Introduction

In contrast to conventional transplantation methods, tissue engineering provided a new medical therapy which used polymeric biomaterials with or without living precursor [1–4]. The ultimate purpose of tissue engineering is to reestablish the destroyed human tissues or organs by provide scaffolds for functional cells regeneration. In human tissue, Extracellular Matrix (ECM) plays a pivotal role in supporting and controlling cells living, therefore, the tissue engineering scaffolds should be designed to mimic natural ECM. For this aim, the method of electrospinning was applied in recent years [5–7].

Electrospinning technology, which was first developed in 1930s, is a simple and versatile method to prepare ultrathin fibers from polymer solutions or melts. The obtained fibers usually have a diameter from several nanometers to a few micrometers. Electrospun polymer nanofibers possess many extraordinary properties including small diameters and the concomitant large specific surface areas, a high degree of structural perfection [8]. Additionally, the non-woven fabrics (mats) made of electrospun polymer nanofibers offer a unique capability to control the pore sizes. Electrospun nanofibers are produced through a top-down nano-manufacturing process, which results in continuous nanofibers that are also relatively easy to be aligned, assembled and processed into applications. Many synthetic and natural polymers including, but not limited to, Polylactide (PLA) [9], Poly(Glycolic-acid) (PGA)[10], Poly(L-Lactide-co-Caprolactone) (PLLACL) [11], proteins (e.g., Collagen)

[12], and Polysaccharides (e.g., Chitosan) [13] have been electrospun into nanofibrous mats as innovative tissue engineering scaffolds for growing various kinds of cells. Furthermore, polymer nanofibers obtained through electrospinning have been proposed for using as drug release systems because of outstanding features such as extremely high surface area to volume ratio [14, 15]. Electrospun nanofibers have several advantages when compared with other dosage forms; the drug release profile can be finely tailored by a modulation on the morphology, porosity, and composition of the nanofibers membrane; the very small diameter of the nanofibers can provide short diffusion passage length; and the high surface area is helpful to a mass transfer and efficient drug release [16].

In wound caring applications, when the nanofibers are biodegradable and absorbable by human body, the drug or other therapeutic agents incorporated in the fibers will release and play a desired role. By encapsulating drugs into the core of nanofibers, the controlled release of active agents and physical structure for tissue regeneration could be achieved at the same time [17]. Recently, many researches have focus on the developments of fabricating core-shell structure nanofibers by emulsion electrospinning and coaxial electrospinning [18, 19]. Unlike emulsion electrospinning, the electrospun solutions always contain a surfactant and eject from a single channel, in coaxial electrospinning process, two liquids are ejected out though

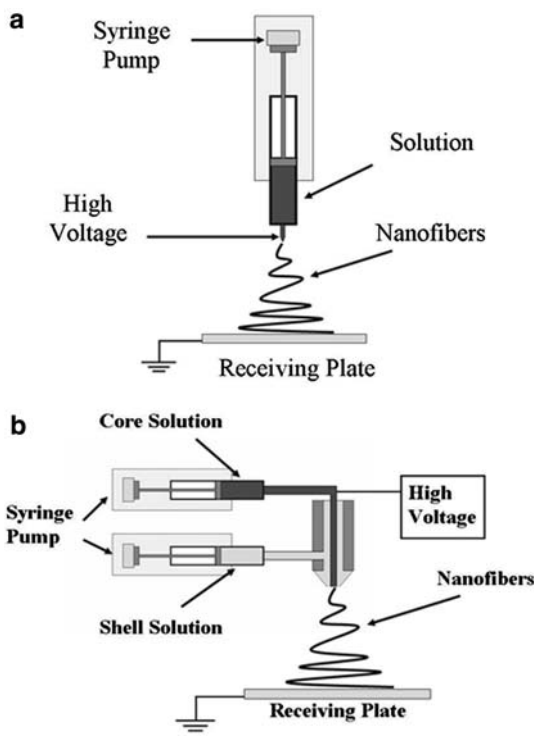


Fig. 1 The set-up for mix (**a**) and coaxial (**b**) electrospinning

Fig. 2 SEM images of the PLLACL [50:50], PLLACL [50:50]/TCH nanofibrous mats prepared by mix and coaxial electrospinning with TCH contents of 5 and 20 wt% compared with PLLACL [50:50]. Image (**a**) was the morphology of pure PLLACL [50:50] nanofibers. Images of (**c**) and (**e**) were the morphology of PLLACL [50:50]/TCH with 5% and 20% (with respect to polymer) TCH, prepared by mix electrospinning. Images of (**g**) and (**i**) were the morphology of PLLACL [50:50]/TCH with 5% and 20% (compared with polymer) TCH prepared by coaxial electrospinning. And the pictures of (**b**), (**d**), (**f**), (**h**) and (**j**) were the statistical analysis of (**a**), (**c**), (**e**), (**g**) and (**i**), respectively

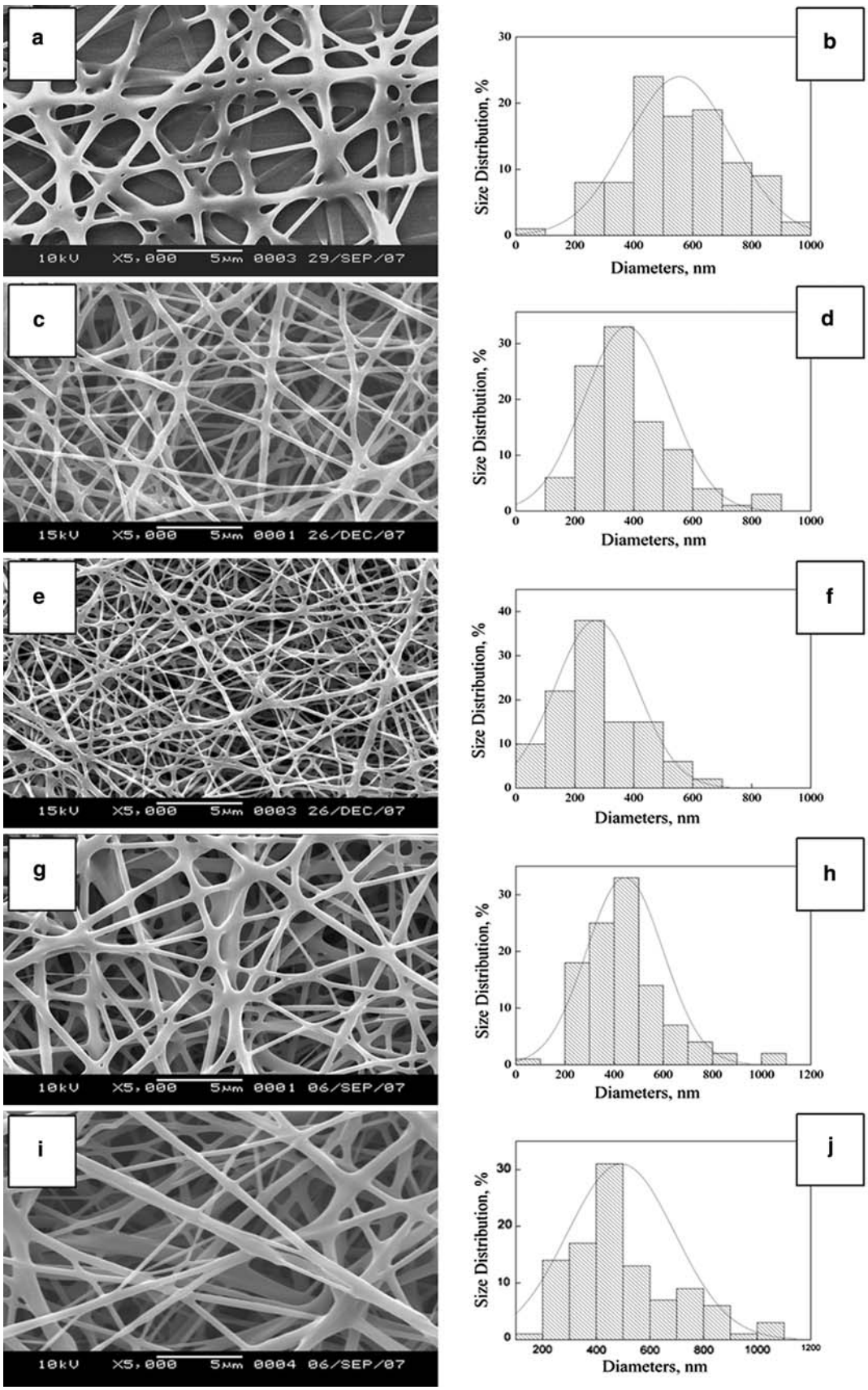
different but coaxial capillary channels and forced by the same electrostatic potential to generate the core-shell structured nanofibers [20]. As most conditions the shell fluid is able to be processed with electrospinning, while the core fluid cannot be electrospinnable. One of the best advantages using core-shell type nanofibers is to encapsulate and effectively protect proteins and/or biological agents which easily denatured by the electrospun process and outer environments.

The objective of this study is to develop drug-loaded Poly(L-lactid-co-ε-caprolactone) [PLLACL] nanofibers in the form of core-shell structure, which have potential applications in functional dressing for wound healing. PLLACL has been selected as shell polymer because of its toxicity-free, low cost, and biocompatibility for animal cells. One model drugs, Tetracycline Hydrochloride (TCH) which is low molecular weight have been chosen as cores. No other carrying agent, such as a high molecular weight polymer, except for the respective solvents, was mixed with drug in making the cores, and the pure drug solutions alone cannot be made into any fiber. Different ultrafine fibers containing drugs were obtained by only varying the drug concentrations in the core solution. Morphology of the composite nanofibers was characterized by scanning electron microscopy (SEM). In vitro drug release behavior was also assessed. As control, the conventional type of nanofibers contained PLLACL and TCH were also prepared by mix electrospinning.

2 Experimental

2.1 Materials

PLLACL copolymer (Mw = 140,000 g/mol) with molar ratio of 50% and 75% being L-lactide were got from Nara Medical University. Tetracycline Hydrochloride (TCH) and Phosphate-Buffered Saline (PBS, pH7.2) were purchased from Sigma-Aldrich Co., (Milwaukee, Wisconsin). 2,2,2-Frifluoroethanol (TFE) was purchased from Shanghai Fine-Chemicals Co., Ltd. (Shanghai, China). All of the materials were used without further purification.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2.2 Electrospinning of medicated nanofibrous scaffolds containing TCH

PLLACL with different component ratios were dissolved in TFE and sufficiently stirring at room temperature as the shell solution. Previous experimental results demonstrated that the very low (below to 0.02 g/ml) concentration of PLLACL/TFE solutions were unfavorable for electrospinning. In this work, 0.06 g/ml PLLACL/TFE solution was chosen to prepare electrospun nanofibers.

Figure 1 shows the basic experimental setup for mix and coaxial electrospinning processes.

The mix electrospinning solutions were simply dissolved polymer and drug in TFE as the certain concentration. During mix electrospinning, the mass flows were maintained at 1.2 ml/h, and a positive high voltage of 20 kV was applied at the tip of syringe needle with the inner diameter of 0.9 mm.

The coaxial spinneret apparatus was consist two needles which coaxially placed together. Two syringe pumps were used to deliver the core and shell solutions, respectively. Core solution was prepared by dissolving TCH in TFE to become the concentration of 0.03 g/ml. During coaxial electrospinning, the flow rates of core solutions were set as 0.01, 0.02 and 0.04 ml/h, respectively, and the shell solution was 1.0 ml/h. In the present work, a high voltage DC power supply was used to provide high voltages, and a foil film was used as receiving plate to collect electrospun nanofibers. The distance between the tip of the syringe needle and collecting plate was 12 cm.

All the processes of electrospinning were operating at room temperature with the humidity of 50%. The received nanofibrous mats were placed in vacuum over night to remove the residual solvent.

2.3 Morphologies of nanofibrous mats

A JSM-5600 LV digital vacuum Scanning Electron Microscope (SEM), produced by Japan Electron Optical Laboratory (JEOL), was employed to examine the morphologies of the prepared nanofibrous mats. The specimens of SEM examination were sputter-coated with gold to avoid charge accumulation. The diameter of the electrospun ultrafine fibers was measured with image visualization software Image-J 1.34 (National Institutes of Health, USA). Average fiber diameters and diameter distribution were determined by measuring about 100 random fibers from the SEM images.

2.4 In vitro release measurement

PLLACL/TCH nanofibrous mats were electrospun with the methods described above. The fibrous mat, each sample with the dry weight of 0.28 ± 0.05 g, was soaked in a vial filled with 10.0 ml of PBS (pH7.2). The nanofibrous mats were incubated under static conditions at 37°C. At various time points, 2.0 ml of supernatant was retrieved from the vials and an equal volume of fresh PBS was replaced. The concentration of TCH in the supernatant was then determined by an Agilent UV–vis spectrophotometer (WFZ UV-2102 Unique Technology Shanghai) at an optical wavelength of 360 nm. Experiments were performed in triplicate with the bars indicated on standard deviation.

Fig. 3 SEM images of the PLLACL [75:25], PLLACL [75:25]/TCH nanofibrous mats prepared by mix and coaxial electrospinning with TCH contents of 5 and 20 wt% with respect to PLLACL [75:25]. Image (**a**) was the morphology of pure PLLACL [75:25] nanofibers. Images of (**c**) and (**e**) were the morphology of PLLACL [75:25]/TCH with 5% and 20% (with respect to polymer) TCH prepared by mix electrospinning. Images of (**g**) and (**i**) were the morphology of PLLACL [75:25]/TCH with 5% and 20% (compare with polymer) TCH, prepared by coaxial electrospinning. And the pictures of (**b**), (**d**), (**f**), (**h**) and (**j**) were the statistical analysis of (**a**), (**c**), (**e**), (**g**) and (**i**), respectively

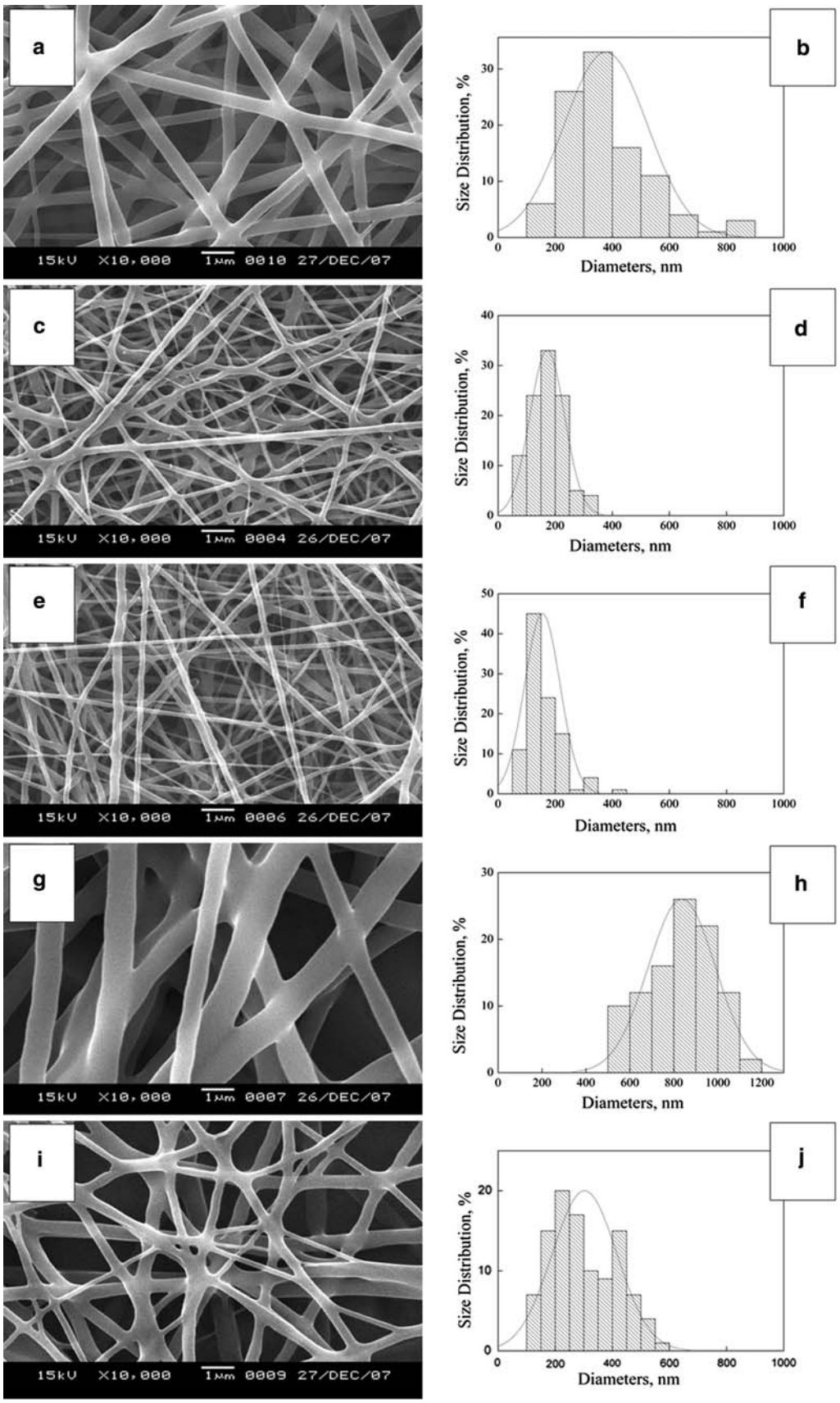
2.5 Antibacterial assessment

The antibacterial activities of the PLLACL/TCH nanofibrous mats were tested against Gram-negative *Escherichia coli* (*E. coli*) (ATCC 25922) according to Melaiye et al. [21]. The PLLACL[75:25]/TCH and PLLACL[50:50]/TCH nanofibrous mats (the TCH content by weight in the electrospinning solution with respect to PLLACL was 10 wt%) were introduced into the Luria–Bertani (LB) broth solution, which contains about 1×10^5 colony forming units (CFU) of *E. coli*. The mixtures were incubated at 37°C for 6 h, after then 100 μl of each bacteria suspension were seeded onto LB agar using surface spread-plate method. The plates were cultured at 37°C for 24 h, thereafter, counted for viable CFU of bacteria. Pure PBS and tetracycline hydrochloride solution were assessed as blank control and positive control, respectively. The antibacterial efficacy (ABE) of bacteria was calculated according to the following equation: $\text{ABE}\ (\%) = (\text{B} - \text{A})/\text{B} \times 100$, where A and B were the surviving cells (CFU) for the plates containing the test samples and the control (pure PBS), respectively.

3 Results and discussion

3.1 Morphology study of nanofibers

The details of mix and coaxial electrospinning have been described in Sect. 2. In the processes of electrospinning, electrostatic force applied by an electric field on a droplet of polymer solution can generate a polymer jet from its tip.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j
Size Distribution, %
Diameters, nm

After the solvent evaporates, nanofibers with a submicron-level diameter are deposited on a collecting plate. When the applied voltage is high enough and the electrostatic force can overcome the surface tension, fibers can be produced. In electrospinning, as described above, the traveling jet solidifies through solvent evaporation and the solidified jet thus turns into nanofibers. The solvent evaporation during electrospinning occurs under special conditions including (1) the jet has micron- or submicron-level diameter, (2) the jet carries excess charges, and (3) the solvent evaporates under the influence of a strong electric field. Nonetheless, the carried charges of the polymer solutions still significantly affect the solidification process as well as the diameters of the resultant nanofibers, and further influence the morphologies of the electrospun nanofibrous mats.

Figures 2 and 3 are the SEM images showing the representative morphologies of the PLLACL, PLLACL/TCH nanofibrous mats prepared by mix and coaxial electrospinning. The relationship between processing variables and the results of diameter information of PLLACL nanofibers are listed in Table 1. It was found that different contents of lactic acid in copolymer lead to different morphology of the electrospun nanofibers. Furthermore, it was evident that the nanofibers fabricated by mix electrospinning were thinner than nanofibers from pure polymer. TCH has relatively high conductivity compared with the solvent and the copolymer used in this study. Therefore, TCH can provide substantial charge iron. The mix solutions of PLLACL/TCH had higher conductivity and the nanofibers were easier to be elongated. Thus, the diameters of mix electrospun nanofibers were much smaller than those of PLLACL nanofibers produced via the same electrospun process. As for the nanofibers fabricated by coaxial electrospinning, the diameter was larger than that of electrospun PLLACL, although there was TCH in the inner part of electrospun solutions. It is noted that the high voltages used in coaxial electrospinning were lower than the pure or mix electrospinning. It is reasonable that addition of salt and higher voltage have the same effect on the diameter of nanofibers.

Fig. 4 In vitro release profiles (differential curve-bottom and cumulative curve-top) from electrospun scaffolds. Image (**a**) and (**c**) were the differential curve bottom release profiles of mix-electrospun PLLACL/TCH nanofibers, (**e**) and (**g**) were the differential curve bottom release profiles of coaxial electrospun PLLACL/TCH nanofibers, And the pictures of (**b**), (**d**), (**f**), and (**h**) were the cumulative curve-top of (**a**), (**c**), (**e**), and (**g**), respectively

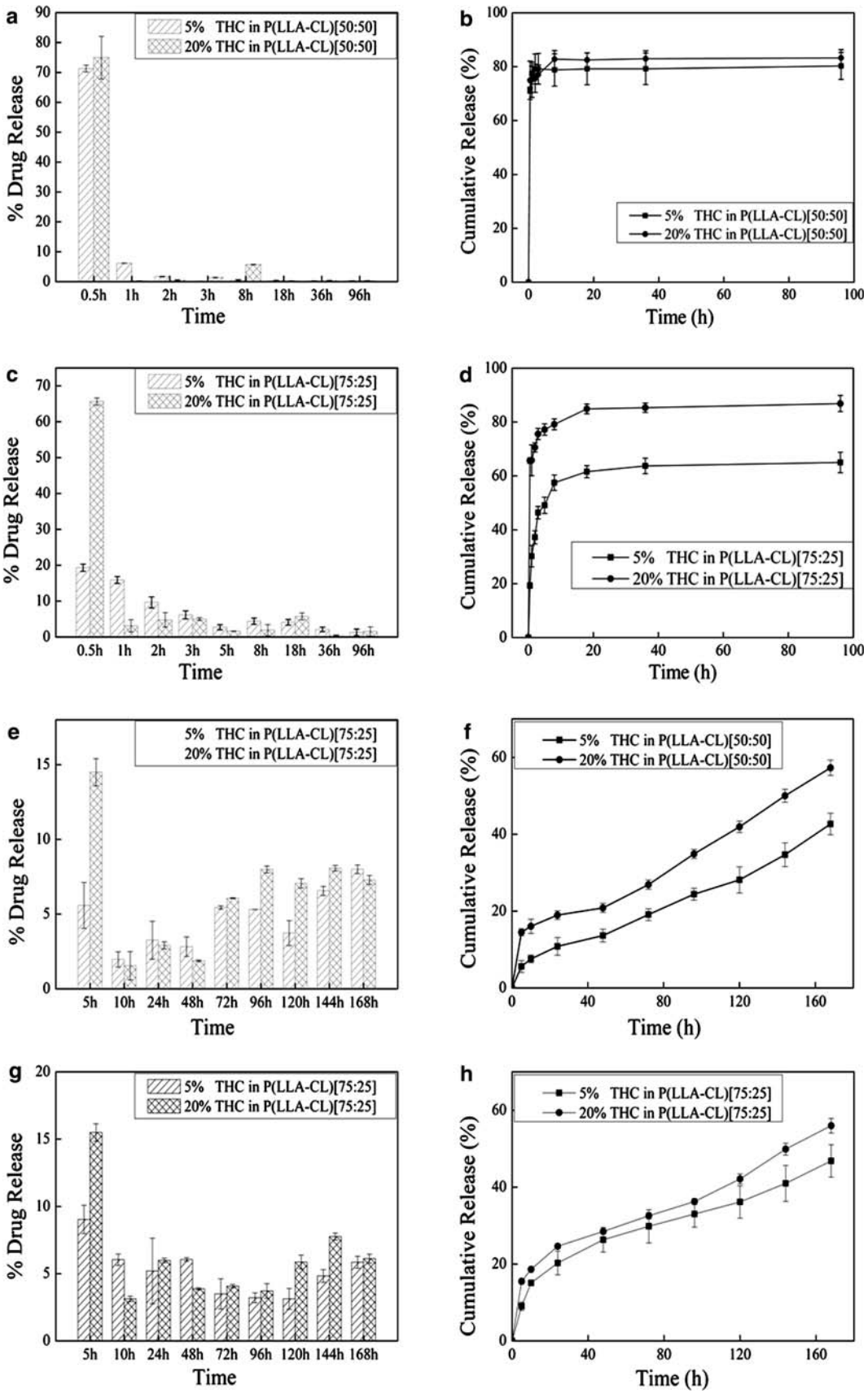
3.2 In vitro drug release study

The release of TCH from electrospun scaffolds is shown in Fig. 4. The release kinetics for mix electrospinning cases can be illustrated by two stages: an initial fast release before the inflections (stage I), followed by a constant release (stage II). In stage I, there were initial burst releases from mix electrospun mats, then the release was ceased in stage II and the total amount of release was 60–80%. Xu et al. [18] have reported a water-soluble drugs capsulated in a oily phase of chloroform solution of amphiphilic poly (ethylene glycol)-poly (L-lactic acid) (PEG-PLLA) diblock copolymer, and it has been found that the drug release behavior was related with the distribution of drug in the fibrous mats. In the process of electrospinning, the irons were easily attracted at the surface of nanofibers. Namely, the irons of THC were easily located at the surface of

Table 1 Processing variables and results of diameter information for P(LLA-CL)/TCH nanofibers prepared by mix and coaxial electrospinning

Sample code	Flow rate ml/h		Applied voltage, kV	Average diameter, nm	Average diameter error, nm
	Inner	Outer			
a	1.0		20.0	555.6	±177.4
b	1.0		20.0	377.0	±146.2
c	1.0		20.0	271.6	±138.7
d	0.10	1.0	11.0	443.8	±156.5
e	0.40	1.0	12.5	492.8	±200.6
f	1.0		20.0	413.7	±94.7
g	1.0		20.0	172.0	±60.7
h	1.0		20.0	155.1	±62.1
i	0.10	1.0	12.5	836.5	±153.8
j	0.40	1.0	13.7	302.7	±113.4

Samples of a–e were P(LLA-CL)[50:50] nanofibers, and samples of f–j were P(LLA-CL)[75:25] nanofibers. Samples of a–c and f–h were prepared from mix electrospinning using set up in Fig. 1a; while d–e and i–h were prepared from coaxial electrospinning using set up in Fig. 1b. Sample a and f were pure polymer. Sample b–c and g–h were mix electrospinning with 5% and 20% (compare with polymer) TCH in 0.06 g/ml polymer/TFE. The inner solution of sample d–e and i–j was 0.03 g/ml TCH/TFE, while the outer solutions were 0.06 g/ml P(LLA-CL)/TFE. Therefore, the loading of TCH in sample d–e and i–j were 5% and 20% compare to polymer, respectively


a
% Drug Release
Time
0.5h 1h 2h 3h 8h 18h 36h 96h
5% THC in P(LLA-CL)[50:50]
20% THC in P(LLA-CL)[50:50]
b
Cumulative Release (%)
Time (h)
5% THC in P(LLA-CL)[50:50]
20% THC in P(LLA-CL)[50:50]
c
% Drug Release
Time
0.5h 1h 2h 3h 5h 8h 18h 36h 96h
5% THC in P(LLA-CL)[75:25]
20% THC in P(LLA-CL)[75:25]
d
Cumulative Release (%)
Time (h)
5% THC in P(LLA-CL)[75:25]
20% THC in P(LLA-CL)[75:25]
e
% Drug Release
Time
5h 10h 24h 48h 72h 96h 120h 144h 168h
5% THC in P(LLA-CL)[75:25]
20% THC in P(LLA-CL)[75:25]
f
Cumulative Release (%)
Time (h)
5% THC in P(LLA-CL)[50:50]
20% THC in P(LLA-CL)[50:50]
g
% Drug Release
Time
5h 10h 24h 48h 72h 96h 120h 144h 168h
5% THC in P(LLA-CL)[75:25]
20% THC in P(LLA-CL)[75:25]
h
Cumulative Release (%)
Time (h)
5% THC in P(LLA-CL)[75:25]
20% THC in P(LLA-CL)[75:25]

nanofibers. During the release processes, the TCH presented on the surface was dissolved in PBS solution in the stage I. Thereafter, the TCH encapsulated in fibers released via diffusion in the later stage.

On the other hand, the mats derived from coaxial electrospinning showed a relative stable release behavior of TCH. In our previous study [22], it had been demonstrated that small molecules could be encapsulated in the core of nanofibers by coaxial electrospinning. Therefore, we believed that TCH was also encapsulated in the core of fibers with the same method. There were initial stages in the release profiles of TCH from coaxial electrospun PLLACL/TCH nanofibrous mats. Because the inner solution and outer solution can be mixed together completely, a little TCH might transfer onto the surface of PLLACL nanofibers. However, the released amount of initial stage of coaxial electrospinning was only 10–20%, and thereafter, the release curves exhibited the sustained and stable release behavior. The whole process of release lasted for 180 h till the total amount reached about 60%. It is obvious that the release was not completed, and the rest of TCH may release with the degradation of polymer fibers.

3.3 Antibacterial activity

Tetracycline hydrochloride has a broad antibiotic spectrum that includes Gram-negative and Gram-positive bacteria. The functionality of released TCH was investigated using *E. coli* that is a widespread intestinal parasite of mammals. Bacterial aliquots were inoculated with pure and released drug solutions. The abilities of PLLACL/TCH nanofibrous mats to inhibit the growth of the test bacteria are show in Table 2. The antibacterial efficacy (ABE) of the PLLACL [75:25]/TCH and PLLACL [50:50]/TCH nanofibers prepared by mix electrospinning against *E. coli* were 98.8% and 98.7%, respectively. And, the antibacterial efficacy (ABE) of the PLLACL [75:25]/TCH and PLLACL [50:50]/TCH nanofibers prepared by coaxial electrospinning against *E. coli* were 93.9% and 92.1%. The blank control (pure PBS) shows no inhibition on bacterial growth. Figure 5 also shows the antimicrobial activities of TCH released from nanofibrous mats against *E. coli*. The growth of *E. coli* can be visualized directly from the plates to assess the viability of these nanofibrous mats incorporating TCH. The numbers of their colonies were significantly reduced after incubation.

Relatively, the ABE of PLLACL/TCH nanofibers prepared by coaxial electrospinning against *E. coli* is lower than that of the nanofibers prepared by mix electrospinning. There were initial burst releases from mix electrospun mats within the first hour, and the released TCH reached 80% of the total amount. However, the mats derived from coaxial electrospinning showed a constant behavior at the same released time and only approximately 20% was released. These results confirm that the two different processes of electrospinning had no adverse effect on the structural changes of incorporated TCH, and the TCH released from the electrospun medical scaffolds retained its biological function.

4 Conclusion

Biodegradable copolymers PLLACL [50:50] and PLLACL [75:25] nanofibers containing TCH were fabricated by mix and coaxial electrospinning in this study. The drug was successfully incorporated into electrospun nanofibrous mats. Fibers morphologies and their diameter distribution were found to be dependent on the concentration of drug added, voltage, and the fabricating methods. Release of tetracycline hydrochloride from mats made by mix electrospinning and coaxial electrospinning was studied. It was found that there were initial burst releases from mix electrospun mats in stage I, then the release was ceased and the total releasing amount was 60–80% in stage II. For the same released time, the mats derived from coaxial electrospinning showed a constant behavior. The released tetracycline hydrochloride from electrospun mats was found to be effective in inhibiting *E. coli* growth. In view of these results, it is promising to use coaxial electrospinning in the biomedical applications or pharmaceutical devices, such as drug delivery vehicle and tissue engineering scaffold.

Table 2 The antibacterial effect of P(LLA-CL)/TCH nanofibers against *E. coli* (The TCH content by weight in the electrospinning solution with respect to P(LLA-CL) is 10 wt.%)

Materials	Initial CFU	CFU after 24 h	ABE (%)
THC	5×10^5	≤ 10	99.9
Mix electrospun P(LLA-CL)[75:25]/TCH	5×10^5	7.3×10^6	97.8
Mix electrospun P(LLA-CL)[50:50]/TCH	5×10^5	4.7×10^6	98.7
Coaxial electrospun P(LLA-CL)[75:25]/TCH	5×10^5	2.0×10^7	93.9
Coaxial electrospun P(LLA-CL)[50:50]/TCH	5×10^5	2.6×10^7	92.1
Blank (PBS)	5×10^5	3.3×10^8	–

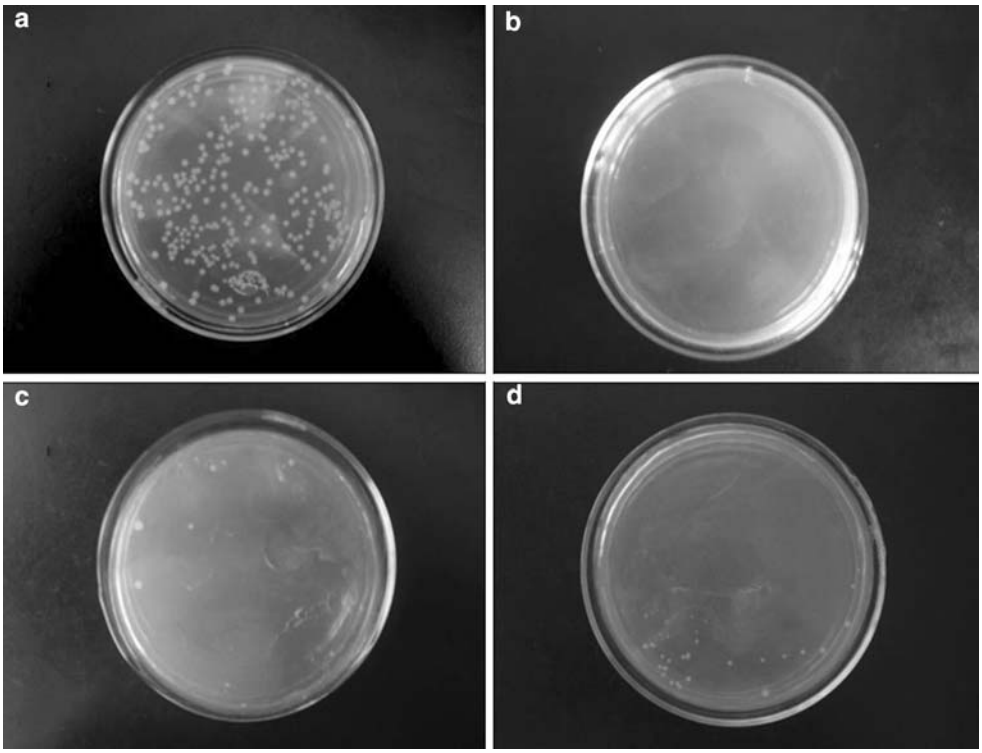


Fig. 5 Antimicrobial activities of PLLACL [50:50]/TCH after incubation for 24 h: **a** PBS; **b** incubated with TCH; **c** incubated with TCH released from mix-electrospun mat (the TCH contents by weight in the electrospun nanofibers with respect to PLLACL are 10%); **d** incubated with TCH released from coaxial electrospun mat (the TCH contents by weight in the electrospun nanofibers with respect to PLLACL are 10%)

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