# Morphology and Surface Properties of Poly (L-lactic acid)/Captopril Composite Nanofiber Membranes

Anfang Wei[1], Juan Wang[2], Xueqian Wang[3], Dayin Hou[3], Qufu Wei[1]

[1]Jiangnan University, Wuxi, Jiangsu CHINA

[2]Wannan Medical College, Wuhu, Anhui Province CHINA

[3]Anhui Polytechnic University, Wuhu, Anhui Province CHINA

Correspondence to:
Qufu Wei email: qfwei@jiangnan.edu.cn

**ABSTRACT**

In this study, Poly (L-lactic acid)/Captopril composite nanofiber membranes were electrospun for drug delivery. Different mass fractions of Poly (L-lactic acid), different ratios of Captopril and the influences of PEG4000 added in the spinning solution are discussed. The morphology, chemical components, the surface areas and pore sizes, wettability of the composite nanofiber membranes were investigated. The results showed that the diameters of the composite nanofibers increased with the increase of Poly (L-lactic acid) mass fractions, the diameters decreased with the increase of Captopril content as well as the addition of the surfactant. Fourier Transform Infrared (FT-IR) showed the chemical components of Captopril remained unchanged when it was electrospun into the composite nanofibers. The surface areas pore width and pore volume of the composite nanofibers became a little larger than those of poly (L-lactic acid) nanofibers, and the wettability of the composite nanofiber membranes was better than those of poly (L-lactic acid) nanofiber membranes. Wettability was improved by an increase of the drug load amount.

**INTRODUCTION**

Captopril is used widely for the treatment of hypertension and congestive heart failure [1]. In clinic, the general Captopril tablets often need to be used three times a day for a long time, it is easy to lead to some side-effects such as making patients feel vertigo and headache [2]. So it is necessary to develop a new kind of dosage form for Captopril to overcome these side-effects.

The electrospun nanofibers are a new kind of novel formulation with promising clinical applications in the future. The drug is dissolved in the polymer solution, then electrospun into the composite nanofibers, which can make the drug load in the carrier of polymer nanofibers. It not only can achieve a relatively high bioavailability of the loaded drug but also can minimize their severe side-effects, and more than one drug can be encapsulated directly into the electrospun fibers.

Since Kenawy first studied drug delivery from poly(ethylene-co-vinyl-acetate), poly(lactic-acid) and a 1:1 blend of the two polymers electrospun from chloroform solution with tetracycline hydrochloride as the model drug[3], many researchers have paid attention to this field. Sascha studied the release characteristics of four model drugs from drug-loaded electrospun cellulose acetate fiber mats [4]. Xiabin Jing prepared the ultrafine PEG–PLA fibers loaded with both paclitaxel and doxorubicin hydrochloride and discussed their in vitro cytotoxicity [5]. However, their work focused on the release regularity of loaded drugs, little work has been done on the surface properties of the electrospun nanofiber membranes.

In the present study, poly (L-lactic acid) (PLLA) was chosen and used as the drug carrier because of its good biocompatibility and biodegradability [6]. The nanofiber membranes of PLLA/Captopril were prepared by electrospinning. Scanning Electron Microscopy (SEM) was used to observe the fibers morphology and Fourier transform infrared spectrophotometer was used to confirm the composite chemical components. The surface area and pore analyzer, surface/interface tension meter were applied to investigate the surface structures and properties of the electrospun nanofiber membranes.

## MATERIALS AND METHODS

### Materials

Captopril (purity more than 99%) was provided by Shandong Weifang Pharmaceutical Factory Co., Ltd (China) and stored in the refrigerator at -20℃.Its chemical structure is showed in *Figure 1*. Poly (L-lactic acid) (PLLA) ($M_\eta$=100,000) was purchased from Bright China Industrial Co., Ltd. (Shenzhen, China). Acetone and dichloromethane were obtained from Sinopharm Chemical Reagent Co., Ltd. (China) and were used without further purification.

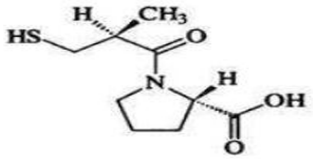



FIGURE 1. Chemical structure of Captopril.

Some amounts of Captopril were first dissolved in acetone, then dichloromethane and slices of PLLA were added and stirred for 5 h to obtain a concentration of 12 wt. % solution. The ratios of Captopril (relatively to PLLA used) in the composite were changed from 0, 5, 10 to 20 wt. %. The as-prepared solution was put into the electrospinning apparatus for spinning. The electric field was set at 13-19 kV and the distance between the needle tip and the collector was 18-22 cm. All electrospinning experiments were carried out at about 20℃ in air. In order to remove the residual solvent, the fiber mats collected were dried under vacuum at room temperature for 24h.The control fibers were fabricated by the same method without Captopril incorporation. Their cast films were also prepared by casting the same concentration of solution on the culture dish and dried in air.

### SEM Observation

The surface topography of the composite nanofiber membranes was observed by a scanning electron microscope (Hitachi S-4800, Japan). The membranes were cut into small pieces and placed on a metal stud, fixed with double-sided conductive tape. A very thin layer of gold was applied to the fibers by sputtering for 40 seconds. The gold-coated membranes were then placed in the microscope and scanned in 5kV mode.

### FTIR Scanning

KBr pellets of Captopril and the composite nanofiber membranes were prepared and scanned by Fourier transform infrared spectrophotometer (IRPrestige-21, Shimazu, Japan). The scanning was set at a resolution of 4$cm^{-1}$ with an accumulation time of 100s.

### Surface Area and Pore Size

The specific surface area of the nanofiber membranes was measured by a NOVA 2000e surface area analyzer. The composite membranes were put into the glass sample tube, and then heated in the vacuum for cleaning the surface. The temperature of the sample was kept as constant and a little of nitrogen was input. The surface area of the membranes was calculated by BET theory and their pore size was calculated by BJH method.

### Dynamic Contact Angles

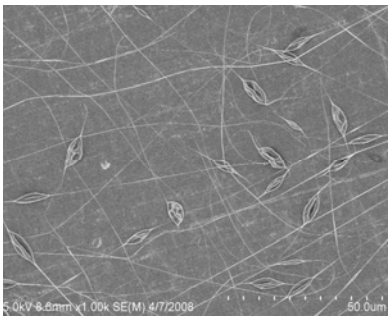
The dynamic contact angle measurement of the composite membranes was performed by DCAT11 (DataPhysics Instruments GmbH, Germany). The dynamic contact angles were determined by the modified Wilhelmy technique. The vessel full of water was placed on the balance table. The vessel was moved upward at a speed of 0.05 mm/s until part of the composite membranes was immersed into water. Afterward, the vessel was lowered into the initial position, and water completely dewetted from the membrane surfaces. All test processes and collections of data were automatically controlled through the software SCAT32.

## RESULTS AND DISCUSSION

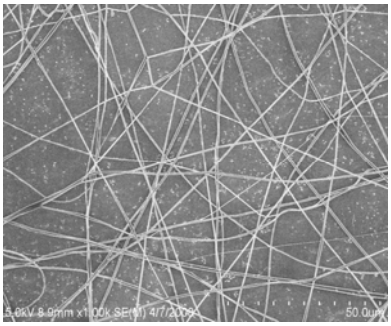
### Morphological Characteristics

As is known, electrospining is a technique that utilizes the electric force to drive polymer fluid and to produce polymer nanofibers. The viscosity, electrical conductivity, and surface tension of the polymer solution are the most important factors affecting the formation of nanofibers[7].The concentration of the polymer is closely related to the above factors, which is represented by the mass fraction of the polymer.

*Figure 2* shows the surface topography of PLLA electrospun fibers with different mass fractions and *Figure 3* is the diagram of their average diameters distribution. When 8 percent of PLLA were electrospun, the collected nanofibers were very thin and some beads were found, as indicated in *Figure 2a*.



(a)



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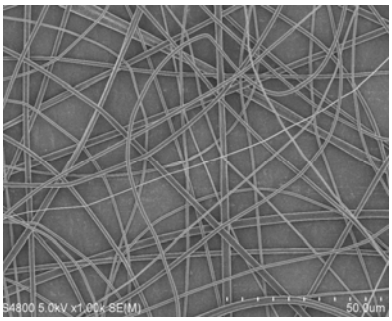
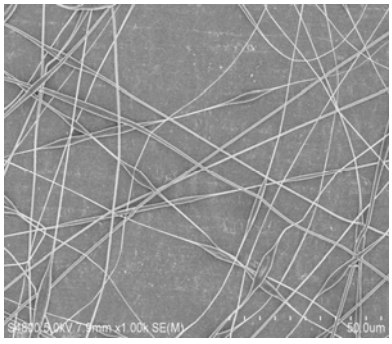


(c )



(d)

FIGURE 2. SEM of electrospun PLLA with different mass fractions. (a) 8%, (b) 10%, (c) 12%, (d) 12% PLLA added 5% PEG4000.

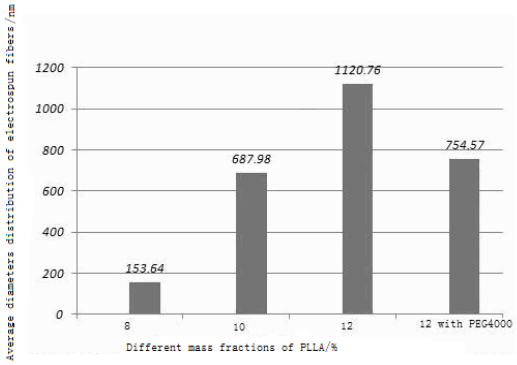
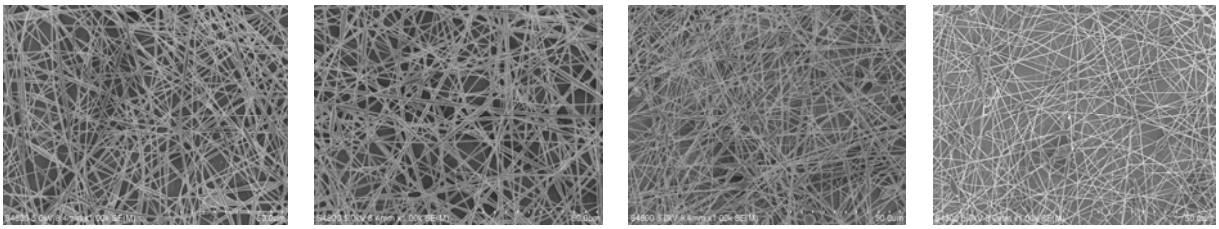



FIGURE 3. Average diameters distribution of electrospun PLLA fibers with different mass fractions.

With the increase of PLLA mass fraction, the elctrospun fibers looked obviously thicker and their mouldability became better, as presented in *Figure 2b*. When 12 percent of PLLA were electrospun, the diameters of the obtained fibers were much thicker, as revealed in *Figure 2c*. When 5 percent of PEG4000 was added into the spinning solution, it was obviously observed that the diameters of the electrospun fibers decreased and some beaded structures were formed on the electrospun fibers, as illustrated in *Figure 2d*. The average diameters for the electrospun fibers increased with the increase of the PLLA mass fraction. When the polymer mass fraction added up to 12 percent, the average diameter increased from 153.64 nm to 1120.76 nm. The addition of the surfactant led to the decrease in the diameters of the electrospun fibers, as shown in *Figure 3*. This could be explained that the increase of the polymer mass fraction in the solution led to the increase of the entangled actions of polymer molecule chains, which facilitated the formation of the electrospun nanofibers[8].The addition of the surfactant decreased the surface tension of the polymer solution and increased the bending instability in electrospinning process, which was also favorable for forming electrospun nanofibers[9].

*Figure 4* shows the morphology of PLLA nanofibers containing different ratios of Captopril and their average diameters distribution is presented in *Figure 5*. When 5 percent of Captopril (relatively to 12 percent of PLLA) was added in the solution, the diameters of the composite nanofibers decreased, as showed in *Figure 3a*. With the increase of the Captopril loaded amount, the elctrospun composite nanofibers looked thinner and their arrangements became more random, as illustrated in *Figure 3b*. When the ratio of Captopril increased to 20 percent, a lot of beads among fibers were formed and the

diameters became much thinner, as revealed in *Figure 3c*. The addition of the surfactant improved the fiber morphology and reduced beads as illustrated in *Figure 3d*.The average diameters of the composite nanofibers decreased with the increase of the ratios of Captopril in PLLA, when the amount of Captopril increased to 20 percent, the average diameter decreased from 863.98 nm to 339.43 nm, as shown in *Figure 5*. This was due to the decrease of the PLLA content in the spinning solution, which reduced the amount of the polymer formed nanofibers and increased the bending instability with the increase of the drug ratio. The affection of the surfactant addition on the eletrospinning was the same as the above.



(a) (b) (c) (d)

FIGURE 4. SEM photographs of PLLA nanofibers containing (a) 5, (b) 10, (c) 20 % Captopril, (d) 20 % Captopril and 5% PEG4000.

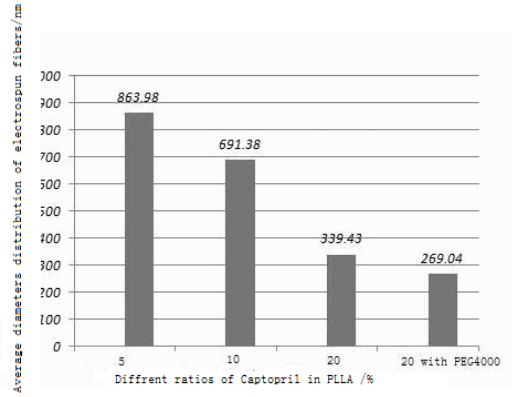



FIGURE 5. Average diameters distribution of electrospun PLLA fibers with different ratios of Captopril.

## FTIR Analysis

FT-IR is often used to confirm if the composite have the chemical reactions. Proline carbonyl and sulfhydryl groups are three main important groups for Captopril to reduce the blood pressure, so it is very necessary to identify the chemical components of the composite for confirming if there were the chemical reactions during preparing the composite nanofibers.

As shown in *Figure 6*, these groups of Captopril could be found in the PLLA/Captopril composite, but the positions of the characteristic peaks in the composite migrated. The hydroxyl group of Captopril was shifted from 3330cm$^{-1}$ to 3490 cm$^{-1}$ in the IR spectra of the composite, which could be attributed to weakening the association of the hydrogen group with the addition of PLLA because the oxygen of the carbonyl group in PLLA could form the hydrogen bond with the hydroxyl of Captopril carbonyl.

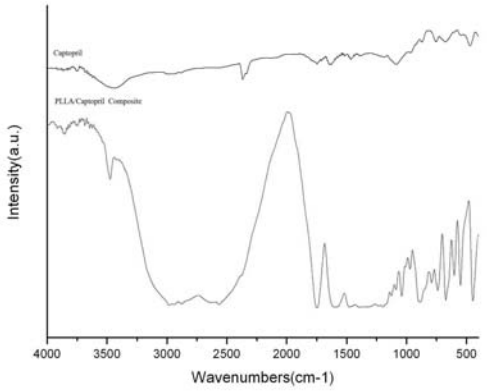



FIGURE 6. FT-IR spectra of Captopril and PLLA/Captopril composite nanofiber membranes.

The sulfhydryl group of Captopril moved from 2370 cm$^{-1}$ to 2560 cm$^{-1}$, which could be caused by the mesomeric effect between the sulfhydryl group and the carbonyl group in Captopril. The carbonyl group of the composite was at 1750 cm$^{-1}$ and almost the same with the position of the carbonyl group in Captopril. The results of FT-IR confirmed the chemical components of Captopril did not change when it was electrospun into the composite nanofibers.

**Surface Area and Pore Size Analysis**

In the electrospining process, the solvent evaporates from the polymer jet and ultrafine fibers are formed, which results in the larger surface area and porous structure of the electrospun fibers. *Table I* shows the BET results of the electrospun composite nanofiber membranes. When pure PLLA was electrospun, the formed fiber had small surface area and pore size. When 5 percent of Captopril was loaded in the electrospun PLLA fiber, the obtained fiber had larger surface area.

TABLE I. BET results of electrospun composite nanofiber.

| Ratios of Captopril (wt %) | Specific surface area ( $m^2$/g) | Total pore volume ( $cm^3$/g) | Average Pore Width (nm) |
|---|---|---|---|
| 0 | 70.241 | 0.009 | 16.268 |
| 5 | 73.657 | 0.009 | 16.271 |
| 20 | 85.643 | 0.010 | 16.282 |

With the increase of Captopril loading amount, the surface area of the composite increased. The amount of PLLA was decreased in the spinning solution with the increase of the drug ratio, which decreased the diameters of the electrospun nanofibers and resulted in increased surface areas. The pore volume and pore size of the nanofiber did not show obvious changes as indicated in *Table I*, this could be attributed to the decrease of the PLLA nanofiber diameters while the amount of the solvent remained unchanged [10].

**Dynamic Contact Angle and Hysteresis**

The hydrophilicity of the electrospun membranes could play an important role in the determination of their overall performances as drug delivery and tissue engineering scaffolds. As shown in *Table II*, the advancing contact angle of PLLA cast film was about 83.83°, its receding contact angle was about 44.78° and the contact angle hysteresis reached 39.05°. It is known that the advancing contact angle is more sensitive to the hydrophobic component while the receding angle is more sensitive to the hydrophilic one if the surface is made up of heterogeneous components [11-12].

TABLE II. Measurement results of dynamic contact angles.

| Items | Advancing contact angle (°) | Receding contact angle (°) | Contact angle hysteresis (°) |
|---|---|---|---|
| PLLA cast film | 83.83 | 44.78 | 39.05 |
| PLLA nanofiber membranes | 89.83 | 73.01 | 16.82 |
| Membranes with 5% Captopril | 89.92 | 85.51 | 4.41 |
| Membranes with 20% Captopril | 58.51 | 28.97 | 29.54 |

The difference between the advancing and receding contact angles is known as the contact angle hysteresis which has been attributed to solid surface roughness, surface heterogeneity, and some other surface chemical properties [13]. PLLA should be hydrophobic because it is a kind of aliphatic polyester. But its cast film could contain residues of organic solvent and its surface could be rough, which resulted in its advancing angle less than 90° and the contact angle hysteresis was much larger .

When PLLA was electrospun into fibers, the advancing contact angle increased to 89.83° and the contact angle hysteresis decreased to 16.82°. The residues of organic solvents in the electrospun fibers were less than those in the casted film because the process of electrospinning facilitated the evaporation of the solvent. The electrospun membranes were made up of many nanofibers which could make their surface smoother than cast film. When 5 percent of Captopril was loaded in PLLA membranes, the advancing contact angles almost did not change, but their receding contact angles increased to 85.51° and the hysteresis angle decreased to 4.41°. This was due to the addition of the water-soluble Captopril with the hydrophilic carboxyl group and the increase of the hydrophilicity of the composite membranes. When 20 percent of Captopril was loaded in PLLA membranes, the advancing contact angles decreased to 58.51° and the contact angle hysteresis increased to 29.54° as

shown in *Table II*. The hydrophilicity of the membranes was greatly improved with more Captopril mixed into PLLA, but there were more drugs distributed on the surface of nanofibers which resulted in increasing the surface roughness and heterogeneity of the composite.

## CONCLUSIONS

This work revealed that the electrospun nanofibers contained many beads and the average diameter was about 153.64 nm when the mass fraction of PLLA was 8 percent. With the increase of PLLA mass fraction, the diameters of the electrospun nanofibers increased and the formability of the electrospun fibers tended to be improved. While 5 percent of Captopril was added, the relative content of PLLA in the composite decreased, which resulted in the decrease of the diameter for the electrospun fibers. The addition of the PEG4000 surfactant decreased the surface tension of the polymer solution, increased the bending instability in electrospinning process and led to the decrease of fiber diameters. It was confirmed by FT-IR analysis that the process of electrospinning changed the physical form of Captopril, but its chemical structure remained unchanged. The surface areas, pore size and volume of the composite nanofibers were a little larger than PLLA nanofibers because of the decrease of the PLLA relative content in the composite with the addition of the drug. The wettability of the composite nanofiber membranes was improved due to the introduction of Captopril, which is the water-soluble drug.

## ACKNOWLEDGMENTS

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**AUTHORS' ADDRESSES**

**Anfang Wei**
**Qufu Wei**
Key Laboratory of Eco-Textiles,
Jiangnan University
Wuxi, Jiangsu 214122
CHINA

**Juan Wang**
Wannan Medical College
Wenchang Road No.22
Wuhu, Anhui Province 241002
CHINA

**Dayin Hou**
**Xueqian Wang**
Anhui Polytechnic University
Beijing middle road NO.8
Wuhu, Anhui Province 241000
CHINA