

## Formation of drug-loaded electrospun twin fibers

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Electrospinning is a well-known process for producing submicrometer fibers, which have wide applications in many fields, especially in tissue engineering scaffolds and drug-delivery systems. This paper presents the formation of drug-loaded electrospun twin fibers. The correlations between the twin fiber formation and the polymer materials or the loaded drugs were studied by using poly(l-lactide) and poly(l-lactide-co-glycolide) as electrospinning materials, and rifampin and paclitaxel as loaded drugs. Scanning electron microscopy showed that the formation of twin fibers is significantly affected by the loaded drug but not the polymer material. A possible reason for twin fiber formation was analyzed.

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Electrospinning is a well-known process [1–4] for producing micro- or nanofibers for use as tissue engineering scaffolds, drug controlled-release carriers, filtration, and biosensors. The materials used and the preparation conditions influence the shape of the ultrafine fibers formed. To date, several kinds of electrospun fibers have been prepared, including ultrafine fibers with beads on the string [5,6], fibers with ribbon cross-sections [7,8] and in particular, fibers with round cross-sections [9–11]. Furthermore, electrospun fibers with nanopores on the fiber surface have been prepared and characterized [12–15]. Recently, Varesano et al. [16] fabricated crimped polymer nanofibers by air-driven electrospinning.

One of the most important medical applications of electrospun ultrafine fibers is their use as drug controlled release carriers. Although there are limited studies on this application, it has attracted increasing attention [17–21]. For example, Tungprapa et al. [17] examined the release characteristics of four model drugs from drug-loaded electrospun cellulose acetate fiber mats. The results showed that the release rate of the four model drugs from the drug-loaded electrospun cellulose acetate fiber mats were greater

than that from the corresponding as-cast films. Zeng and co-workers [18,19] explored the preparation of rifampin-loaded electrospun PLLA fibers and later studied the influence of the drug compatibility with the polymer solution on the release kinetics of such electrospun fiber formulations. It showed that the burst release of the drug can be avoided by using compatible drugs with polymers and that drug release can follow nearly zero-order kinetics due to degradation of the PLLA fibers in the presence of proteinase K.

This paper presents the formation of drug-loaded electrospun twin fibers. The correlations between the twin fiber formation and the polymer materials used for electrospinning or the loaded drugs were studied and a possible mechanism for twin fiber formation analyzed. The results have great significance for designing and preparing new drug controlled-release systems and for further study into the mechanisms of drug controlled release.

### 1 Materials and methods

Poly(l-lactide) (PLLA) and poly(l-lactide-co-glycolide) (PLGA) (80/20 in weight) were synthesized in our lab. The viscosity average molecular weight of PLLA was 225 kg/mol. The

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intrinsic viscosity of PLGA (80/20) was 2.0. Rifampin (a drug for tuberculosis, Sinopharm Chemical Reagent Co., Ltd, Shenyang, China) and paclitaxel (an anti-cancer drug, Huiang Biochemical Reagent Co., Ltd, Guilin, China) were commercial products. Chloroform and acetone (Sinopharm Chemical Reagent Co., Ltd) were of analytical purity.

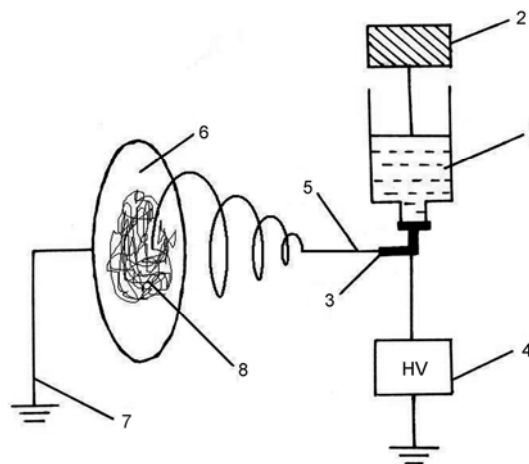
A 2:1 (v/v) mixture of chloroform and acetone was used as the solvent for PLLA and 4:3 (v/v) for PLGA. The polymer concentrations of PLLA and PLGA were 3.9 wt% and 6.6 wt%, respectively. Different amounts of rifampin (5 wt%–100 wt%) and paclitaxel (5 wt%–50 wt%) were added to the solution. Weight percentages are expressed relative to the polymer content.

The electrospinning arrangement is shown in Figure 1. The polymer solution was added in a 5-mL syringe with a right angle-shaped metal capillary attached. The circular orifice of the capillary had an inner diameter of 0.4 mm. A round counter electrode was located about 20 cm from the capillary tip. A pressure was applied to the solution in the syringe by placing a particular weight on the top of the piston to maintain a steady flow of the solution from the capillary outlet. The applied voltage was in the range 30–45 kV.

The morphology of the electrospun fibers was observed with a scanning electron microscope (SEM; JXA-840 from JEOL) at an accelerating voltage of 20 kV.

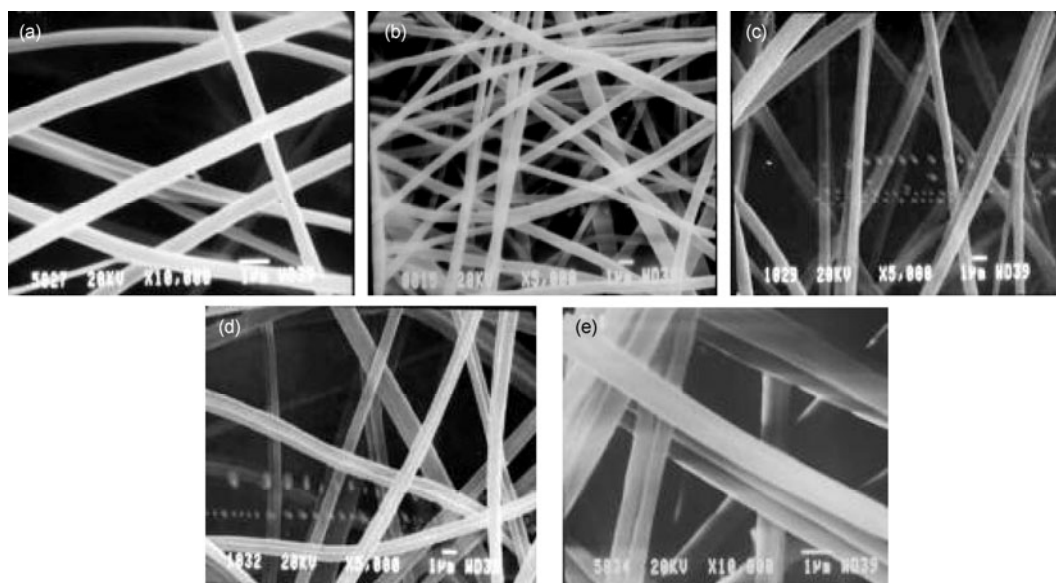
## 2 Results and discussion

Figure 2 shows SEM photographs of PLLA electrospun fibers containing different amounts of rifampin. It can be seen that only single electrospun fibers were obtained at

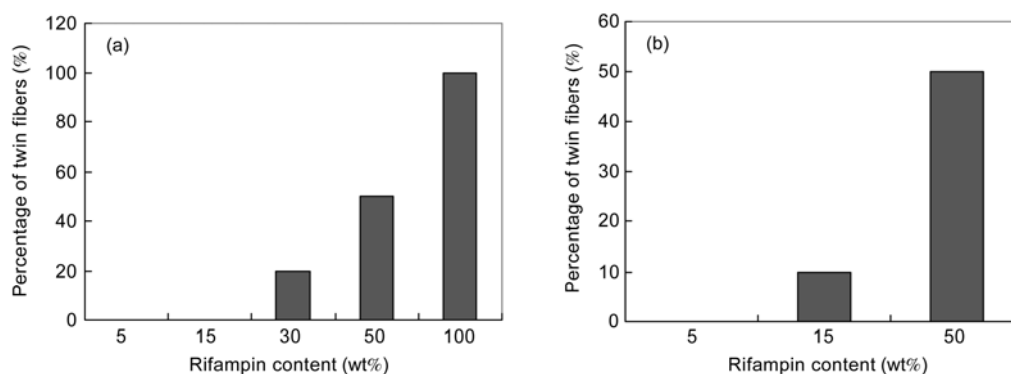


**Figure 1** A diagram of the electrospinning system. 1, Polymer solution; 2, syringe pump; 3, capillary nozzle; 4, high voltage generator; 5, jet; 6, collector; 7, grounding; 8, dried electrospun fibers.

15 wt% rifampin (Figure 2(a)). However, when at 30 wt% rifampin, twin fibers were observed in the SEM photograph, as can be seen in Figure 2(b). Clearly, formed twin fibers were also formed with increasing rifampin content (Figure 2(c)–(e)). The percentage of the generated twin fibers related to the rifampin content was calculated by dividing the number of twin fibers by the total number of the fibers in the SEM photographs, and the data were averaged from three replicates. The results are shown in Figure 3(a). Approximately 50% twin fibers was obtained (Figure 2(c)) when adding 50 wt% rifampin to the PLLA/chloroform-acetone solution, while only 20% twin fibers was observed at 30 wt% rifampin. When 100 wt% rifampin was added to



**Figure 2** SEM photographs of PLLA electrospun fibers containing different amounts of rifampin. (a) 15 wt%; (b) 30 wt%; (c) 50 wt%; (d) 100 wt%, 5000 $\times$  magnification; (e) 100 wt%, 10000 $\times$  magnification. The rifampin content is given relative to PLLA content. Staff gauge: 1  $\mu$ m.



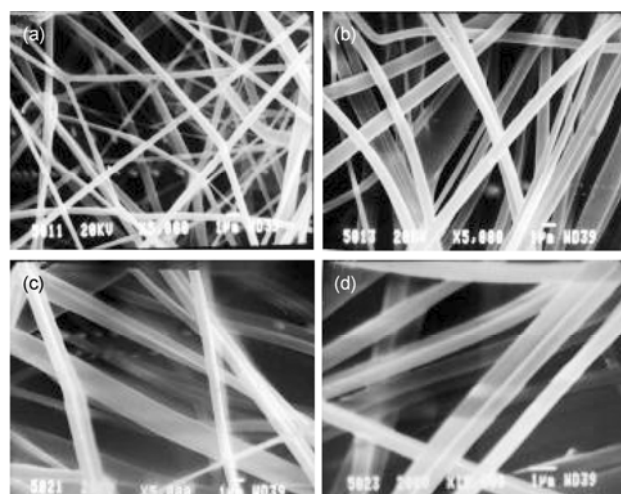
**Figure 3** The percentage of the formed twin fibers with different amounts of rifampin in PLLA (a) and PLGA(80/20) (b) solutions.

the PLLA electrospinning solution, almost all of the fibers were twin formed (Figure 2(d) and (e)).

To explore whether or not twin fiber formation was related to the polymers used for electrospinning, PLGA was chosen for loading rifampin during electrospinning. As shown in Figure 4(b), an obvious tendency to form twin fibers was observed at 15 wt% rifampin while no such phenomenon was seen at 5 wt% rifampin (Figure 4(a)). Using the calculation procedure described above, the percentage of twin fibers formed also increased with increasing rifampin content (Figure 3(b)). It can be seen in Figure 4(c) and (d) that nearly half of the electrospun fibers were twin formed when the rifampin content reached 50 wt%. It can therefore be concluded that twin fibers formation had little relation to the above two polymer materials used for electrospinning.

To determine whether the generation of twin fibers was correlated to the loaded drug, paclitaxel was utilized as an alternative drug for incorporation into the PLLA electrospun fibers. It was shown that no twin fibers resulted even when the paclitaxel content reached 50 wt%, as shown in Figure 5. Therefore, the loaded drug significantly affected twin fiber formation, although it was probably only one of the factors affecting twin fiber generation.

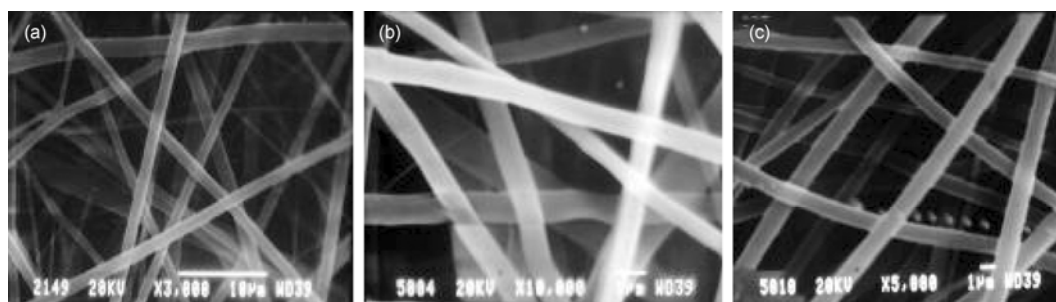
The characteristics of the electrospinning polymer/drug solutions are shown in Table 1. Whether the viscosity or the conductivity was in the same level, as shown in Table 1, so the electrospinning fibers from these polymer/drug solutions



**Figure 4** SEM photographs of PLGA(80/20) electrospun fibers containing different amounts of rifampin. (a) 5 wt%; (b) 15 wt%; (c) 50 wt%, 5000 $\times$  magnification; (d) 50 wt%, 10000 $\times$  magnification. The rifampin content is given relative to PLGA (80/20). Staff gauge: 1  $\mu$ m.

were comparable.

The difference between the drug influences on the formation of twin fibers is probably related to their hydrophilic or hydrophobic properties. Rifampin has an amphipathic structure, and the hydrophilic property may lead to a fast phase separation. Paclitaxel is a hydrophobic drug, as are the PLLA and PLGA polymers, so phase separation may

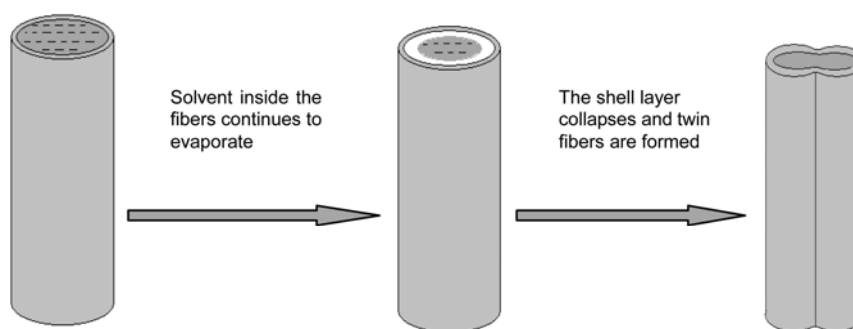


**Figure 5** SEM photographs of PLLA electrospun fibers containing different amounts of paclitaxel. (a) 5 wt%; (b) 15 wt%; (c) 50 wt%. The paclitaxel content is given relative to PLLA. Staff gauge: (a) 10  $\mu$ m; (b) and (c) 1  $\mu$ m.

**Table 1** Characteristics of the electrospinning polymer/drug solutions

Solution	Concentration (wt%)	Drug	Ratio of drug to polymer (wt%)	Viscosity <sup>a)</sup> (mPa s)	Conductivity <sup>b)</sup> ( $\mu\text{S}/\text{cm}$ )
PLLA/chloroform-acetone (2:1, v/v)	3.9	Rifampin	15	105	0.12
PLLA/chloroform-acetone (2:1, v/v)	3.9	Rifampin	30	103	0.16
PLLA/chloroform-acetone (2:1, v/v)	3.9	Rifampin	50	100	0.15
PLLA/chloroform-acetone (2:1, v/v)	3.9	Rifampin	100	99	0.17
PLGA/chloroform-acetone (4:3, v/v)	6.6	Rifampin	5	103	0.15
PLGA/chloroform-acetone (4:3, v/v)	6.6	Rifampin	15	100	0.13
PLGA/chloroform-acetone (4:3, v/v)	6.6	Rifampin	50	99	0.16
PLLA/chloroform-acetone (2:1, v/v)	3.9	Paclitaxel	5	99	0.15
PLLA/chloroform-acetone (2:1, v/v)	3.9	Paclitaxel	15	100	0.15
PLLA/chloroform-acetone (2:1, v/v)	3.9	Paclitaxel	50	102	0.16

a) The viscosity of the electrospinning polymer/drug solutions was measured at 20°C by an Ubbelodhe viscometer. b) The conductivity of the electrospinning polymer/drug solutions was measured at 20°C with a conductivity meter (DDS-307, Shanghai, China). The data are an average of three replicates.

**Figure 6** Conceptual diagram of the twin fiber formation process.

not have occurred as readily. Further study on how twin fiber formation is related to the loaded drugs is required.

A possible mechanism for twin fiber formation is as follows: With increasing rifampin content, the shell layer of the semi-formed ultrafine fibers becomes thinner during electrospinning. Thus, a shell forms prior to solidification, along with evaporation of solvent. However, this initial shell layer is very thin, so collapses with further evaporation of solvent inside the fibers, thus forming the twin fibers. Figure 6 shows a conceptual diagram of the twin fiber formation process.

### 3 Conclusions

The formation of drug-loaded electrospun twin fibers was studied using PLLA and PLGA as polymer materials. A high rifampin content led to twin fiber formation, regardless of whether PLLA or PLGA was used during electrospinning

and increased rifampin content led to greater twin fiber formation. However, no twin fibers were observed when PLLA was loaded with paclitaxel. Therefore, it can be concluded that the formation of electrospun twin fibers is significantly affected by the nature of the loaded drugs but not by the polymer materials.

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