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Controlled dual release of hydrophobic and hydrophilic drugs from electrospun poly (l-lactic acid) fiber mats loaded with chitosan microspheres

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ABSTRACT

This work is to develop novel electrospun poly(L-lactic acid) (PLLA) fiber mats for controllable delivery of hydrophobic and hydrophilic drugs. For this aim, bovine serum albumin (BSA, used as a hydrophilic model drug) was firstly enveloped into chitosan microspheres by spray drying. Benzoin (used as a hydrophobic model drug) was directly dissolved in PLLA solution and then the chitosan microspheres were suspended into the PLLA solution, which was used to prepare PLLA fiber mats by electrospinning. Polyvinylpyrrolidone (PVP) was added into the PLLA solution to tune the drug release behaviors. The results showed that the chitosan microspheres were uniformly distributed in the fibers. BSA had a short-term release while benzoin had a long-term and sustained release in all the dual drug delivery systems, and the release of both hydrophobic and hydrophilic drugs could be adjusted by changing the ratio of PVP/PLLA.

1. Introduction

Electrospun fibers, with diameters ranging from several microns to 100 nm [1], have outstanding characteristics such as flexible morphology, large surface area to volume ratio and unique nanometer scale architecture, and therefore have been widely used in many biomedical fields [2,3]. Particularly, electrospun fibers have been intensively investigated for drug delivery systems because they confer higher drug encapsulation efficiency and better structural stability than other drug carriers [4,5].

Presently, most studies focus on single drug delivery systems [6,7], which often could not satisfy the requirements in clinical therapies [8]. Hence, various dual-drug delivery systems [9,10] have been developed to improve therapy efficacy, in which two drugs with different therapeutic effects are loaded. Recently, coaxial or emulsion electrospinning has been reported for preparing core-shell type fibers, but a special apparatus and operation parameters are necessary [11] and some surfactants are used [12]. In this study, novel electrospun poly(L-lactic acid) (PLLA) fiber mats were prepared by spray-drying and electrospinning process for the controllable co-delivery of hydrophobic benzoin and hydrophilic bovine serum albumin (BSA). The release behaviors of the drugs were studied and modulated by adding polyvinylpyrrolidone (PVP) to the electrospun PLLA fiber mats.

2. Experimental

Benzoin and BSA were purchased from Beijing Dingguo Biotechnology Co., Ltd. (China). PLLA (Mw = 100 kDa) and PVP (k30) were purchased from Jinan Daigang Biological Technology Co., Ltd. (China). Chitosan (Mw = 50 kDa, the degree of deacetylation of 95%) was purchased from Jinan Haidebei Ocean Biological Engineering Co., Ltd. (China). Other chemicals and solvents were of analytical grade.

With high-speed stirring, aqueous sodium tripolyphosphate solution (1%, w/v) as crosslinking agent was added into 2% (w/v) chitosan solution in aqueous acetic acid. Spray-drying was concurrently performed using a spray drier (Büchi B-290) with fixed inlet temperature (153 °C), spray flow (6 mL/min) and compressed spray air flow (10 L/min), respectively. The BSA-loaded or fluorescent chitosan microspheres were prepared by dissolving BSA (2%, w/v) or fluorescein sodium in the chitosan solution prior to spray-drying, respectively.

Electrospinning was performed using a high-voltage power supply (GF-2, Gen Sheng Painting Co., Ltd.) at 15 kV, an infusion pump (KDS-100, RWD Life Science Co., Ltd) at a constant flow rate (1.2 mL/h), and a syringe equipped with a stainless steel blunt-ended needle (inner diameter, 0.57 mm) with an gap of 12–15 cm separating the collector and the needle tip. The composition of the samples A, B, C, D and E used for *in vitro* release experiment was listed in Table 1.

The microspheres and composite fiber mats were coated with gold and examined by scanning electron microscope (SEM) (PHILIPS XL-30ESEM) at an acceleration voltage of 20 kV. The microsphere distribution in the composite fiber mats were characterized by inverted fluorescence microscope.

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Table 1
Compositions of the samples used for *in vitro* release experiment.

Samples	Compositions
A	Chitosan microspheres (BSA-loaded)
B	PLLA and benzoin
C	PLLA, benzoin and chitosan microspheres (BSA-loaded)
D	PLLA, benzoin, chitosan microspheres (BSA-loaded) and 5% PVP
E	PLLA, benzoin, chitosan microspheres (BSA-loaded) and 10% PVP

To study drug release behaviors, BSA-loaded chitosan microspheres or electrospun composite fiber mats (100 mg) were soaked in 40 mL of Tris–HCl buffer (pH = 7.4). The incubation was conducted at 37 °C with shaking speed of 90 rpm. The concentration of benzoin in the release buffer was then determined at 250 nm by an UV–vis spectrophotometer (SHIMADZU uv-2550), while BSA concentration was determined by BCA Protein Assay Kit (KeyGEN Biotechnology Development Co., Ltd. (China)).

3. Results and discussion

From Fig. 1 A, the diameter of BSA-loaded chitosan microspheres was about 1–3 μm. The smaller microspheres have a quicker evaporation during spray drying than the larger ones, probably leading to the smoother surface compared to that of the larger ones. The smaller chitosan microspheres were separated by an 800-mesh standard sieve. From Fig. 1B, C and D, the electrospun fiber mats looked uniform and presented porous structure on their surfaces. This morphology is attributed to the rapid evaporation of organic solvent during electrospinning. From Fig. 1B and C, it seems that the addition of chitosan microspheres into the electrospun fiber mats did not make significant difference in morphology and average diameter. The average diameter of the electrospun fibers of sample D was much smaller than that of others, because the addition of PVP caused higher conductance of PLLA solution, which could strongly affect the electrospinning process.

The SEM observations did not provide information about the distribution of drug-loaded chitosan microspheres in the composite fiber mats. Therefore, chitosan was fluorescence-labeled to show their dispersion in the composite fiber mats, which was examined by inverted fluorescence microscope. As shown in Fig. 2, the fluorescent chitosan microspheres were uniformly distributed in the composite PLLA fiber mats.

Fig. 3 shows the cumulative release profiles of BSA from chitosan microspheres (sample A) and the composite electrospun fiber mats (samples C, D and E). There was an obvious burst release in the very beginning of the release profile of sample A, probably because the protein tended to move to the surface of the microspheres in the process of spray-drying along with the water evaporation [13]. Such microspheres can not be used as drug delivery systems, because the loaded drug can diffuse into blood or tissue fluid quickly, leading to uncontrollable drug release rate. However, the electrospun fibers (samples C, D and E) showed a lower cumulative release percentage of BSA than the naked chitosan microspheres, which may be due to the slow diffusion of BSA out of the fibers. Obviously, the BSA release was not complete, and the remaining BSA would be released along with the degradation of the polymer fibers. In addition, after the first hour of release, there was more BSA released from PVP-containing electrospun fiber mats (samples D and E) than that from PVP-absent ones (sample C). Sample C released about 95% of loaded BSA at 30 d, and sample D about 85%, while sample E only released about 60%. The results demonstrate that increasing PVP/PLLA ratio can significantly accelerate BSA release.

Fig. 4 shows the cumulative release profiles of benzoin from the electrospun fiber mats (samples B, C, D and E). All the samples presented a sustained release behavior of benzoin without an initial burst release. Benzoin was released from the electrospun fiber mats from 18% to 98% in 30 d. It could be expected that the remaining benzoin would be released along with the degradation of the electrospun PLLA fiber mats in the later period. Compared to the single drug-loaded PLLA fiber mats (sample B), the composite electrospun fiber mats loaded with chitosan microspheres had a higher cumulative release percentage, which may

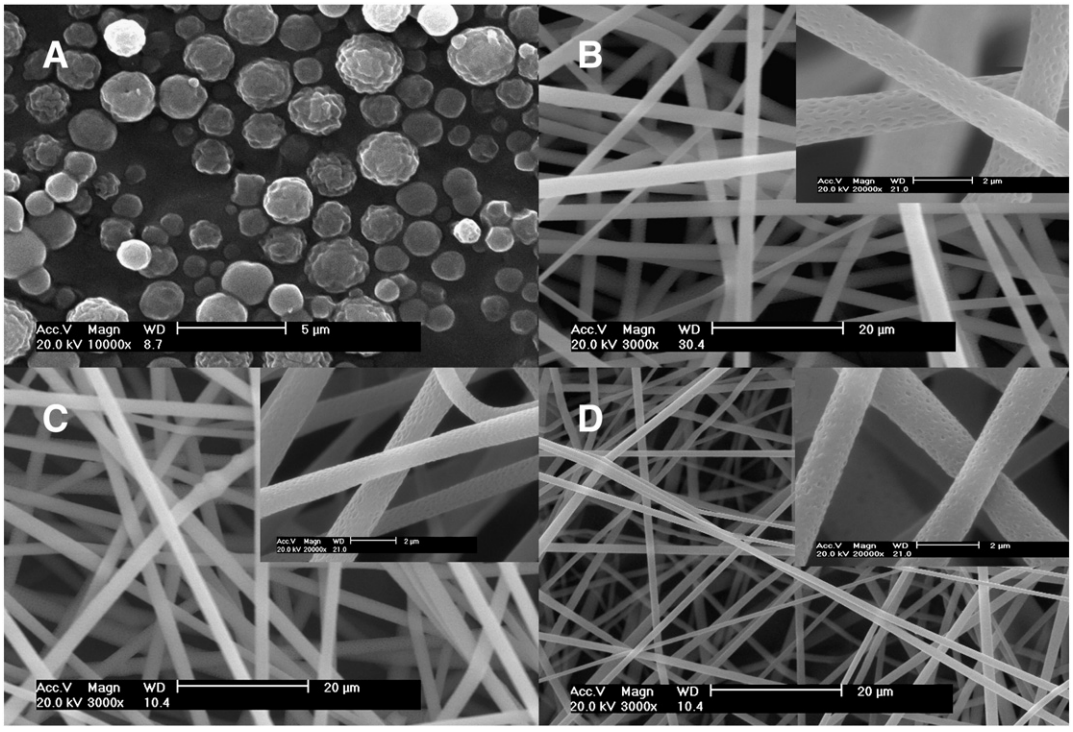

Fig. 1. SEM images of chitosan microspheres and electrospun PLLA fiber mats: A, chitosan microspheres (sample A); B, electrospun PLLA fiber mats (sample B); C, composite electrospun PLLA fiber mats loaded with chitosan microspheres (sample C); D, composite electrospun PLLA fiber mats loaded with chitosan microspheres and 10% PVP (sample E).

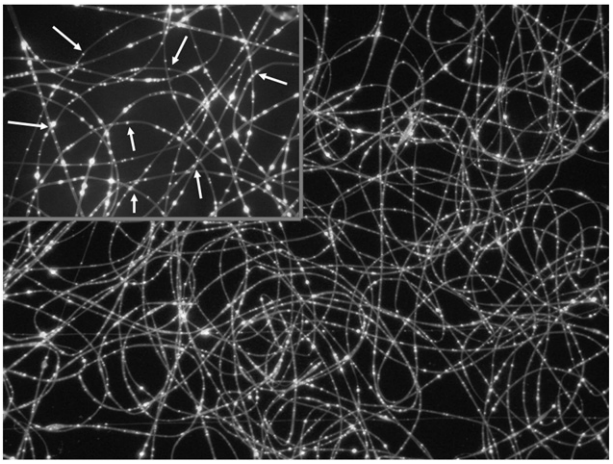

Fig. 2. Distribution of fluorescence-labeled chitosan microspheres in the electrospun PLLA fiber mats.

be due to the breakage of the fiber microstructure [14]. The release profiles of benzoin from samples D and E were similar to BSA release profiles (sample D and E), but both of them presented a sustained release behavior with the ultimate release percentage of about 70% and 98% after immersing in Tris–HCl for 30 d. The results demonstrate that the PVP presence in the fibers leads to the tunable release of benzoin.

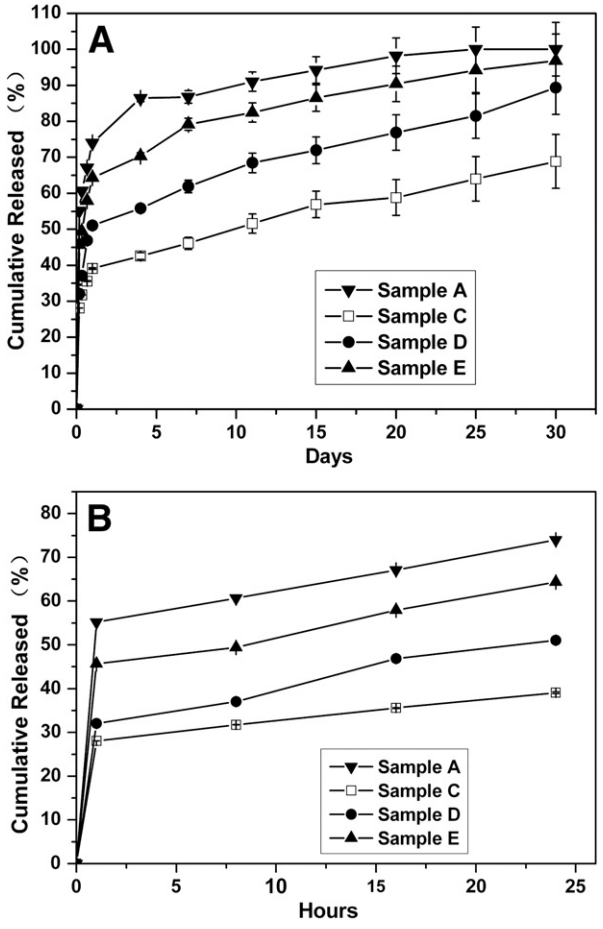

Fig. 3. Release profiles of BSA from samples A, C, D and E for 30 d (A) or 24 h (B), respectively.

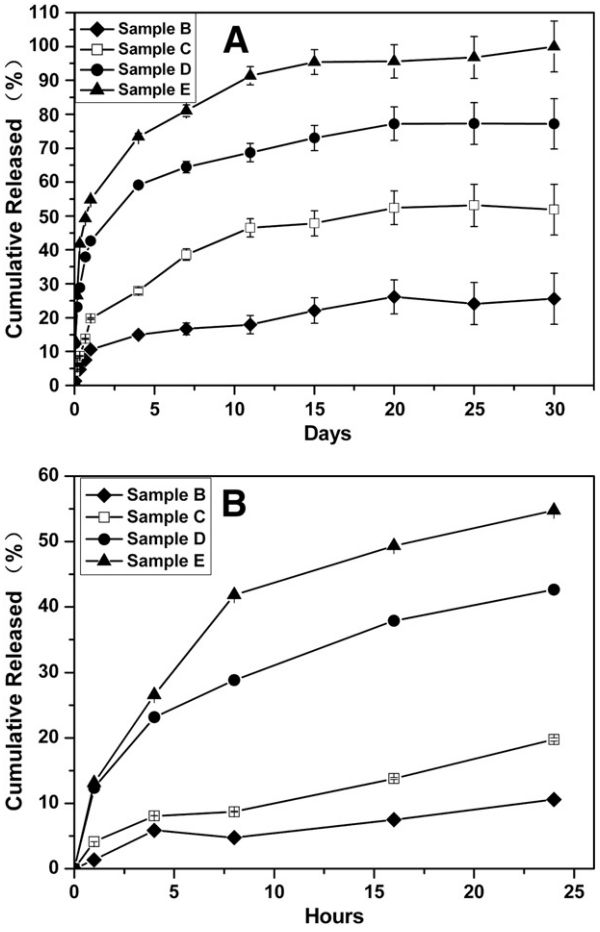

Fig. 4. Release profiles of benzoin from samples B, C, D and E for 30 d (A) or 24 h (B), respectively.

4. Conclusion

In this paper, we prepared a dual-drug delivery system of chitosan microspheres-loaded, electrospun PLLA fiber mats. The characterizations confirmed that chitosan microspheres were encapsulated and uniformly distributed in the electrospun fiber mats. The dual release *in vitro* showed a short-term BSA release but a sustained long-term benzoin release in all the dual-drug delivery systems. Moreover, the release rate of BSA and benzoin from the systems was significantly accelerated by increasing PVP/PLLA ratio.

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