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A novel multiple drug release system in vitro based on adjusting swelling core of emulsion electrospun nanofibers with core–sheath structure

Yazhou Wang *, Zong Li, Pengyu Shao, Shilei Hao, Wei Wang, Qian Yang, Bochu Wang *

Key Laboratory of Biorheological Science and Technology, Ministry of Education, College of Bioengineering, Chongqing University, Chongqing 400030, China

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ABSTRACT

We have developed a novel drug delivery system with the swelling core for differential release of multiple drugs by emulsion electrospinning, in which the aqueous phase is composed of polyvinyl alcohol and the oil phase consists of poly(ε-caprolactone). The microscopy images indicate that the W/O nanofibers with swelling core structure are successfully prepared and the model drugs, Rhodamine B and bovine serum albumin, were encapsulated in the fibers. In vitro drug release study demonstrated that this core–sheath structure could significantly alleviate the initial drug burst release and provided a differential diffusion pathway to release. It could be found that the postponement of the maximum accumulated release of bovine serum albumin was found due to the presence of sodium citrate and different types of polyvinyl alcohol. This study would provide a basis for optimization of encapsulation conditions to control the release of multiple agents and ultimately be applied in cancer chemotherapy.

1. Introduction

Patients are suffering from taking anticancer drugs orally or intravenous injection during clinical treatment of cancer. They usually have to take excessive amount of drugs, however, the single drug could not achieve the purpose of killing tumor cells due to the diversity of the mechanism and tumor target sites, which may easily induce multidrug resistance [1,2]. Moreover, as a new strategy for efficient treatment of cancer, administration of multiple drugs could adjust various signal transmission channels to regulate proliferation, invasion, and metastasis process of cancer cells with the synergy and complementary effects among drug molecules [3–5].

Therefore, it has a great significance for the postoperative treatment of tumors to integrate the advantages of drug combination and local therapy to establish a multi-drug delivery system based on the composite structure of vehicle. For example, leucovorin can significantly enhance the activity of 5-fluorouracil of blocking the thymidylate synthase for treatment of colon cancer while they are loaded in a multidrug delivery system. Several drug delivery systems have been applied in drug combination delivery, such as multilayer nanoparticles, multifiber mats and the electrospun fibers with core–sheath structure [6–8]. In these systems, drugs are encapsulated in different positions of the nanoparticles or nanofibers, where the drugs could be released in different paths at different times after arriving at the target sites. It is well known that the electrospinning fibers with a wide distribution of diameter from 10 to 1000 nm have been widely used in the development of new strategies for drug delivery and cancer treatment [9–11] because they can provide a high surface area to volume ratio and thus increasing the contact area and facilitating interactions between host cells and the material [12]. Electrospinning solution is stretching and swinging under the electric force, forming continuous fibers after volatilization of solvent finally through electrospinning [13,14]. This process is based on the principle that electric force could surmount weaker force of surface tension while the emulsions would move along the direction of electric field and extend according to external and internal electric forces at the same time [15–17]. Electrospinning fibers can be modified in different physical or chemical ways to adjust their properties such as surface properties and degradation rate [18]. And the drugs would be released in differential pattern due to different release paths when they were encapsulated in a certain type of polymer [19,20].

We prepared electrospinning nanofibers with core–sheath structure (shown in Fig. 1a) for dual release in this study. Briefly, the core consists of the polyvinyl alcohol (PVA) aqueous solution and the sheath consists of poly(ε-caprolactone) (PCL) dissolved in chloroform. Previous studies showed that PVA was hydrophilic polymer with swelling property which was inhibited by salt and that the PVA with hydrolyzed degree (*HD*) of 96% or 97.5% has the best swelling degree due to absorbent ability [21–23]. However, the past studies rarely applied swelling regulatory factor in adjusting model drug release behavior for better efficacy. We present a new type of W/O emulsion based on sodium citrate (SC), acting as a swelling regulatory factor, different types of PVA and PCL to provide W/O fibers loading Rhodamine B (RhB) and bovine serum albumin (BSA). The addition of SC into the mats resulted in increasing of the concentration of core region, leading to decrease the release of model agents by adjusting the swelling degree of the core and prolonging the

* Corresponding authors. Tel.: +86 15803055446.
E-mail address: yazhou_wang@cqu.edu.cn (Y. Wang).

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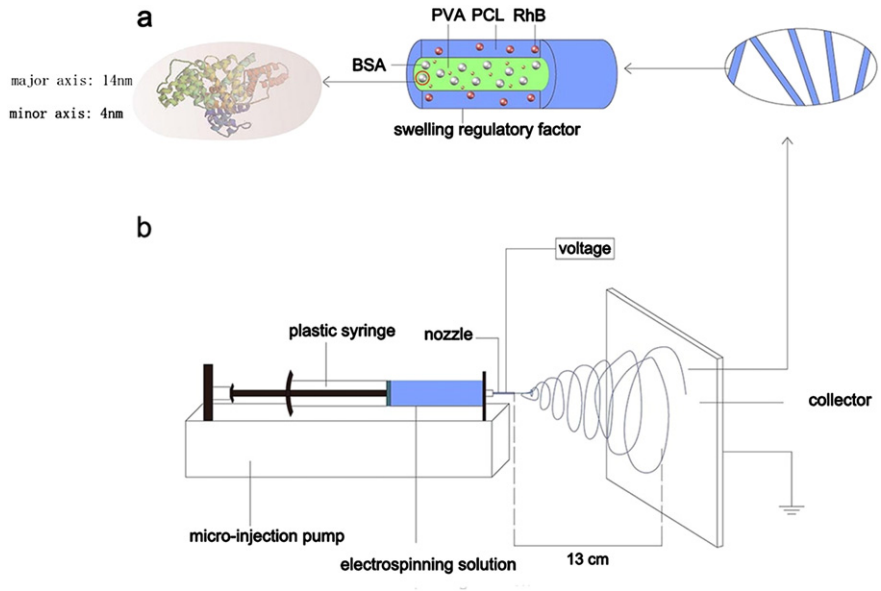

Fig. 1. Schematic of core–sheath structure (a) and electrospinning apparatus (b).

release path of model agents encapsulated in the core. In addition, different ratios of SC to BSA can prepare fibers with different surface morphologies and consequently the eligible fibers can be prepared under the optimal preparation conditions. The core–sheath nanofibers based on swelling core as drug delivery system are successfully fabricated and show different release behaviors.

2. Materials and methods

2.1. Materials

RhB was purchased from Songon (Shanghai, China). Span 80, BSA and sodium citrate were supplied by Sinopharm Chemical Reagent Co., Ltd. PCL (M = 80 Kd) was obtained from Daigang (Jinan, China). CST-PVA (*HD* = 96%, medium hydrolyzed), 217-PVA (*HD* = 88%, partially hydrolyzed) and 117-PVA (*HD* = 98%, fully hydrolyzed) used as materials in core portion were purchased from Kuraray Co., Ltd., China. FITC was supplied by Sigma-Aldrich, Inc. Other reagents were of analytical grade commercially.

2.2. Preparation of nanofibers

2.2.1. Preparation of PVA/PCL nanofibers

7 wt.% CST-PVA aqueous solution was emulsified with 9 wt.% PCL in chloroform followed by the addition of Span 80 while stirring for 2 h. The emulsions labeled E1, E2, E3 and E4 were prepared with the following ratios of CST-PVA to PCL: 5%, 10%, 15% and 30% (v/v), respectively, for the optimal preparation conditions [24]. The resulting fibers labeled F1, F2, F3 and F4 were obtained by electrospinning using the following device configuration: a plastic syringe, a micro-injection pump, and a collector [25,26] (shown in Fig. 1b). The electrospinning nozzle with inner diameter of 0.6 mm was fixed on the metal sink connected to ground. The emulsions were delivered at a constant flow rate of 1 mL/h using micro-injection pump (Baoding Longer Precision Pump Co., Ltd.), with an air gap of 13 cm separating the nozzle tip and a grounded aluminum foil as sample collector [27]. The driving voltage was 16 kV (a high-voltage electrostatic generator, MGD1-A, Dongwen High Voltage Power Supply Co., Tianjing, China). The electrospun fiber mats were dried in vacuum at room temperature and stored at 4 °C.

2.2.2. Preparation of drug-loaded PVA/PCL nanofibers

Targeted to study the effect of swelling degree of PVA on model drug release, emulsion type was set at five levels as listed in Table 1. Specifically, the electrospinning emulsion labeled EL which consisted of CST-PVA solution (7 wt.%), 3 wt.% BSA (BSA to distilled water) and 9 wt.% PCL solution containing 1 wt.% RhB (RhB to PCL) was emulsified to provide fiber mat and labeled A. RhB was replaced to the aqueous phase of EL to provide fiber mat B to characterize the effect of model drug location on release behavior.

The CST-PVA in the aqueous phase of EL was replaced by 117-PVA and 217-PVA, respectively, to prepare fiber mat C and D to study the effect of *HD* on release of model agents.

In order to determine whether SC could regulate the release behavior, it was dissolved in the CST-PVA solution to prepare SC–CST-PVA mixture with the following concentrations of SC: 10 mg/mL–50 mg/mL. BSA was dissolved in the mixture for preparation of BSA–SC–CST-PVA solution with the following concentrations of BSA: 10 mg/mL–50 mg/mL. The dissolved state of BSA in the mixture of SC–CST-PVA was observed after agitation for 2 h to ensure aqueous phase with the best dissolved state and then prepared fiber mat E.

2.3. Characterization

2.3.1. Morphology characterization

The fibers F1, F2, F3 and F4 were observed by SEM at an acceleration voltage of 20.00 kV with a magnification of 2.00k× after being coated with gold for 50 s.

CST-PVA was labeled by fluorescein isothiocyanate (FITC) to gain further information on the distribution of CST-PVA in nanofibers to find the optimal preparation conditions of CST-PVA/PCL core–sheath

Table 1
Component of mats.

Nanofiber mat	Core region	Sheath region
A	3 wt.% BSA, 7 wt.% CST-PVA	1% RhB, 9 wt.% PCL
B	1% RhB, 3 wt.% BSA, 7 wt.% CST-PVA	9 wt.% PCL
C	3 wt.% BSA, 7 wt.% 117-PVA	1% RhB, 9 wt.% PCL
D	3 wt.% BSA, 7 wt.% 217-PVA	1% RhB, 9 wt.% PCL
E	3 wt.% BSA, 7 wt.% CST-PVA, SC	1% RhB, 9 wt.% PCL