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Tamoxifen-loaded silk fibroin electrospun fibers

Wen Liu, Yu Wang, Jinrong Yao, Zhengzhong Shao, Xin Chen *

State Key Laboratory of Molecular Engineering of Polymers, Collaborative Innovation Center of Polymers and Polymer Composite Materials, Department of Macromolecular Science, Laboratory of Advanced Materials, Fudan University, Shanghai 200433, China

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ABSTRACT

In this article, the regenerated silk fibroin/2-hydroxypropyl-β-cyclodextrin/tamoxifen (RSF/2-HP-β-CD/TAM) composite fibers are successfully prepared via an electrospinning technique. 2-HP-β-CD/TAM inclusion complex is firstly formed to increase the TAM solubility in the spinning dope. The morphology of the electrospun fibers is investigated, which shows the addition of 2-HP-β-CD/TAM significantly decreases the fiber diameter. Raman spectra confirm the effective loading of TAM in the resulting electrospun fibers. The drug release behavior of RSF/2-HP-β-CD/TAM composite fibers indicates that the TAM loaded in such a composite fibers is able to perform a sustainable release. Thus, the TAM-loaded RSF electrospun fibers presented in this report may have a great potential as be a promising local drug delivery system for breast cancer therapy.

1. Introduction

Electrospinning is a straightforward and efficient technique to produce continuous fibers with diameters ranging from tens of nanometers to a few micrometers [1]. Recently, electrospinning technique has aroused great scientific interest due to its versatility and potential for applications in various fields such as tissue engineering scaffolds [2], sensors [3], drug delivery [4], separation membranes [5], which is mainly due to the superior properties of the electrospun fibers [6]. In particular for drug delivery applications, electrospun fibers have been considered to be a unique drug delivery system because they have little influence on the drug activity, and the drug release profile can be controlled by adjusting the structure, morphology and composition of fibers, loading dose, and drug incorporation manner [7]. Compared to other synthetic/natural polymers to prepare electrospun fibers, regenerated silk fibroin (RSF), a natural fibrous protein derived from *Bombyx mori* silk, is more suitable to be used as matrix for drug delivery because of its combination of excellent mechanical properties, biocompatibility, biodegradability, environmental stability, and benign processing conditions [8].

Tamoxifen (TAM), a selective estrogen receptor modulator, has the capacity to act as anti-estrogens by binding to the estrogen receptors to inhibit the growth of malignant mammary tumors in some tissues. However, it acts as estrogens in other tissues (e.g., uterus) and can result in lots of significant side effects [9], which is dose dependent [10]. On the other hand, TAM is a weak base (pKa=8.8) with a low water solubility [11]. Therefore, TAM has been mainly formulated in various carriers to minimize the side effects and achieve high water solubility [12]. Among them, β-cyclodextrin has been proved to be an effective carrier for TAM [12] and other drugs [13–16]. However, to our best knowledge, there is no report on encapsulation of TAM in electrospun fibers. Therefore, in this article we report our successful trial to load TAM into RSF electrospun fibers with the aid of 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD), which could serve a matrix for the local drug delivery during the cancer therapy.

2. Experimental

2.1. Preparation of RSF/2-HP-β-CD/TAM composite fibers

The RSF aqueous solution was prepared from *Bombyx mori* silkworm cocoons followed a well-established procedure [17,18]. The final concentration of the RSF aqueous solution was 28 wt%. TAM was first mixed with 2-HP-β-CD in 1:2 molar ratio to obtain the inclusion complex [12], then 2-HP-β-CD/TAM complex aqueous solution (with final mass ratio of TAM/RSF=1/50) was added into RSF solution. The final concentration of RSF in electrospinning dope was 25 wt%. The electrospinning process was carried out under ambient condition with a collect distance of 20 cm, an operating voltage of 25 kV and a feeding speed of 0.5 mL/h. After

* Corresponding author.
E-mail address: chenx@fudan.edu.cn (X. Chen).

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spraying with ethanol (ES method, because TAM is soluble in ethanol, so cannot immerse in ethanol) for 30 min or immersing in acetone (AI method) for 24 h, the electrospun RSF/2-HP-β-CD/TAM composite fibers were solidified, and then dried under vacuum at room temperature for 24 h.

2.2. Characterization of RSF/2-HP-β-CD/TAM composite fibers

The morphology of the electrospun fibers were observed with a Hitachi S-4800 FESEM at 1 kV. Raman spectra of 2-HP-β-CD, TAM and all electrospun fibers were collected using a Renishaw inVia Reflex Raman spectrometer.

2.3. In vitro release of TAM from RSF/2-HP-β-CD/TAM composite fibers

In vitro drug release behavior of RSF/2-HP-β-CD/TAM electrospun fibers was investigated in both phosphate buffer saline (PBS) solution and another one containing 30% ethanol (both at pH = 7.4) at 37 °C. Ethanol was used to increase the solubility of TAM in the PBS buffer solution to confirm if TAM can be released from the fibers due to its poor solubility in water [19]. The concentration of released TAM was determined using a Hitachi UV 2910 UV–vis spectrophotometer at 238 nm.

3. Results and discussion

3.1. Morphology of RSF/2-HP-β-CD/TAM composite fibers

The morphology of the pristine RSF electrospun fibers and RSF/2-HP-β-CD/TAM composite fibers before and after ES or AI treatment are shown in Fig. 1. It shows the average diameter of composite fibers (150 ± 34 nm) is much smaller than that of pristine RSF fibers (1.15 ± 0.34 μm). Meanwhile, the composites fibers seem become more round compared to the pristine RSF fibers. We suppose the change in fiber diameter and roundness is due to the change of the spinning dope (such as conductivity or viscosity) after the incorporation of 2-HP-β-CD/TAM, which greatly improves the spinnability of RSF solution. As TAM is well dissolved in ethanol, we were unable to use conventional method, i.e., immersing in ethanol solution to make the electrospun fibers insoluble to water. Therefore we chose ES or AI to treat the as-spun fibers. The morphology of the fibers after ES or AI did not have much change, which indicated such treatments were acceptable.

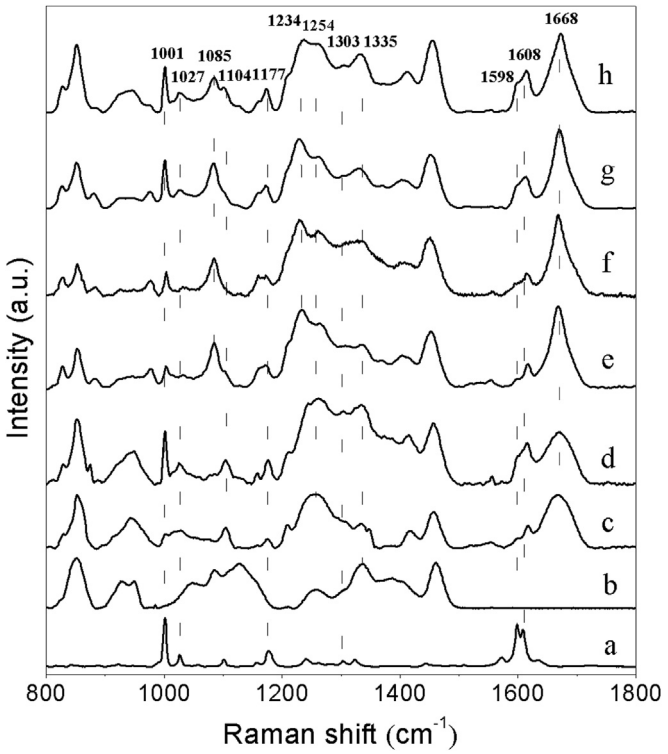

Fig. 2. Raman spectra of (a) TAM, (b) 2-HP-β-CD, (c) as-spun RSF fibers, (d) as-spun RSF/2-HP-β-CD/TAM fibers, (e) RSF fibers after ES treatment, (f) RSF fibers after AI treatment, (g) RSF/2-HP-β-CD/TAM fibers after ES treatment, (h) RSF/2-HP-β-CD/TAM fibers after AI treatment.

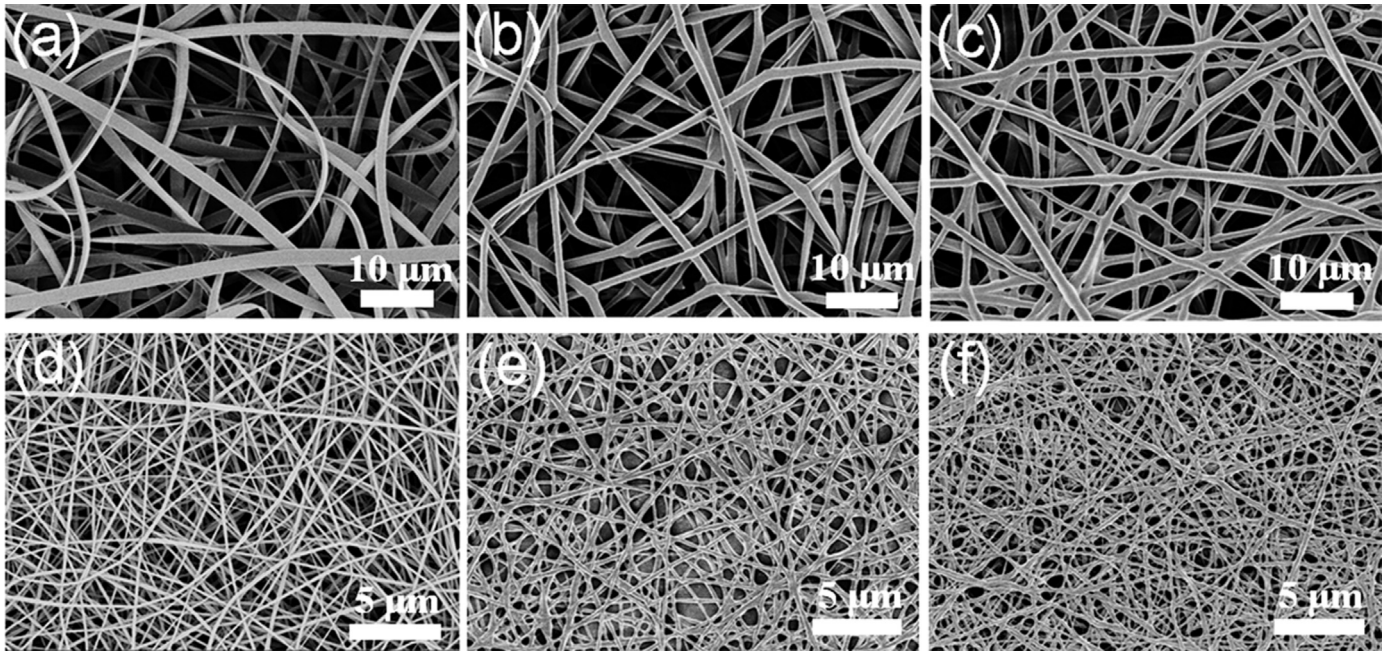

Fig. 1. SEM micrographs of (a) as-spun RSF fibers, (b) RSF fibers after ES treatment, (c) RSF fibers after AI treatment, (d) as-spun RSF/2-HP-β-CD/TAM fibers, (e) RSF/2-HP-β-CD/TAM fibers after ES treatment, (f) RSF/2-HP-β-CD/TAM fibers after AI treatment.