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The control of beads diameter of bead-on-string electrospun nanofibers and the corresponding release behaviors of embedded drugs

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ABSTRACT

Bead-on-string nanofibers, with appropriate control of the beads diameter, are potential fibrous structures for efficient encapsulation of particle drugs in micron scales and could achieve controlled drug release for tissue engineering applications. In this study, the beads diameter of electrospun bead-on-string nanofibers was controlled by adjusting the concentration of spinning polymer, poly (lactic-co-glycolic acid) (PLGA), and the solvent ratio of chloroform to acetone. The images of the scanning electron microscopy (SEM) suggested that bead-on-string nanofibers could be successfully obtained only with a certain range of PLGA solution concentration. Moreover, with the decrease in the solvent ratio of chloroform to acetone, the range was left-shifted towards a smaller concentration. In addition, increase in the PLGA solution concentration within the range the beads diameter became greater and the shape of the beads changed from oval to slender when increasing the PLGA concentration within the range. The bead-on-string nanofibers with different beads diameter were further used to load micro-particle drugs of tetracycline hydrochloride, as a model drug, to examine the release behavior of nanofibers scaffold. The release profiles of drug loaded bead-on-string nanofibers demonstrated the possibility to alleviate the burst drug release by means of beads diameter control.

1. Introduction

Electrospinning, an economic technique to fabricate nanometric fibers with great advantages such as high surface areas to volume and porosity, has great prospects in fabrication of biomaterial scaffolds for drug delivery and tissue engineering applications [1–4]. Biodegradable polymers have been electrospun to fabricate tissue engineering scaffolds encapsulating various drugs, such as antibodies, growth factors and small molecule drugs, to mimic the extracellular matrix structurally and functionally [5,6]. Sustained release of the drugs from the scaffolds supported the efficient tissue repair and regeneration.

For particle drugs, the sizes are usually in the micron level. It was a challenge to encapsulate these micro-sized particle drugs by nano-scale electrospun fibers. The bead-on-string nanofiber as a unique phenomenon has frequently been reported in electrospinning. The beads always have diameters in the range of 1–2 μm, or even more. This special structure was proved to be effective to load micro-particle drugs and showed encouraging benefits in sustainable drug release [7–9]. Tetracycline hydrochloride (TCH) was chosen as a model drug in this paper for further study about the release behaviors of beaded nanofibers along with different morphologies.

With the beaded nanofibers applied in more applications, such as in drug release system, researchers drew their attention from improving nanofibers uniformity by eliminating such "by-products" [13–15] to investigating the optimized condition for the formation of beaded nanofibers. The competition of surface tension and viscoelasticity were the key parameters that drove the formation of such beaded structures [16,17]. The concentration of polymer solution had been suggested as the most fundamental and practical factor to obtain beaded nanofibers easily [18,19].

Bead-on-string nanofiber, served as a potential drug carrier, to our knowledge there is no further study on how bead-on-string nanofibers would affect its application in drug delivery system and tissue engineering. In the case of microsphere as drug carrier, microspheres with bigger diameter showed better release behavior for encapsulation of equal quantity drug [10,11]. For core-shell fibers loading drugs, the fibers which have bigger shell thickness possessed lower drug release rate [12]. For bead-on-string nanofibers encapsulating particles drugs, beads diameter contained the information of embedding depth of drug. The previous research illustrated the feasibility of proper

Abbreviations: BD, bead diameter; BL/BD, bead length/bead diameter; TCH, tetracycline hydrochloride; PLGA, poly (lactic-co-glycolic acid); SEM, scanning electron microscopy.

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encapsulation of drug particles in the center of beads part of the nanofibers [7]. Therefore, the encapsulation capability of the nanofiber is determined by the beads properties, especially bead diameter (BD). In conclusion, it would lead to a conjecture that the diameter of the forming beads of the bead-on-string fibers has an impact on the release profiles of the electrospun bead-on-string nanofibers.

Few studies [18,20], nevertheless, concentrated their interests on the further beads morphologies control of the bead-on-string nanofibers. A wide range of parameters, as spinning solution properties (i.e. concentration [21]), processing parameters (i.e. electrospinning distances, spinning needle gauge or diameter [22]) and ambient atmospheric conditions (i.e. relative humidity [23]) were known to affect the morphology of beaded nanofiber. Under stable ambient conditions with controllable temperature and relevant humidity, the solution properties were the critical parameters having a potential to adjust the bead morphologies, especially the bead diameter.

To address the problem described above, in this study, we investigated the accurate control of the beads diameter as well as the corresponding effects of the diameter control on the release profiles. Poly (lactic-co-glycolic acid) (PLGA), a synthetic biodegradable co-polymer of lactic and glycolic acid, has been wildly used in drug delivery system and was chosen to fabricate nanofibers. Attention was paid to the control of the beads diameter by modifying the properties of the spinning solution. For this purpose, the concentration of PLGA and the composition of solvent in the spinning solution were selected as the governing parameters due to their direct and controllable characteristics. Then, we embedded micro-particle drugs, tetracycline hydrochloride, into the beads of the bead-on-string nanofibers. Finally, we recorded the drug release profiles and, thus, demonstrated the influence of the beads diameter in the release behaviors.

2. Experimental

2.1. Materials

Poly (lactic-co-glycolic acid) (PLGA, 50:50, Mw 93000) was purchased from Jinan Daigang Biomaterial Co., Ltd., China. The solvents of PLGA solutions were chloroform and acetone (both was analytic pure and purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd., China. Tetracycline hydrochloride (TCH), used as a model drug, was also purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd., China.

2.2. Preparation of electrospinning solutions/suspensions

In order to control beads diameter of the bead-on-string nanofibers, a series of spinning solutions with different PLGA concentrations were prepared by dissolving the PLGA in a mixed solvent of chloroform and acetone, with different mixing ratios, and stirring by magnetic stirrers (Jiangsu JinCheng GuoSheng Experiment Instrument Plant, China) for 3 h at room temperature. According to our preliminary experiments, the concentrations of the PLGA solution were 75, 100, 140, 180, 200 and 250 mg/mL. The solvent was prepared by mixing chloroform and acetone in volume proportions of 2:1, 1:1 and 1:2. The conductivities of solvents were tested using conductivity meter (Jenway 3540, Kension, UK).

After the successful control of beads diameter of the bead-on-string nanafibers, beaded fibers embedding with micro-particle drugs of TCH were fabricated. For this purpose, PLGA/TCH suspensions were prepared (Fig. 1). Firstly, micro-particles of the TCH were dispersed in a mixed chloroform/acetone solvent followed by continuous stirring using an ultrasonic processor (Q700, Qsonica, LLC, US) for 10 min to obtain a homogenous TCH suspension, labeled as suspension I. TCH particles were insoluble but completely dispersed in solvent. At the same time, PLGA solutions were prepared by dissolving PLGA in mixed chloroform/acetone solvent and stirring for 3 h. Then, the prepared TCH suspension

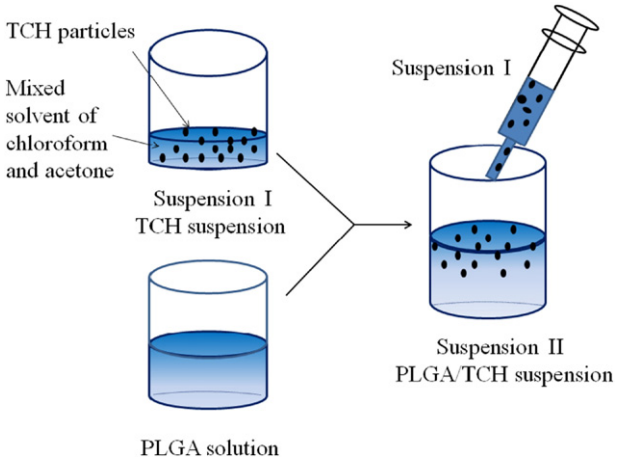

Fig. 1. Preparation of PLGA/TCH suspensions.

was added dropwise to the PLGA solution and magnetic stirred for 30 min to acquire PLGA/TCH suspension, marked suspension II, in which the loading rate of TCH was determined at 2 wt% according to preliminary experiment. The loading rate equaled the ratio of TCH amount to the polymer amount. The TCH particles in suspension I have irregular shapes which was shown in Fig. 2 (a). Fig. 2 (b) showed TCH particles in suspension II and the diameter distribution of the TCH particles shows in Fig. 2 (c). The average diameter of the particles was about 0.92 μm.

2.3. Electrospinning of beaded nanofibers

The prepared PLGA solutions/suspensions were placed into standard syringe fitted with 21 G stainless steel needle and pumped at a constant feeding rate of 1 mL/h by a syringe pump (LSP01-2A, LongerPump Co., Ltd., China). A voltage of 20 kV was applied by a high voltage DC power supply (DM-P5032, Tianjin Dongwen Plant, China) and the collecting aluminum foil was 15 cm away from the needle tip. The electrospinning was conducted in an environment of room temperature and relative humidity around 40%. The acquired nanofibers membranes were stored in fume hood overnight to remove any residual solvent.

2.4. Characterization of electrospun beaded nanofibers

The morphologies of the beaded nanofibers and TCH particles were studied by a scanning electron microscopy (SEM, TM-1000, Hitachi, Japan) at an accelerating voltage of 15 kV. The size of TCH particles, fibers and beads was calculated by ImageJ software (National Institutes of Health, USA). 100 beads were counted. The encapsulated of TCH in beaded nanofibers were investigated by a transmission electron microscope (JEM 3010, JEOL, Japan).

2.5. In vitro release profile study

To evaluate the release behaviors of the TCH particles encapsulated in electrospun nanofibers, about 10 mg nanofibers membranes were soaked in a 10-mL centrifuge tube with 5 mL phosphate-buffered saline (PBS, pH = 7.4) and shaken horizontally at 37 °C in a constant temperature shaker (TC-2112B, Changzhou Feipu Instrument Co., Ltd., China). All 5 mL TCH/PBS solution was collected and the same volume of fresh PBS was replenished at preset time intervals. The contents of TCH were measured by a double beam UV–visible light spectrophotometer (TU-1901, Beijing's Puxi Analysis Instrument Co., Ltd., China) at the wavelength of 360 nm. The detected absorbance was converted into the concentration of TCH dissolved in the PBS according to the standard