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Higher quality quercetin sustained release ethyl cellulose nanofibers fabricated using a spinneret with a Teflon nozzle

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ABSTRACT

This study investigates the usage of a spinneret with a Teflon nozzle for fabrication of higher quality drug sustained-release electrospun nanofibers. Ethyl cellulose (EC) and quercetin were used as a filament-forming polymer matrix and an active pharmaceutical ingredient, respectively. The electrospinning was conducted using both a traditional stainless steel spinneret and a spinneret with a Teflon nozzle. Experimental results demonstrated that a Teflon-fluid interface at the spinneret's nozzle provided a better performance for implementing electrospinning than a traditional metal-fluid interface in the following aspects: (1) keeping more electrical energy on the working fluids for an efficacious process; (2) exerting less negative effect on the fluid to draw it back to the tube; and (3) making less possibility of clogging. The resulted nanofibers from the spinneret with a Teflon nozzle exhibited higher quality than those from the traditional spinneret in those: (1) smaller diameter and narrower distribution, 520 ± 70 nm for the former and 750 ± 280 nm for the later, as indicated by the field emission scanning electron microscopic images; and (2) better sustained-release profiles of quercetin from the former than the latter, as demonstrated by the *in vitro* dissolution tests. The new protocols about usage of Teflon as a spinneret's nozzle and the related knowledge disclosed here should promote the preparation and application of electrospun functional nanofibers.

1. Introduction

As a flexible and facile route for the preparation of nanofibers with potential applications in a variety of fields, electrospinning is one of the most popular methods for nanotechnology [1–5]. Electrospinning has experienced tremendous developments most recently, a range of innovations have recently been introduced to the electrospinning system (typically including a high-voltage power supply, a collector, a fluid driving device and a spinneret) [6–11]. Most of the modifications and the most brilliant innovations to electrospinning are directly connected with the spinneret among the four components [12–16], by which different processes have been successfully developed, such as coaxial electrospinning, side-by-side electrospinning, edge and needleless electrospinning [17–21]. Regardless of improvement of these modifications are, almost all the concepts about new spinnerets focus on the spinnerets' inner structure and outer shape, little attention has been paid to the constituent of spinneret.

Electrohydrodynamic atomization (EHDA, including electrospinning, electrospray and e-jet printing) generates materials directly through the interaction of electrical energy with the fluids being processed [22]. It is intuitive that the spinneret must have good conductivity to transfer charge effectively. Hence, almost all spinnerets are made of metal, and most of them comprise stainless steel tubing [1–22]. However, this neglects the fact that electrospinning can only commence when the electrical forces overcome the forces holding the liquid in the spinneret: the most important of the latter is probably surface tension. Very little attention has been paid to the interactions between the working fluid and the fluid-directing tubing. A spinneret composed of metal can effectively convey electrical energy to the fluids being spun, but its surface may also exert a negative influence during the spinning process and thereby affect the properties of the resultant nanofibers.

Although electrospinning has developed from the synchronous treatment of one to two fluids and multiple fluids; from the generation of a monolithic to structural nanofibers; from the preparation of polymer nanofibers to polymer-based composites; it is always a straightforward one-step nanofiber fabrication process [23–28]. During the simple process, many factors associated with the working solutions' properties, operating parameters and also the environmental conditions would exert their influence on the process and also the resultant nanofibers [29]. Thus, nanofiber production is always a sensitive process and the mechanism

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is complicated due to the involvement of complex electrofluid mechanical issues, which in turn make the scaling-up electrospinning for possible commercialized nanofibers very difficult. Two main concerns must be resolved before electrospinning becomes up-scalable from laboratory to industrial applications. One problem, the mass production of nanofibers, has been recognized broadly in reports of multiple needle electrospinning, needleless electrospinning and edge electrospinning [18,19]. However, few studies have reported the systematic improvement of the quality of nanofibers, other than how to synthesize thinner nanofibers [30,31]. Quality issue should be addressed besides productivity in the future commercialization of elctrospun nanofibers products.

The parameters for evaluating the quality of electrospun nanofibers often include structural uniformity of the collecting nanofibers, their size and size distribution, morphology and surface smoothness, and also the designed functional performance [30,31]. For applications of electrospun nanofibers in biomedical area such as drug delivery, the quality of nanofibers is even more important for providing drug release profiles with larger stability and more robustness for a safe and effective therapeutic action. Traditionally, most of the electrospun drug-loaded nanofibers are prepared by treatment of co-dissolving solutions of a guest active ingredient and the host polymer excipient in a single fluid process [32–34]. The sensitivity of electrospinning to the environment and also the clogging of spinneret would degrade the resultant nanofibers' quality.

Building on the above discussion, this study investigates the preparation of drug-loaded ethyl cellulose (EC) nanofibers using a spinneret with a Teflon nozzle and the influence of the resultant nanofibers' quality on the drug sustained release profiles. EC, an inert, non-toxic and stable hydrophobic polymer suitable for drug sustained release carrier, was used as the filament-forming polymer matrix [35,36]. Quercetin is a plant pigment (flavonoid). It is found in many plants and foods, such as red wine, onions, green tea, apples, berries, *Ginkgo biloba*, St. John's wort, American elder, and others. Quercetin is used for treating conditions of the heart and blood vessels including "hardening of the arteries" (atherosclerosis), high cholesterol, heart disease, and circulation problems. It is also used for diabetes, cataracts, hay fever, peptic ulcer, schizophrenia, inflammation, asthma, gout, viral infections, chronic fatigue syndrome, preventing cancer, for treating chronic infections of the prostate, and for increasing endurance and improving athletic performance [37,38]. In china, traditional medicine, quercetin is often used to prevent asthma, eliminate phlegm and relieve cough, a sustained release profile after oral administration is highly desired for the convenience of patients and high therapeutic effects.

2. Experimental

2.1. Materials

Quercetin (purity > 98%, No. MUST-12072505) was purchased from the Beijing Aoke Biological Technology Co., Ltd. (Beijing, China). EC (6–9 mPa s) was obtained from Aladdin Chemistry Co., Ltd. (Shanghai, China). *N*,*N*-Dimethylacetamide (DMAc), methylene blue, and anhydrous ethanol were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All other chemicals used were analytical grade, and water was doubly distilled before use.

2.2. Electrospinning

The spinnable solutions were prepared by dissolving 24 g EC and 2 g quercetin in l00 mL of a mixed solvent of ethanol and DMAc (v/v 85:15). The co-dissolving solution was colored brown.

A syringe pump (KDS100, Cole-Parmer, IL, USA) and a high-voltage power supply (ZGF 60 kV/2 mA, Shanghai Sute Corp. (Shanghai, China)) were used for electrospinning. All electrospinning processes were carried out under ambient conditions ((22 ± 3 °C) and relative humidity (58 ± 5%)). The electrospinning process was recorded using a digital video recorder (PowerShot A490, Canon, Tokyo, Japan). For optimization, the applied voltage was fixed at 15 kV, the flow rate of co-dissolving solution was 1.0 mL h^{-1}, and the fibers were collected on an aluminum foil placed 20 cm from the nozzle of spinneret. The spinnerets comprised a traditional stainless steel capillary and a homemade spinneret with a Teflon nozzle. The nanofibers prepared from the metal and Teflon nozzle were denoted as F1 and F2, respectively.

The interfacial tensions between the polymer solutions and the spinneret nozzles were explored with a DSA100 drop shape analysis instrument (Krüss GmbH, Hamburg, Germany) to investigate the influence of a Teflon nozzle on the electrospinning processes.

2.3. Characterization

2.3.1. Morphology

The morphology of the nanofiber mats was assessed using a Quanta FEG450 field emission scanning electron microscope (FESEM) (FEI Corporation, Netherlands). Prior to examination, the samples were rendered electrically conductive by gold sputter coating under a nitrogen atmosphere. The average fiber diameter was determined by measuring diameters in the SEM images at more than 100 locations using Image J software (National Institutes of Health, MD, USA). The topography of the quercetin particles was observed under cross-polarized light using an XP-700 polarized optical microscope (Shanghai Changfang Optical Instrument Co., Ltd.).

2.3.2. Physical status of components and compatibility

X-ray diffraction (XRD) patterns were obtained on a D/Max-BR diffractometer (RigaKu, Tokyo, Japan) using CuKα radiation with 2θ ranging from 5 to 60°. Voltage and current settings were 40 mV and 30 mA, respectively. Attenuated total reflectance (ATR) Fourier transform infrared (FTIR) analyses were performed on a Nicolet-Nexus 670 FTIR spectrometer (Nicolet Instrument Corporation, WI, USA) from 500 to 4000 cm^{-1} at a resolution of 2 cm^{-1}.

2.3.3. In vitro dissolution tests

In vitro dissolution tests were carried out according to the Chinese Pharmacopoeia (2010 ed.). Method II, a paddle method that adopts an RCZ-8A dissolution apparatus (Tianjin University Radio Factory, Tianjin, China), was used. About 200 mg of drug-loaded nanofibers were placed in 900 mL of physiological saline (PS; 0.9 wt.%) at (37 ± 1) °C. The instrument was then set to 50 rpm, providing sink conditions in which $C < 0.2\,C_s$. At predetermined time points, 5.0 mL samples were withdrawn from the

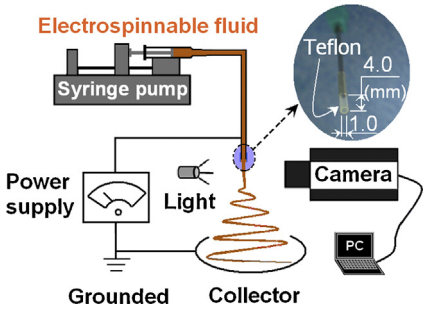

Fig. 1. Diagram of an electrospinning process and a digital image of a spinneret with a Teflon nozzle (the inset).