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Nanosized sustained-release drug depots fabricated using modified tri-axial electrospinning

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ABSTRACT

Nanoscale drug depots, comprising a drug reservoir surrounded by a carrier membrane, are much sought after in contemporary pharmaceutical research. Using cellulose acetate (CA) as a filament-forming polymeric matrix and ferulic acid (FA) as a model drug, nanoscale drug depots in the form of core-shell fibers were designed and fabricated using a modified tri-axial electrospinning process. This employed a solvent mixture as the outer working fluid, as a result of which a robust and continuous preparation process could be achieved. The fiber-based depots had a linear morphology, smooth surfaces, and an average diameter of 0.62 ± 0.07 μm. Electron microscopy data showed them to have clear core-shell structures, with the FA encapsulated inside a CA shell. X-ray diffraction and IR spectroscopy results verified that FA was present in the crystalline physical form. In vitro dissolution tests revealed that the fibers were able to provide close to zero-order release over 36 h, with no initial burst release and minimal tailing-off. The release properties of the depot systems were much improved over monolithic CA/FA fibers, which exhibited a significant burst release and also considerable tailing-off at the end of the release experiment. Here we thus demonstrate the concept of using modified tri-axial electrospinning to design and develop new types of heterogeneous nanoscale biomaterials.

Statement of Significance

Nanoscale drug depots with a drug reservoir surrounded by a carrier are highly attractive in biomedicine. A cellulose acetate based drug depot was investigated in detail, starting with the design of the nanostructure, and moving through its fabrication using a modified tri-axial electrospinning process and a series of characterizations. The core-shell fiber-based drug depots can provide a more sustained release profile with no initial burst effect and less tailing-off than equivalent monolithic drug-loaded fibers. The drug release mechanisms are also distinct in the two systems. This proof-of-concept work can be further expanded to conceive a series of new structural biomaterials with improved or new functional performance.

1. Introduction

Nanosized drug depots, in which a drug reservoir is surrounded by pharmaceutical excipients, have attracted much attention in the biomedical field recently [1–6]. They have been explored for drug delivery through a variety of administration routes (such as oral, injected, inhaled, and implanted) and also as stents in tissue engineering [7–11]. Two trends are clear with this type of biomaterials. One is that almost all the depots take the form of nanoparticles, microspheres or microemulsions [12–14]. The second is that the fabrication methods are mainly "bottom-up" approaches, including chemical synthesis, molecular self-assembly, and emulsion methods; these are often time-consuming and very difficult to perform on a large scale [15–18]. New approaches for creating this kind of nanostructure, particularly "top-down" methods that can be scaled up easily, would offer great benefit to the fields of biomaterials and pharmaceutics.

One such route is the electrospinning technology, which uses electrical energy to produce nanoscale fiber composites from solutions of a polymer and functional component. After rapid

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development in the last two decades, the most exciting new work on electrospun fibers falls in two areas. The first is scale-up, with production on an industrial scale now possible. This has mainly been investigated in the context of monolithic fibers with one or two functional ingredients/nanoparticles distributed homogeneously in the filament-forming polymer matrix [19–22]. The second is the creation of more complex nanostructures (such as core-shell and Janus systems, and combinations thereof) in order to yield materials with improved functional performance [23–26]. If a drug reservoir could be formed as the core of electrospun core-shell fibers, then new fiber-based nanoscale drug depots could be created, such as an electrospun suture [27]. These would differ significantly from the nanoparticle-based depots which have mainly been explored to date. In the cases of coaxial and tri-axial electrospinning, it is possible to run these with only one of the working fluids being electrospinnable alone [28,29]. In standard coaxial electrospinning, the sheath fluid must be electrospinnable to support the electrospinning process and the formation of core-shell structures [30]. However, a modified coaxial electrospinning process, characterized by the utilization of un-spinnable liquids as the sheath working fluids, can also be implemented [29,30]. Similarly, traditional tri-axial electrospinning always uses an electrospinnable outer fluid [31–39]. A modified tri-axial process focused on the exploitation of un-spinnable liquids has also been reported [28]. These might comprise solvents, small molecule solutions, emulsions and suspensions, and should lead to a range of novel structures. Thus, it can be hypothesized that these technologies can be exploited to create drug-loaded nanofibers containing drug reservoirs even though the drug itself has no filament-forming properties.

A wide variety of raw materials have been investigated as the shell for encapsulating a core drug reservoir. These materials include the traditional pharmaceutical excipients approved by the FDA such as natural polymers, a range of synthetic polymers, and phospholipids, but also more exotic systems including hydrogels and even inorganic material such as TiO_2 [40–43]. Naturally-occurring polymers remain a key focus of research interest, however, because of their abundant supply and relatively environmentally-friendly preparation routes. This is reflected in the frequent use of cellulose and its derivatives not only in the scientific literature but also in the food and pharmaceutical industries [44,45]. In particular, cellulose acetate (CA), the acetate ester of cellulose, has broad applications – for instance in the coatings of pharmaceutical and food products, and as film in photography [46]. CA has been also frequently been utilized as the filament-forming polymer for creating drug-loaded nanofibers through single-fluid electrospinning spinning [47]. However, the direct electrospinning of CA is non-facile because the need to use volatile solvents in this process causes frequent clogging of the spinneret [30]. Furthermore, monolithic drug loaded CA nanofibers tend to exhibit an undesirable initial burst release [48,49], which inhibits their potential as sustained-release biomaterials.

In this work, with the phytochemical ferulic acid (FA) as a model drug, we explore the preparation of CA-based nanoscale drug depots using a modified tri-axial electrospinning process. As a control, monolithic drug-CA fibers were produced using a modified coaxial process. The fiber morphologies, structures, functional performance, and the distribution and physical form of the drug in the formulations are compared in detail.

2. Experimental section

2.1. Materials

Ferulic acid (FA; purity >98%) was purchased from the Yunnan Yunyao Lab Co., Ltd. (Kunming, China). CA (M_w = 100,000 Da) was obtained from Acros Organics (Geel, Belgium). Methylene blue, methylene orange, N,N-dimethylacetamide (DMAc), anhydrous ethanol and acetone were obtained from the Shanghai SSS Reagent Co., Ltd. (Shanghai, China). All other chemicals were analytical grade commercial products. Freshly double distilled water was used where required.

2.2. Electrospinning

Three kinds of electrospinning processes (traditional coaxial, modified coaxial and modified tri-axial) were explored for preparing fibers. The outer fluids for modified coaxial and tri-axial electrospinning comprised a solvent mixture of acetone, ethanol and DMAc in a volume ratio of 4:1:1 [30]. For the traditional coaxial process and the modified tri-axial process, an electrospinnable solution of CA (12% w/v in a mixture of acetone, ethanol and DMAc, 4:1:1 v/v/v) was used to surround an unspinnable 15% w/v FA solution in acetone/ethanol/DMAc (4:1:1 v/v/v). For the modified coaxial process, the core fluid comprised CA and FA at 12 and 3% w/v in the same solvent system. These experimental conditions are summarized in Table 1.

Each of the working fluids was driven by a syringe pump (KDS100, Cole-Parmer, Vernon Hills, IL, USA). A high voltage generator (ZGF 60 kV/2 mA, Wuhan Huatian Corp., Hubei, China) was applied to create an electric potential between the spinneret and collector. A flat piece of cardboard wrapped with aluminum foil was used as the collector plate. Both the concentric (coaxial) spinneret and tri-layer spinneret were produced in-house. After a series of initial optimization experiments, the applied voltage and spinneret to collector distance were fixed at 18 kV and 20 cm. The flow rates of the working fluids are listed in Table 1. To aid optimization of the experimental conditions, 2 μg/mL of methylene blue and methylene orange were added to the inner and middle working fluids, respectively.

2.3. Characterization

2.3.1. Morphology

The morphology of the fibers and their cross-sections were probed using a Quanta FEG450 field emission scanning electron microscope (SEM; FEI Corporation, Hillsboro, OR, USA). Before examination, samples were sputter-coated with platinum under argon. A polarized optical microscope (XP-700, Chang-Fang Optical Instrument Co., Ltd., Shanghai, China) was used to study the raw drug powders and CA particles. The fiber diameters were estimated from SEM images using the ImageJ software (National Institutes of Health, Bethesda, MD, USA). Samples of fibers for cross-section analysis were prepared by immersion in liquid nitrogen for 20 min, after which they were manually broken.

2.3.2. Physical form

X-ray diffraction patterns (XRD) were recorded on a Bruker AXS diffractometer (Bruker, Karlsruhe, Germany). Fourier transform infrared (FTIR) analysis was carried out on a Spectrum 100 FTIR Spectrometer (Perkin Elmer, Billerica, MA, USA). For the latter, samples were prepared using the KBr disc method.

2.3.3. In vitro drug release

FA has a maximum absorbance at λ_{max} = 322 nm [50], and was quantified on a Lambda 950 UV/vis/NIR spectrophotometer (Perkin Elmer, Billerica, MA, USA) following construction of a calibration curve. The in vitro drug release profiles were measured according to the Chinese Pharmacopoeia (paddle method, 2015 Ed.) using a dissolution apparatus with six cells (RCZ-8A, Tianjin University Radio Factory, Tianjin, China). 40 mg of FA powder (particle size < 20 μm) or 0.2 g of the F2 and F3 fibers (containing the