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Electrospun pH-sensitive core–shell polymer nanocomposites fabricated using a tri-axial process



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ABSTRACT

A modified tri-axial electrospinning process was developed for the generation of a new type of pH-sensitive polymer/lipid nanocomposite. The systems produced are able to promote both dissolution and permeation of a model poorly water-soluble drug. First, we show that it is possible to run a tri-axial process with only one of the three fluids being electrospinnable. Using an electrospinnable middle fluid of Eudragit S100 (ES100) with pure ethanol as the outer solvent and an unspinnable lecithin-diclofenac sodium (PL–DS) core solution, nanofibers with linear morphology and clear core/shell structures can be fabricated continuously and smoothly. X-ray diffraction proved that these nanofibers are structural nanocomposites with the drug present in an amorphous state. *In vitro* dissolution tests demonstrated that the formulations could preclude release in acidic conditions, and that the drug was released from the fibers in two successive steps at neutral pH. The first step is the dissolution of the shell ES100 and the conversion of the core PL–DS into sub-micron sized particles. This frees some DS into solution, and later the remaining DS is gradually released from the PL–DS particles through diffusion. *Ex vivo* permeation results showed that the composite nanofibers give a more than twofold uplift in the amount of DS passing through the colonic membrane as compared to pure DS; 74% of the transmitted drug was in the form of PL–DS particles. The new tri-axial electrospinning process developed in this work provides a platform to fabricate structural nanomaterials, and the core–shell polymer-PL nanocomposites we have produced have significant potential applications for oral colon-targeted drug delivery.

Statement of Significance

A modified tri-axial electrospinning is demonstrated to create a new type of core–shell pH-sensitive polymer/lipid nanocomposites, in which an electrospinnable middle fluid is exploited to support the unspinnable outer and inner fluids. The structural nanocomposites are able to provide a colon-targeted sustained release and an enhanced permeation performance of diclofenac sodium. The developed tri-axial process can provide a platform for fabricating new structural nanomaterials with high quality. The strategy of a combined usage of polymeric excipients and phospholipid in a core–shell format should provide new possibilities of developing novel drug delivery systems for efficacious oral administration of poorly-water soluble drugs.

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1. Introduction

The fabrication of advanced drug delivery systems (DDSs) is increasingly dependent on the creation of complex architectures and understanding structure-activity relationships at the nanoscale [1–3]. To this end, core–shell nanostructures have been very widely studied in the production of functional nanomaterials, including those for biomedical applications [4–6]. For drug

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delivery and controlled release, both the core and shell can be loaded with an active pharmaceutical ingredient (API) and/or with different types of pharmaceutical excipients. Applications of such systems include improving the solubility of poorly water-soluble drugs, controlled release of multiple APIs from a single dosage form, or tunable multiple phase release [7–9].

Over recent years, polymers and lipids have been the most widely used pharmaceutical excipients, and these materials have acted as the basis for a broad gamut of novel DDSs, being exploited to alter the biopharmaceutical and pharmacokinetic properties of the drug molecule for favorable clinical outcomes [3,10,11]. Numerous core-shell polymeric nanoparticles (NPs) and lipid-based DDS (such as solid lipid dispersions and liposomes) have been investigated for drug delivery through varied administration routes [12–15]. Novel strategies derived from the combined usage of polymers and phospholipids (PLs) have been reported for some biomedical applications (including controlled release) and are presently of intense interest in the pharmaceuticals field. However, virtually all the reported polymer-lipid composites are in the form of microparticles or NPs [4,8,16–18]. Core-shell nanofiber-based DDS have received relatively little attention, and to the best of our knowledge there are no reports of drug-loaded polymer-lipid nanofibers being used in drug delivery.

Electrospun nanofibers, comprising an API loaded into a filament-forming polymer, have been the focus of much research. They are prepared from a co-dissolving solution of a drug and polymer; this is ejected from a syringe with electrical energy used to rapidly evaporate the solvent and yield one-dimensional fibers with diameters frequently on the nanoscale. This technique is scalable, and several recent reports address large scale fabrication and the potential for commercial products [19–22]. The intense research effort invested in these materials thus appears to be about to yield products which can make a major difference to patients' lives. Electrospinning is a facile, one-step procedure, and the products form as a visible and flexible mat which can easily be recovered from the collector without significant loss of material or damage. The nanofibers produced can further be used as templates to manipulate molecular self-assembly to create drug-loaded NPs or liposomes; the electrospinning technique thus provides not only a bridge between fiber-based and NP-based DDSs, but also between solid and liquid dosage forms [23–26].

The most simple, single-fluid, electrospinning process has been explored for approaching two decades, and the applications of the resultant monolithic nanofibers have been probed in a wide range of fields. Current developments in electrospinning are focused in two key areas. The first is the manufacture of electrospun nanofibers on an industrial scale [27–29]. The second line of research involves developing advanced electrospinning techniques to yield nanofibers with sophisticated structural characteristics (such as multiple-compartment nanofibers, core-shell nanofibers, or structured fibers with varied distributions of the API), which in turn impart tunable and multiple functionalities [30–32]. Because of the popularity of core-shell nanostructures and the relative ease of the process, coaxial electrospinning (in which two needles, one nested inside another, are used to handle two working fluids) has been the focus of much research. Other advanced approaches such as side-by-side electrospinning (to yield Janus fibers), tri-axial electrospinning (giving three-layer composites), and other types of multiple-fluid electrospinning have been neglected in comparison [6,9,33].

Compared with single-fluid electrospinning, the standard coaxial experiment has greatly expanded the range of fibers which can be produced. These include not only core-shell fibers [34,35], but also fibers prepared from materials without filament-forming properties [36] and used as templates for creating nanotubes (from the fiber as a whole) or the “bottom-up” generation of NPs (self-

assembled from the components loaded in the fibers) [26,37]. For biomedical applications, core-shell nanofibers proffer a series of new possibilities; for instance, it is possible to protect a fragile active ingredient such as a protein from the stresses of the electrospinning processes by confining it to the core, or to vary the APIs concentration in the core and shell to achieve complex drug release profiles [38–41]. In the traditional coaxial process the sheath working fluid must be electrospinnable, but a modified process in which one can utilize unspinnable liquids as the sheath fluid is also possible. The number of polymers which can be directly electrospun is rather limited, but there are numerous unspinnable liquids, and the modified coaxial process should hence further expand the range of functional nanofibers which can be produced [38,42,43].

The above discussion is focused on the simultaneous processing of two fluids; working with three or even four fluids simultaneously is also possible, however [44–49]. For example, Han and Steckl reported tri-layer nanofibers for biphasic controlled release, using dyes as model active ingredients [49]. In very recent work, we successfully developed a tri-axial electrospinning process to generate nanofibers with a gradient distribution of the API, allowing us to achieve zero-order drug release profiles [31]. However, in all the tri-axial electrospinning processes reported to date, the three working fluids are all electrospinnable. This limits the applications of the process. If unspinnable liquids can be processed in combination with spinnable working solutions, a much broader selection of functional products could be designed and generated.

Building on our previous work developing modified coaxial [38,42,43] and standard tri-axial electrospinning [50], here we report the first modified tri-axial electrospinning process. We have used this process to create core-shell fibers comprising a lipid-drug core and a pH sensitive shell, thereby allowing us to demonstrate that only an electrospinnable central fluid is required to achieve a successful tri-axial process. The polymer-lipid nanocomposites produced showed desirable functional performance in altering the release behavior of the model drug diclofenac sodium and improving its permeation through the colonic membrane.

2. Experimental

2.1. Materials

Eudragit S100 (ES100, $M_w = 135,000$), a methacrylic acid/methyl methacrylate copolymer which only dissolves at $\text{pH} > 7.0$, was obtained from Röhm GmbH (Darmstadt, Germany). Diclofenac sodium (DS, a non-steroidal anti-inflammatory drug with potent anti-inflammatory, analgesic and antipyretic properties) was purchased from the Hubei Biocause Pharmaceutical Co., Ltd. (Hubei, China). Lecithin (PL, extracted from egg yolk, and containing lysophosphatidylcholine, sphingomyelin, and neutral lipids in minor quantities), N,N-dimethylacetamide (DMAc), anhydrous ethanol, methylene blue and basic fuchsin were purchased from the 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 tri-layer concentric spinneret was homemade. Three syringe pumps (KDS100, Cole-Parmer, Vernon Hills, IL, USA) and a high-voltage power supply (ZGF 60 kV/2 mA, Shanghai Sute Corp., Shanghai, China) were used for electrospinning. The collector comprised a flat piece of cardboard wrapped with aluminum foil. All electrospinning processes were carried out under ambient conditions ($21 \pm 5^\circ\text{C}$ with a relative humidity of $47 \pm 5\%$). Experiments were recorded using a digital camera (PowerShot A490, Canon,

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