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# Electrospun biphasic drug release polyvinylpyrrolidone/ethyl cellulose core/sheath nanofibers

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ABSTRACT

The capability of core/sheath nanofibers prepared using coaxial electrospinning to provide adjustable biphasic drug release was investigated. Using ketoprofen (KET) as the model drug, polyvinylpyrrolidone as the sheath polymer, and ethyl cellulose as the core matrix, the coaxial process could be conducted smoothly and continuously without spinneret clogging. Scanning electron microscopy and transmission electron microscopy revealed linear nanofibers with homogeneous and clear core/sheath structures. Differential scanning calorimetry and X-ray diffraction verified that the core/sheath nanofibers were nanocomposites, with the drug present in the polymer matrix in an amorphous state. Attenuated total reflectance–Fourier transform infrared spectra demonstrated that the sheath polymer and core matrix were compatible with KET owing to hydrogen bonding. In vitro dissolution tests showed that the core/sheath nanofibers could provide typical biphasic drug release profiles consisting of an immediate and sustained release. The amount of drug released in the first phase was tailored by adjusting the sheath flow rate, and the remaining drug released in the second phase was controlled by a typical diffusion mechanism. The present study shows a simple and useful approach for the systematic design and fabrication of novel biomaterials with structural characteristics for providing complicated and programmed drug release profiles using coaxial electrospinning.



## 1. Introduction

In clinical applications, the desired drug release profiles should obey biological rhythm for effective and safe drug delivery and convenient administration. For some pharmaceutical ingredients such as non-steroidal anti-inflammatory drugs (NSAID), as well as antihypertensive, antihistaminic and anti-allergic agents [1,2], an initial release of a fraction of the dose in the shortest time after administration is favored for relieving the symptoms of the disease. Meanwhile, sustained release of the remaining dose over a defined period can optimize the therapy and avoid repeated administration, for the patients' convenience [3,4]. During biphasic release, a drug is released at two rates or in two periods. A typical biphasic release system can provide immediate drug release followed by a constant release.

In recent decades, different traditional pharmaceutical techniques such as tableting, casting and spraying have been investigated for preparing biphasic drug delivery systems (DDS). Some of these systems include mixed films, multi-layered films, multiple tablets, multi-layered tablets, film-coated tablets and eluting stents [5–8]. Meanwhile, advanced technologies are continuously exploited in the literature to produce novel materials or DDS for furnishing biphasic release, taking advantage of more accurate time-programmed administration of active ingredients and fulfilling the specific therapeutic needs of some diseases. These techniques include three-dimensional printing, nanotechniques [9–12] and single fluid electrospinning [13].

Electrospinning has attracted considerable attention as a nanotechnology for nanofiber production because of its simplicity and cost effectiveness. It can produce nanofibers with unique properties and versatile applications [14–21]. One of the most significant breakthroughs in this area is coaxial electrospinning, in which a concentric spinneret can accommodate two liquids [22,23]. Coaxial electrospinning is widely used in controlling the secondary structures of nanofibers, encapsulating drugs or biological agents into polymer nanofibers, preparing nanofibers from materials that lack filament-forming properties, enclosing functional liquids within the fiber matrix, manipulating the size of self-assembled nanoparticles, preparing ultrafine fibers from concentrated polymer solutions, and improving the quality of nanofibers [24–29]. Recently, advanced functional materials fabricated using electrospinning have attracted considerable attention because of their ability to allow the controlled release of multiple active ingredients [30,31]. Electrospinning could be used to control the microstructure and spatial deposition of components. Thus, with the appropriate

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polymer matrix, it is hypothesized that this technique could also be used to develop nanoproducts with biphasic drug profiles.

Polyvinylpyrrolidone (PVP), a hydrophilic polymer excipient with a wide variety of applications in medicine, food, pharmacy and cosmetics, was selected as the filament-forming matrix of the sheath part for immediate drug release [32–34]. Ethyl cellulose (EC) is an inert, non-toxic and stable hydrophobic polymer suitable for sustained release matrices [13,35].

Accordingly, the present study investigates the preparation of core/sheath nanofibers for providing biphasic drug release using coaxial electrospinning. Ketoprofen (KET), a NSAID active ingredient with poor water solubility [36,37], was used as the model drug loaded into the sheath and core parts of the nanofibers.

## 2. Experimental

### 2.1. Materials

PVP K60 ($\overline{M}_w = 360,000$) was purchased from Shanghai Yunhong Pharmaceutical Aids and Technology Co. Ltd. (Shanghai, China). KET was purchased from Wuhan Fortuna Chemical Co. Ltd. (Hubei, China). EC (6 mPa s to 9 mPa s) was obtained from Aladdin Chemistry Co. Ltd. (Shanghai, China). Methylene blue, *N*,*N*-dimethylacetamide (DMAc) 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 core solutions were prepared by dissolving 24 g EC, 3 g KET and 2 mg methylene blue in 100 ml ethanol. The sheath solution was prepared by placing 9 g PVP and 1 g KET in 100 ml of a solvent mixture of DMAc and ethanol in a volume ratio of 1:9.

Two syringe pumps (KDS100 and KDS200, Cole-Parmer, IL, USA) and a high-voltage power supply (ZGF 60 kV/2 mA, Shanghai Sute Corp., Shanghai, China) were used for coaxial electrospinning. All electrospinning processes were carried out under ambient conditions (22 ± 3 °C with relative humidity 58 ± 5%). A homemade concentric spinneret [38] was used to conduct both single fluid (adjusting the core or sheath fluid flow rate to 0 ml $h^{-1}$) and coaxial electrospinning processes. 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, and the fibers were collected on an aluminum foil at a distance of 20 cm. All other parameters are listed in Table 1.

### 2.3. Characterization

#### 2.3.1. Morphology

The morphology of the fiber mats was assessed by field emission scanning electron microscopy (FESEM) using an S-4800 microscope (Hitachi, Tokyo, Japan). Prior to the examination, the samples were platinum sputter-coated under a nitrogen atmosphere to render them electrically conductive. Images were recorded at an excitation voltage of 10 kV. The average fiber diameter was determined by measuring their diameters in FESEM images at more than 100 places, using the NIH Image J software (National Institutes of Health, MD, USA). Before platinum coating, the cross sections of the fiber mats were prepared by placing them in liquid nitrogen before they were manually broken.

Transmission electron microscopy (TEM) images of the samples were recorded on a JEM 2100F field emission transmission electron microscope (JEOL, Tokyo, Japan). TEM samples of the core/sheath nanofibers were collected by fixing a lacey carbon-coated copper grid on the collector.

#### 2.3.2. Physical status and compatibility

Differential scanning calorimetry (DSC) was carried out using an MDSC 2910 differential scanning calorimeter (TA Instruments Co., USA). Sealed samples were heated at 1 at 10 °C $min^{-1}$ from 20 °C to 250 °C. The nitrogen gas flow rate was 40 ml $min^{-1}$.

The X-ray diffraction (XRD) analysis was conducted using a D/Max-BR diffractometer (RigaKu, Japan) with Cu $K_\alpha$ radiation in a $2\theta$ range of 5–60° at 40 mV and 300 mA.

Attenuated total reflectance–Fourier transform infrared (ATR-FTIR) spectroscopy was carried out on a Nicolet-Nexus 670 FTIR spectrometer (Nicolet Instrument Corporation, Madison, USA) at a range of 500 $cm^{-1}$ to 4000 $cm^{-1}$ and 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* (2005 edn.) Method II, which is a paddle method using a RCZ-8A dissolution apparatus (Tianjin University Radio Factory, Tianjin, China). Drug-loaded nanofibers (200 mg) were placed in 600 ml physiological saline (PS, 0.9 wt.%) at 37 ± 1 °C. The instrument was set to 50 rpm, providing sink conditions with $C < 0.2C_s$. At predetermined time points, 5.0 ml aliquots of the samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain a constant volume. After filtration through a 0.22 μm membrane (Millipore, MA, USA) and appropriate dilution with PS, the samples were analyzed at 260 nm, using a UV–vis spectrophotometer (UV-2102PC, Unico Instrument Co. Ltd., Shanghai, China). The concentration of released KET was back-calculated from the data obtained against a predetermined calibration curve.

The actual content of KET in the fibers was quantified by dissolving each sample in ethanol for extraction and later proceeding to the above-mentioned procedure. The accumulative percentage of drug released from the electrospun fibers was calculated using the following equation:

$$P(\%) = \frac{\rho_n \times V_0 + \sum_{i=1}^{n-1} \rho_i \times V}{Q_0} \times 100$$

where $V_0$ is the volume of the dissolution medium (ml), $V$ is the volume of the withdrawn sample (ml), $Q_0$ is the total amount of KET in

**Table 1**
Experimental parameters for the fabrication of different nanofibers.

| No. | Process | Fluid and flow rate (ml $h^{-1}$) | | Fiber morphology[c] | Diameter (nm) |
|---|---|---|---|---|---|
| | | Sheath fluid[a] | Core fluid[b] | | |
| F1 | Single | – | 1.0 | Linear | 710 ± 130 |
| F2 | Single | 1.0 | – | Linear | 910 ± 240 |
| F3 | Coaxial | 0.5 | 0.5 | Linear | 780 ± 90 |
| F4 | Coaxial | 0.8 | 0.5 | Linear | 940 ± 80 |

[a] Sheath fluid consists of 9% (w/v) PVP K60 and 1% (w/v) KET in a mixture of ethanol and DMAc (1:9, v:v).
[b] Core fluid consists of 24% (w/v) EC and 3% (w/v) KET in ethanol.
[c] In this column, "Linear" morphology refers to nanofibers with few beads or spindles.