Tunable drug release from nanofibers coated with blank cellulose acetate layers fabricated using tri-axial electrospinning

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Abstract

In this study, novel core-shell nanostructures were fabricated through a modified triaxial electrospinning process. These comprised a drug-protein nanocomposite coated with a thin cellulose acetate (CA) shell. They were generated through the simultaneous treatment of an outer solvent, an unelectrospinnable middle fluid, and an electrospinnable core solution in triaxial electrospinning. SEM and TEM results revealed that the core-shell nanofibers had linear and cylindrical morphologies with a diameter from 0.66 to 0.87 μm, and distinct core-shell structures with a shell thickness from 1.8 to 11.6 nm. The presence of a CA coating eliminated the initial burst release of ibuprofen seen from a monolithic drug-protein composite, and allowed us to precisely manipulate the drug release (for a 90% percentage) over a time period from 23.5 to 43.9 h in a tunable manner. Mathematical relationships between the processing conditions, the nanostructures produced, and their functional performance were elucidated.

Keywords: Modified triaxial electrospinning; detachable tri-layer spinneret; cellulose acetate nanocoating; structural nanohybrids; linear drug release; process–nanostructure–performance relationship

Chemical compounds studied in this article

Ibuprofen (PubChem CID: 3672); Gliadin (PubChem CID: 17787981); Cellulose acetate (PubChem CID: 3084039); Methylene blue (PubChem CID: 6099); Basic fuchsin (PubChem CID: 12447); 1,1,1,3,3,3-hexafluoro-2-propanol (PubChem CID:13529); Trifluoroacetic acid (PubChem CID: 6422); Acetone (PubChem CID: 180); Acetic acid (PubChem CID: 176).
1. Introduction

The ability to fabricate structures with controllable nanoscale architectures has enabled the development of much new science and technology (Isaacoff & Brown, 2017), and is of vital importance in the development of new kinds of functional nanomaterials, particularly for biomedical fields (Hubbell & Chikoti, 2012; Mehta, et al., 2017; Haider, et al., 2018; Mitragotri, Burke, & Langer, 2014; Khoshnevisan, et al., 2018; Wen, et al., 2017). Beyond simple monolithic structures, where the composition is the same throughout, a range of more complicated nanostructures can be envisaged. Of these, the most widely explored by far is the core-shell (or core-sheath) structure, which contains separate and different core and shell compartments (Li, et al., 2018; Lu, et al., 2018). These can either both be solid-state phases (i.e., two different solids, one nested inside another), or the core could be a liquid or even a gas (giving a hollow material) (Chang, et al., 2017; Wang, et al., 2018; Mao, et al., 2018; Masoumifard, Guillet-Nicolas, & Kleitz, 2018; Nie, Fu, & Wang, 2010; He, et al., 2017; Eltayeb, Stride, & Edirisinghe, 2013; Lauhon, Gudiksen, Wang, & Lieber, 2002). A simple search in Web of Science using “core shell” as the topic reveals that 32,988 such studies (April 29, 2018) have been published within the last 5 years, equating to 18 publications on the topic per day. There are numerous methods which can be used to generate this simple structure, and some excellent reviews have focused on the preparation and application of core-shell materials (Chaudhuri & Paria, 2012; Qu, Wei, & Guo, 2013).

Electrospinning is a simple and straightforward process which can be used to
create nanofibers from polymer solutions or melts. It has attracted much attention in the research literature because the resultant nanofibers have many advantageous properties, such as large surface areas, high porosity, and a continuous 3-D web structure (Jiang, Uch, Agarwal, & Greiner, 2017; You, et al., 2018; Wang, et al., 2017; Habiba, et al., 2018; Szabó, et al., 2018; Wali, et al., 2018). The process involves the ejection of a polymer solution through a needle, termed the spinneret, towards a collector plate. A high potential difference is applied between the two, resulting in the conversion of the initial solution into 1-D nanofibers. The macrostructure of the spinneret is mirrored in the products of electrospinning, allowing the generation of complex nanostructures if the process is fully optimized. Such structures include core/shell and Janus (side-by-side) architectures, as well as combinations of the two. Electrospun materials are produced in a single step, and thus intricate nanoscale architectures can be fabricated in a straightforward manner through the simultaneous treatment of multiple working fluids in a direct and top-down manner (Zhao, Cao, & Jiang, 2007; Starr, Budi, & Andrew, 2015; Han & Steckl, 2013; Jiang, et al., 2014; Labbaf, Ghanbar, Stride, & Edirisinghe, 2014; Liu, Ni, Chase, & Rabolt, 2013; Yu, Li, Williams, & Zhao, 2018; Lallave, et al., 2007; Jiang, et al., 2018).

The traditional single-fluid blending electrospinning process uses a single solution to generate monolithic fibers, and accounts for over 95% of the publications concerning electrospinning. However, although it is more complex to implement experimentally, the simultaneous treatment of multiple fluids greatly increases the capability of electrospinning to develop new functional nanomaterials. In a
single-fluid electrospinning process, the working fluid must be electrospinnable, which limits the range of systems which can be worked with. It is estimated that only around 100 different polymers can be electrospun into nanofibers, and even then they can only be processed within a narrow window of conditions (solvent, concentration, molecular weight, etc) (Agarwal, Greiner, & Wendorff, 2013). In multiple-fluid electrospinning processes, only one of the working fluids needs to be electrospinnable. Hence, a very wide variety of unspinnable fluids, such as dilute solutions, solvents, suspensions, and emulsions, can be processed into fibers with the aid of a spinnable fluid companion.

Coaxial electrospinning, involving two liquids, one of which is nested inside another, is by far the most widely explored multi-fluid electrospinning process. It can be implemented with both solutions being spinnable, with a spinnable shell and unspinnable core, or with a spinnable core and unspinnable shell (the latter process is often termed “modified coaxial electrospinning”). The more complex triaxial process (using three concentrically nested needles), while less studied, has also been demonstrated to be useful in creating nanofibers with three-layer structures and improved functional performance (Liao, et al., 2018; Zanjani, et al., 2017; Han, Sherman, Filocamo, & Steckl, 2017; Liu, Ni, Chase, & Rabolt, 2013). Modified triaxial electrospinning processes, where one of more of the fluids being processed is not electrospinnable alone, have additionally been investigated (Yang, et al., 2016). A series of situations can be envisaged depending on the electrospinnability of the outer, middle, and inner working fluids. These processes proceed easily when two of the
three working fluids are electrospinnable and compatible with each other, but become challenging when only one of the fluids is electrospinnable. The production of fibers using a spinnable middle fluid combined with unspinnable outer and inner working fluids has been successfully implemented (Yang, et al., 2017), but Yang et al. previously hypothesized that using an electrospinnable core solution to support unspinnable outer and middle working fluids is not possible (Yang, et al., 2016).

In this paper, we developed a modified triaxial electrospinning process involving an electrospinnable core solution, and were able to successfully use this to support both an unspinnable middle polymer solution and an unspinnable outer fluid (comprising a pure solvent). As a result, we could fabricate high-quality core/shell fibers using this process. The concentration of the middle-layer polymer solution was varied to adjust the thickness of the sheath compartments in the fiber products, allowing the drug release profile to be tuned.

2. Materials and methods

2.1. Materials

Ibuprofen (IBU; 2-(4-isobutylphenyl)propanoic acid), was used as a model poorly water-soluble drug, and was procured from the Zheng-Zhou Chuang-Mei Biotechnology Co., Ltd. (Zhengzhou, China). Gliadin (extracted from wheat) was obtained from the Miao-Sheng Biotechnology Co., Ltd. (Shanghai, China). Cellulose acetate (CA, $M_w = 100,000$ Da, the degree of substitution was 2.5) was sourced from Acros (NJ, USA). Colorants (methylene blue and basic fuchsin) and organic solvents (including 1,1,1,3,3,3-hexafluoro-2-propanol [HFIP], trifluoroacetic acid [TFA],...
acetone and acetic acid) were of analytical grade and purchased from the Shanghai Zi-Yi Chem. Co., Ltd. (Shanghai, China). Water was doubly distilled before use.

2.2. Electrospinning equipment and working fluids

The electrospinning apparatus was self-built, and a detachable trilayer concentric spinneret was designed and manufactured in-house. Other components of the equipment included three syringe pumps (two KDS100 and one KDS200, Cole-Parmer, IL, USA), a high-voltage power supply (ZGF60kV/2mA, Wuhan Hua-Tian Co., Ltd., Wuhan, China), and a flat piece of cardboard wrapped with aluminum foil (employed as a collector). The electrospinning processes were observed using a Canon camera (PowerShot SX50HS, Tokyo, Japan).

To prepare the inner working fluid, 4.0 grams of IBU were firstly placed into 100 mL solvent mixture of HFIP and TFA (8:2 v/v). Later, 16 grams of gliadin powders were put into the drug solution, which was stirred using a magnetic stirrer for several hours. The middle fluid was prepared by dissolving a certain amount of CA powders into the mixture of acetone and acetic acid (2:1 v/v). The outer fluid was a plain solvent of acetone and acetic acid (2:1 v/v).

2.3. Morphology

The morphological characteristics of the electrospun nanofibers were assessed with the aid of a Quanta FEG450 scanning electron microscope (SEM; FEI Corporation, Hillsboro, OR, USA). Prior to SEM observation, samples were sputter coated with platinum under a nitrogen atmosphere to render them electrically conductive. Images were recorded at an excitation voltage of 20 kV. The diameter distributions of the
fiber formulations were analyzed using the ImageJ software (National Institutes of Health, Bethesda, MD, USA) to measure diameters at 100 different points in the SEM images.

2.4. Internal structure

The internal structures of the electrospun nanofibers were studied using a transmission electron microscope (TEM; JEM 2100F, JEOL, Tokyo, Japan) under an excitation voltage of 300 kV. The samples were prepared by fixing a lacey carbon-coated copper grid on the collector and spinning directly onto it for a few seconds.

2.5. X-ray diffraction

The physical form of the raw materials (IBU, CA, and gliadin) and the nanofibers were assessed with an X-ray diffractometer (XRD; D/Max-BR, RigaKu, Tokyo, Japan) supplied with Cu Kα radiation at 40 mV and 30 mA. Patterns were collected over the 2θ range 5°–60°.

2.6. Infrared spectrometry

An attenuated total reflectance–Fourier transform infrared (IR) spectrometer (Nicolet-Nexus 670, Nicolet Instrument Corporation, Madison, USA) was employed to study the raw materials and electrospun formulations. Spectra were obtained over the wavenumber range 500–4000 cm⁻¹ at a resolution of 2 cm⁻¹.

2.7. In vitro dissolution tests

Following the Chinese Pharmacopoeia (Method II), an RCZ-8A paddle instrument (Tianjin University Radio Factory, Tianjin, China) was used for in vitro dissolution
Before the tests were performed, the apparatus was set to 50 rpm and 37 °C. One hundred milligrams of the medicated nanofiber sample was placed into 600 mL of phosphate buffered saline (PBS, pH = 7.0, 0.1 mol/L). At predetermined time points, 5 mL aliquots were withdrawn from the release medium, and 5 mL of fresh pre-headed PBS added to the dissolution vessels to maintain a constant volume. The absorption of each sample was determined at $\lambda_{\text{max}} = 264$ nm, with a Lambda 750S UV-vis spectrophotometer (Perkin Elmer, Waltham, MA, USA). The cumulative amount of IBU released was back-calculated on the basis of a predetermined calibration curve. The dissolution tests of each sample were repeated six times, and results are reported as mean ± S.D.

2.8. Statistical analysis

The experimental data are presented as mean ± SD. The results from the in vitro dissolution tests were analyzed using one-way ANOVA. The threshold significance level was set at 0.05. Thus, $p$ (probability) values lower than 0.05 were considered to be statistically significant.

3. Results and discussion

3.1. Modified triaxial electrospinning

A schematic of the modified triaxial electrospinning equipment is shown in Fig. 1. Similar to a traditional single-fluid electrospinning experiment, the system consisted of four parts: the power supply, spinneret, collector, and fluid-driving pumps. Traditional triaxial electrospinning (with all of the working fluids being electrospinnable) treats three fluids simultaneously, and as a result can create three-layer nanofibers (Han, Sherman, Filocamo, & Steckl, 2017; Liu, Ni, Chase, &...
Rabolt, 2013). The modified tri-axial electrospinning approach explored in this work greatly enhances the possibilities of generating novel materials, because there are only a limited number of electrospinnable solutions but a virtually infinite range of unspinnable liquids (Yang, et al., 2016; Yang, et al., 2017).

![A schematic of the modified triaxial electrospinning process, and its potential applications.](image)

Fig. 1 A schematic of the modified triaxial electrospinning process, and its potential applications.

Here, two unspinnable liquids were implemented as the outer and middle working fluids, with only the core solution being electrospinnable. The core comprises a mixture of IBU and gliadin, while the middle fluid is a dilute CA solution, and the outer liquid consists of acetone and acetic acid (2:1 v/v). The core solution is spinnable and forms the fiber filaments, while the CA middle fluid is deposited on this in the form of a thin “nanocoating”. The outer solvent helps to ensure a stable and continuous preparation process.

The detachable triaxial spinneret. A detachable triaxial spinneret was developed to guide the three working fluids (Fig. 1 and Fig. 2). The assembly of the detachable spinneret is exhibited in Fig. 2a. A traditional two-layer concentric metal spinneret was inserted in a 2.4 cm length of tapering polypropylene (PP) tubing (internal diameter and wall thickness: 1.84 - 2.5 mm and 0.3 mm, respectively), with the wider end of the PP tube located at the spinneret exit (as illustrated in Fig. 2b).
The capillaries comprising the concentric metal spinneret had outer diameters and wall thicknesses of 1.84/0.25 and 0.62/0.15 mm.

**Fig. 2** Photographs showing the homemade trilayer concentric spinneret: (a) a traditional two-layer concentric metal spinneret was inserted in a tapering PP tube; (b) the resulting trilayer concentric spinneret (inset: close-up of the exit nozzles); (c) the silica tube and needle used for the transport of the outer working fluid.

A sharp needle (outer diameter / wall thickness: 0.3/0.05 mm) was connected to a length of highly elastic silica tubing (**Fig. 2c**), which was then connected to the syringe containing the outer working fluid. The outer layer working fluid was then carried to the triaxial spinneret simply by inserting the metal needle through the PP tube.

This set-up differs somewhat from more traditional triaxial spinnerets, which usually consist of three concentrically nested metal capillaries. It offers three advantages. First, the detachable spinneret can be easily prepared and washed after use. This can be very challenging with one-piece metal spinnerets, especially when the core needle is very narrow. Second, the PP tube at the exterior is likely to be more efficient in utilizing the electrostatic energy provided by the high-voltage power supply than an entirely metal spinneret, as has been demonstrated with Teflon-coated concentric spinnerets in coaxial electrospinning (**Wang, et al., 2018**). Third, PP is an
excellent electrical insulator, and will have only minimal interactions with the working fluids. In contrast, metal spinnerets are highly conductive, and there is the potential for the liquids being expelled to interact with the spinneret to a certain extent, rather than travelling directly to the collector and forming fibers. The PP surface thus will have less negative effects on the exterior working fluid than a metal surface would during the triaxial electrospinning process.

3.2. Implementation of the modified triaxial electrospinning processes

A photograph of the modified triaxial electrospinning system is illustrated in Fig. 3a. The syringe containing the middle working fluid was directly connected to the spinneret, while the inner fluid and the outer solvent were pumped to the spinneret through the highly elastic silica gel tubes. Electrical energy was transferred to the working fluids through an alligator clip fixed on the metal surface of the spinneret (Fig. 3b).

Four different fiber formulations were prepared (Table 1). The first used a plain solvent of acetone and acetic acid (2:1 v/v) for both the middle and outer fluids: hence, although three fluids were being dispensed, two were the same, and the process equated to modified coaxial electrospinning. As a result, the F1 fibers generated comprise a monolithic composite with IBU dispersed throughout a gliadin matrix.

A typical modified triaxial electrospinning process (exhibiting a Taylor cone followed by a straight fluid jet and then a whipping and bending region) is shown in Fig. 3c for the preparation of the F3 formulation. In the absence of electrical charge, the three working fluids formed a compound droplet (Fig. 3d), with the three layers clearly visible because of the inclusion of methylene blue in the inner fluid (5 × 10^-6
g/mL) and basic fuchsin in the middle solution. When a voltage of 15 kV was applied, a compound Taylor cone was formed (Fig. 3e). During the electrospinning processes, a stable concave surface of the outer solvent within the PP tube can be observed. This is more obviously when $5 \times 10^{-7}$ g/mL methylene blue was added into the outer solvent mixture (Fig. 3f). When a droplet of the outer solvent mixture (ca. 0.007 mg) was added on a PP film and a stainless steel plate (consisting of 1Cr18Ni9, the same as the metal capillaries), the droplet on the metal plate spread out more open than on the PP film (Fig. 3g). This gave a hint that the PP surface exerted smaller drawing force on the working fluids than the stainless steel surface, favorable for the stable and robust electrospinning processes.

**Fig. 3** Images of the modified triaxial electrospinning processes: (a) the triaxial electrospinning system; (b) the connections of the working fluids and power supply to the spinneret; (c) a typical electrospinning process for the preparation of F3; (d) the compound droplet observed for F3 without an electrical charge; (e) the compound F3 Taylor cone which is observed after the application of a voltage (15 kV); (f) the concave surface within the PP tube; and (g) the spreading of an outer solvent droplet on the PP film and a stainless steel plate.
Table 1 Parameters of the preparation of the four types of nanofibers. The outer fluid in all cases comprised a mixture of acetone and acetic acid in a volume ratio of 2:1.

<table>
<thead>
<tr>
<th>No.</th>
<th>Working process</th>
<th>Middle fluid a (wt%)</th>
<th>Fluid flow rate (mL/h)</th>
<th>Structure</th>
<th>Sheath thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Outer</td>
<td>Middle</td>
<td>Inner b</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>Modified coaxial</td>
<td>0% CA</td>
<td>0.3</td>
<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>F2</td>
<td>Modified triaxial</td>
<td>1% CA</td>
<td>0.3</td>
<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>F3</td>
<td>Modified triaxial</td>
<td>3% CA</td>
<td>0.3</td>
<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>F4</td>
<td>Modified triaxial</td>
<td>5% CA</td>
<td>0.3</td>
<td>0.3</td>
<td>2</td>
</tr>
</tbody>
</table>

a The middle solution comprises CA in a mixture of acetone and acetic acid in a volume ratio of 2:1.

b The inner working fluid consisted of 4% (w/v) IBU and 16% (w/v) gliadin in a solvent mixture of HFIP and TFA (8:2 v/v).

3.3. Morphological characteristics and inner structures of the prepared nanofibers

All of the fibers prepared have linear and cylindrical morphologies with smooth surfaces (Fig. 4). No bead-on-a-string or spindle-on-a-string phenomena could be observed. As the concentration of CA in the middle working fluid increased from 0% w/v (F1) to 1% (F2), 3% (F3), and 5% (F4), the diameters of the nanofibers were raised from $0.54 \pm 0.14 \ \mu m$ to $0.66 \pm 0.13 \ \mu m$, $0.72 \pm 0.13 \ \mu m$, and $0.87 \pm 0.16 \ \mu m$, respectively.

Natural polymers such as CA (and others such as zein and ethyl cellulose) are known to easily form a semi-solid substance at the nozzle of the spinneret during electrohydrodynamic processing, even at low concentrations (Li, et al., 2017; Yang, et al., 2018). Thus, in this study the outer solvent was used to prevent any clinging of semi-solid CA to the spinneret, preventing blocking of the needles and ensuring a stable and continuous electrospinning process. The outer solvent should also help the electrical forces to draw the inner and middle fluids evenly during the solvent exhaustion process (Yao, et al., 2018). These two effects of the outer solvent are
combined synergistically to ensure the formation of high-quality nanofibers regardless of their composition (either monolithic F1 systems or core-shell hybrids in the case of F2 to F4).

**Fig. 4** SEM images of the nanofibers prepared in this work: (a) F1; (b) F2; (c) F3; (d) F4.

The internal structures of F1 to F4 were investigated by TEM (**Fig. 5**). F1 displays a gradual decrease in the gray contrast level moving from the center to the two boundaries, as a result of the thicknesses of the fiber declining (**Fig. 5a**). No phase separation can be seen. This indicates that the IBU molecules are highly dispersed throughout the gliadin matrix on the molecular level, without any drug particles forming.

The F2, F3, and F4 fibers, in contrast, had clear core-shell nanostructures (**Fig. 5b-5d**, respectively). The CA coating of F2 is too thin to be seen in the main TEM image (**Fig. 5b**), but a line around 2 nm in thickness can be seen at the fiber exterior in the inset image, indicating successful fabrication of a core/shell structure. The CA
coatings on F3 and F4 are clearer (see Fig. 5c and Fig. 5d), with estimated average thicknesses of about 8 and 15 nm respectively. The CA coating for all of F2 – F4 is evenly spread over the core IBU-gliadin composite. The outer solvent is thought to be key in promoting such uniform coating during electrospinning.

**Fig. 5** TEM images of the nanofibers: (a) F1; (b) F2; (c) F3; and (d) F4.

The average diameters of the nanofibers were determined using SEM images (see Fig. 4) and found to be ca. 660, 720, and 870 nm for F2, F3, and F4 respectively. Thus, the theoretical values of the different compartments’ thickness can be estimated based on the equation for the volume of a cylinder:

\[
\frac{Q_s}{Q_c} = \frac{(R_f^2 - R_s^2) \rho_f L_f \pi}{R_c^2 \rho_c L_f \pi} = \frac{F_c \times C_c}{F_f \times C_f}
\]

where \(Q, R, L, F, \rho\) and \(C\) represent the quantity of liquid dispensed, fiber radius, fiber length, fluid flow rate, density, and solute concentration, respectively; and the subscripts \(s, f,\) and \(c\) refer to the shell, the entire fiber, and the core. The \(L_f\) terms can be cancelled, and \(R_c\) then calculated based on the known values of \(R_f\) and the densities of IBU-gliadin composite (ca. 0.878 g/cm\(^3\)) and CA (ca. 1.3 g/cm\(^3\)). For F2, F3, and F4,
this yields $R_c$ values of 328.18, 354.15, and 423.40 nm, respectively. Thus, the CA
coating on fibers F2, F3, and F4 is estimated to be of 1.82, 5.85, and 11.60 nm in
thickness. The real thicknesses from the TEM images are slightly larger than these
calculated values. This is because, on one hand, the fast evaporation of solvent from
the surface of ejected fluids should make the shell CA coating have a smaller density
than usual. On the other hand, the medicated core nanocomposite might have a larger
density than both the IBU and gliadin. The filling effect of little IBU molecules in the
voids among gliadin molecules due to the favorable secondary interactions should
make the nanocomposites more compact than anticipation.

3.4. Physical form of the components and component compatibility

In the development of medicated nanomaterials of poorly water-soluble drugs, their
amorphous or crystalline state and their compatibility with carriers are vital for the
materials’ functional performances and stability of long term preservation (Borbás,
et al., 2016; Démuth, et al., 2018). The XRD patterns of the raw material powders
(CA, gliadin, and IBU) and the electrospun nanofibers are shown in Fig. 6a. IBU is a
crystalline material, as demonstrated by a series of sharp Bragg reflections in its XRD
pattern. In contrast, the polymer CA and the protein matrix gliadin displayed no
Bragg reflections in their XRD patterns, suggesting that these materials were
amorphous in nature. The fibers have no Bragg reflections in their patterns, instead
exhibiting broad haloes indicating that they all comprise amorphous solid dispersions.
This is commonly observed in electrospun systems, because of the very rapid nature
of the drying process. The amorphous state of IBU in the fibers allows the tailoring of
its release profile, which can be controlled entirely by the polymer matrix in which it is incorporated (rather than also being effected by the lattice enthalpy) (Kamaly, Yameen, Wu, & Farokhzad, 2016; Déimuth, et al., 2017; Jung, et al., 2018; Borbás, et al., 2018).

![Figure 6](image)

**Fig. 6** (a) XRD patterns of the raw materials and nanofibers, and (b) chemical structures of the fiber components and their IR spectra

The chemical structures of the raw materials (CA, gliadin, and IBU), their IR spectra, and the spectra of the nanofibers are given in Fig. 6b. The spectra of IBU shows a characteristic peak at 1713 cm⁻¹, which corresponds to the stretching vibrations of its –C=O groups. However, this peak disappeared from the spectrum of the IBU-gliadin fiber F1. The lack of IR signs of IBU groups can be attributed to several reasons, including its lower concentration in the fibers, the peak broadening
effect of the amorphous form, and also the secondary interactions between gliadin and IBU. These interactions include hydrogen bonds with the protons provided by gliadin molecules, hydrophobic interactions between the benzene rings of IBU and the carbon skeletons of gliadin, and also the electrostatic interactions (Li, et al., 2018; Wang, et al., 2018). It is just because of good compatibility between gliadin and CA in the electrospun products, good compatibility between the working fluids containing gliadin/IBU and CA for coaxial electrospinning, and that new excipients are highly desired in pharmaceutics (Xu, et al., 2017) that gliadin was chosen as a carrier polymer for IBU in the present study.

A comparison of the spectra of F2, F3, and F4 with that of F1 reveals that the core-shell materials had some additional peaks, for instance at 1724, 1236, and 1051 cm$^{-1}$. These peaks are attributable to CA, and the F2 – F4 spectra can be regarded as combinations of the CA and F1 spectra, indicating that the shell CA and the core IBU-gliadin co-exist in F2 to F4 in a hybrid but not molecular composite manner. As the thicknesses of the shell CA coating increases, the intensities of the characteristic peaks of CA increase correspondingly. This observation can be closely related to use of attenuated reflectance IR in these measurements: the penetration depth of the IR probe in this technique is around 200 nm. Thus, the increase in the shell thickness corresponds to a decrease in the amount of the core illuminated.

3.5. In vitro drug release

The in vitro IBU release profiles of the nanofibers are depicted in Fig. 7a. The period of time taken for 100% release to be reached gradually increases as the thicknesses of
the CA coating increased from 0 nm in F1 to 1.82, 5.85, and 11.60 nm for nanofibers F2, F3, and F4. An enlarged image of the IBU release in the first 2 h is shown in Fig. 7b. In the first hour, F1, F2, F3, and F4 release 34.2 ± 4.5%, 8.3 ± 4.6%, 5.4 ± 4.1%, and 2.7 ± 3.1% of the IBU loading respectively. The monolithic F1 material thus shows a significant initial burst release. The core-shell nanohybrids F2 to F4 have minimal initial bursts of release effects regardless of the thicknesses of the CA shell. The CA coatings clearly improve the functional performance of the nanofibers in terms of providing extended release durations and eliminating the initial burst release.

A zero-order equation was used to model the drug release data (Fig. 7c). For F1 to F4, the linear fit equations were $Q_1 = 24.89 + 6.94t$ ($R_1 = 0.8997$), $Q_2 = 10.36 + 3.19t$ ($R_2 = 0.9926$), $Q_3 = 5.34 + 2.41t$ ($R_3 = 0.9915$), and $Q_4 = 6.37 + 1.87t$ ($R_4 = 0.9854$), respectively. These correlation coefficients, in addition to visual inspection of the plots in Fig. 7c demonstrate that while the core-shell hybrids F2 to F4 have close to zero-order release, F1 very clearly does not.

The in vitro drug release data were further analyzed in accordance with the power law expression to elucidate the drug release mechanisms (Peppas, 1985):

$$Q = \frac{M_t}{M_x} = kt^n$$

$$\log Q = \log\left(\frac{M_t}{M_x}\right) = n \log(t) + \log(k)$$

where $M_t$ is the amount of drug released at time $t$, $M_x$ is the total amount of drug in the fibers, $k$ is the rate constant, and $n$ is a release exponent which is indicative of the drug release mechanism. The regression equations for F1 to F4 (Fig. 7d) were $\log Q_1$, 

20
\[ 21 = 1.56 + 0.41 \log t \ (R_1 = 0.9911), \ \log Q_2 = 0.96 + 0.72 \log t \ (R_2 = 0.9945), \ \log Q_3 = \\
0.71 + 0.80 \log t \ (R_3 = 0.9976), \ \text{and} \ \log Q_4 = 0.49 + 0.90 \log t \ (R_4 = 0.9961), \]
respectively. For F1, the exponent \( n \) was 0.41. This is smaller than the critical value of 0.45 (Peppas, 1985), suggesting that IBU was released through a typical Fickian diffusion mechanism. However, all of the core-shell systems F2 to F4 had \( n > 0.45 \), indicating a combination of diffusion and erosion mechanisms. However, the Peppas power equation assumes that the drug is homogeneously distributed in the polymer matrix, which is not the case for F2 - F4. Given that both CA and gliadin are insoluble in water, it must be the case that diffusion of the drug through the fibers is the major barrier to release, but the presence of the core/shell architecture confounded the Peppas analysis.

**Fig. 7** In vitro dissolution test results (a) throughout the experimental duration and (b) for the first 2 h (b). Data are shown as mean ± S.D. from 6 independent experiments. Fits to the IBU release data with (c) zero-order release kinetics and (d) the Peppas power law expression are also shown.

### 3.6. Process–nanostructure–performance relationship
The core-shell nanostructures developed in this work could be effectively designed by controlling the fluids in the modified triaxial electrospinning processes. Their functional performance is controlled by the CA concentration in the middle working fluid. A linear equation can be developed (Fig. 8a) linking the CA coating thickness \( T \) to the CA concentration \( C \): 
\[
T = -0.371 + 2.306 C \quad (R = 0.9947)
\]
It is thus possible to precisely manipulate the coating thickness by varying the CA concentration.

The CA layer thickness in turn has a major effect on the drug release behaviors of the nanohybrids. The time taken for the release percentages to reach 30, 50, and 90% all increase with the coating thicknesses (Fig. 8b). The CA coating effectively acts as a tool to control and tune the drug release rate from the core compartment.

In conventional medicines, a crystalline drug is dispersed in a carrier matrix, and the physical and chemical properties of the latter control the drug release properties \textit{in vivo} (Qi & Craig, 2016). In the development of electrospun nanofibers via traditional monoaxial blend electrospinning, drug molecules are uniformly distributed throughout a filament-forming matrix in the form of an amorphous solid dispersion,
as is the case for F1 in this study (Fig. 9). As a result, a burst release of drug is observed, since the fibers have large surface areas and a significant proportion of the drug is near the surface and so can dissolve into solution rapidly. When the blank CA coating was added to the IBU/gliadin core in the modified triaxial electrospinning process, this modulated the drug release behavior. A thicker CA coating layer (e.g. in F4 cf. F2) could extend the drug release duration to a greater extent (Fig. 9). The F2 - F4 formulations can be regarded as reservoir-type drug delivery systems, with the CA layer controlling the release properties. A process–nanostructure–performance relationship can hence be determined. This relationship could be used to develop new types of functional nanomaterials allowing individualized administration ensuring patients receive safe, effective, and economical treatments.

Fig. 9 The core-shell structures of the fibers and drug distributions within them.

4. Conclusions

A modified triaxial electrospinning process was successfully developed in this work and used to prepare a series of core-shell nanohybrids. The three fluids used for electrospinning comprised a plain solvent (outer fluid), a non-electrospinnable dilute cellulose acetate (CA) solution (middle) and an electrospinnable ibuprofen-gliadin
solution (inner fluid). This led to the formation of ibuprofen/gliadin amorphous solid
dispersions coated with a thin layer of CA. The thickness of the coating could be
precisely tuned through the CA concentration in the middle solution. SEM and TEM
images revealed that the fibers had linear and cylindrical morphologies with a clear
core-shell nanostructure. The IBU in the nanofibers was amorphously distributed
throughout the core matrix, thought to be because it is able to form intermolecular
interactions with gliadin. In vitro dissolution tests showed an initial burst release to
arise from monolithic ibuprofen/gliadin fibers, but this was completely eliminated in
the systems with a CA coating. The coating also extended the release duration, with a
thicker coating layer leading to longer release times. This study hence provides a new
way to develop advanced functional nanomaterials and to control their properties via
process–nanostructure–performance relationships in triaxial electrospinning.

Conflict of interest
The authors have no conflicts of interest to declare.

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