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Influence of the drug distribution in electrospun gliadin fibers on drug-release behavior

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ABSTRACT

Drug distribution within its carrier in a solid dosage form often generates a profound influence on its release profile, particularly when the physicochemical properties of the carrier are exploited to manipulate drug release behavior. In this job, two different types of distributions of a model drug ibuprofen (IBU) within a protein gliadin in their electrospun nanofibers were intentionally created. One was homogeneous distribution in the monolithic fibers fabricated using a modified coaxial process, and the other one was heterogeneous distribution in the core/shell fibers prepared through a traditional coaxial process. SEM observations clearly demonstrated the different distributions of IBU within gliadin in the two kinds of nanofibers although both of them had smooth surfaces and linear morphology. XRD results showed that IBU was amorphously distributed in the monolithic fibers, but that some IBU crystalline lattices presented in the core/shell fibers. FTIR and RM spectra suggested that gliadin had good compatibility with IBU. In vitro dissolution tests verified that the gliadin nanofibers with a heterogeneous drug distribution could provide a better sustained release profile than its counterpart in terms of initial burst release and sustained release time period. Both the fiber formation and drug-controlled release mechanisms are suggested. The present study demonstrated a concept that drug distribution with the medicated nanomaterials can be exploited as a tool to optimize the drug sustained release profile.

1. Introduction

Conventional drug delivery systems (DDSs) potentially exhibit an uncontrollable initial burst of release, which results in the oscillation of the systemic drug concentration, leading to both under- and over-dosing. A much better therapeutic outcome is usually achieved if the drug can be maintained at a constant concentration in the body (Kazemimostaghim et al., 2015; Kim et al., 2016); in this case, the sustained release of the drug from a DDS is often required for optimum therapeutic effects (Paliwal and Palakurthi, 2014). Sustained (or extended) release DDSs free the loaded drug over a prolonged duration, providing a close to constant systemic concentration. By ensuring that this concentration remains within the therapeutic window, they provide high therapeutic efficacy with minimum side effects (Babić et al., 2015). As they reduce the dosage interval required for successful treatment, oral sustained-release DDSs tend to have good patient compliance (Liu and Feng, 2015). For this reason, materials and methods providing sustained drug release profiles have been widely investigated, with a vast array of reports in the literature. A wide range of formulation types and carriers have been explored, such as Eudragit RLPO® nanoparticles prepared by nanoprecipitation (Gandhi et al., 2014), drug loaded in spherical and tubular nanocarriers via layer-by-layer (LbL) encapsulation (Shutava et al., 2014), TC(tetracycline) loaded onto Ag@SiO2-MIP (molecularly imprinted polymers) (AguilarAarcía et al., 2016), gelatin–montmorillonite nanoparticles prepared by desolvation (Sarmah et al., 2015), microparticles prepared by spray-drying method and polymeric nanofibers fabricated using electrospinning (Sóti et al., 2015).

When developing new drug delivery systems, considering both the type of material and the physical properties of the formulation (e.g. its size, structure and shape) is important. The reason is that all these factors can have a significant influence on the release profile of the drug (Peltonen et al., 2010). Selecting a carrier material that is biocompatible is also vital (Kazemimostaghim et al., 2015). To this end, natural polymers, such as gliadin, have attracted much research attention.

Proteins are popular in developing new kinds of nano drug delivery systems for poorly water-soluble drugs (He et al., 2013; Bohr et al., 2014; Babitha et al., 2017). Gliadin is a plant protein with good biocompatibility and biodegradability (Gulfam et al., 2012). Being derived from natural sources, it does not suffer from the presence of monomer

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or initiator residues, which can bring problems to the synthetic materials (Elzoghby et al., 2012). The use of plant protein is also more "environmentally economical" compared with animal-derived proteins (Wan et al., 2015). Gliadin has been studied extensively: for instance, fibers with excellent mechanical property and water stability have been prepared using wet spinning (Reddy and Yang, 2008), and nanoparticles for food-grade colloidal delivery systems have been reported (Joye et al., 2015). The application of gliadin microspheres as carriers for drug/nutrient delivery have been explored further (Wan et al., 2015). Although there exist several reports on the electrospinning of gliadin, in which acid or basic solutions have been explored as working fluids with the help of additives, such as polyhedral oligomeric silsesquioxane (Soares et al., 2011; Wang and Chen, 2012), no report has yet to explore the applications of electrospun gliadin fibers in drug delivery to the best of our knowledge. According to the most recent investigations, these medicated gliadin fibers have the potentials to be developed into commercial tablets or capsules (Démuth et al., 2015; Illangakoon et al., 2015).

Electrospinning has evoked considerable interest as a simple, versatile, and economical method to produce polymer fibers and polymer-based nanocomposites (Rosic et al., 2012; Yu et al., 2017; Yang et al., 2017). The electrospun fibers often have micro- to nano-meter sizes with a series of unique characteristics, such as a large surface area to volume ratio and high porosity (Ji et al., 2013a, 2013b). In virtue of these characteristics, electrospun fibers have been broadly investigated for potential applications in a wide variety of fields. These include, for instance, removing heavy metals from wastewater (El-Sherif et al., 2013; Taha et al., 2012; Wen et al., 2016), tissue engineering (Ji et al., 2013a, 2013b; Wang et al., 2013), photocatalytic degradation (Choi et al., 2015; Pascariu et al., 2016), thermal energy storage (Chen et al., 2013), supercapacitor electrodes (Tolosa et al., 2016), solar cells (Jin et al., 2014), lithium-ion batteries (Han et al., 2016; Zhu et al., 2016), drug delivery (Borbás et al., 2016; Paaver et al., 2015; Seif et al., 2015), and military protective clothing (Gorji et al., 2012).

In terms of biomedical applications, electrospun fibers allow the production of sophisticated nanostructures with control of the fiber alignment, porosity, and size possible. This has led to a range of new polymer-based DDSs (Rasekh et al., 2015; Yang et al., 2016; Yu et al., 2015). However, obtaining high quality medicated fibers using a simple single-fluid electrospinning process remains difficult, because a series of parameters can affect the process. For example, many pharmaceutical polymers have a very narrow electrospinnable concentration window, which depends on both the polymer and solvent characteristics (Pelipenko et al., 2015). In the literature, many medicated fibers have been fabricated from a co-dissolving solution of a guest drug and a host polymer using a single-fluid or coaxial process (Illangakoon et al., 2015; Wang et al., 2015; Xu et al., 2015). In these monolithic products, the drug is typically homogeneously distributed throughout the resultant fibers. Often, the achievement of a sustained-release profile depends mainly on the physicochemical properties of the filament-forming polymer matrix with little considerations about the drug distribution within the nanofibers. However, drug distributions within the DDSs should have a deep influence on its functional performance regardless of traditional dosage forms (Muehlenfeld et al., 2013; Puncochova et al., 2016; Schrank et al., 2015; Vukosavljevic et al., 2016; Windbergs et al., 2010) or advanced nano DDSs (Hu et al., 2016; Huang et al., 2016; Kim et al., 2016; Saeidpour et al., 2017).

In this work, single-fluid electrospinning was first conducted to determine the electrospinnable concentration window of gliadin. Later, both traditional and modified coaxial electrospinning processes were carried out to tailor the within-fiber drug distribution intentionally. Ibuprofen (IBU) was exploited as the model drug because it is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs), it has a large consumption all over the world, and it is a typical poorly water-soluble drug utilized as a model in literature (Li et al., 2013; Zhang et al., 2017; Shin et al., 2017). Thus, it would be a suitable representative for investigating the influence of drug distribution on its release behavior. The fibers were characterized in terms of their morphology, nanostructures, physical forms of components, and drug sustained-release profiles.

2. Materials and methods

2.1. Materials

IBU was obtained from the Hubei Biocause Pharmaceutical Co., Ltd. (Hubei, China). 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP, purity 99.0%), wheat gliadin (extracted from wheat), anhydrous ethanol, trifluoroacetic acid, and trifluoroethanol were provided by the Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Water was double distilled before use.

2.2. Electrospinning

Two syringe pumps (KDS100 and KDS200, Cole–Parmer, Vernon Hills. IL, USA) and a ZGF2000 high-power supply (60 kV/2 mA, Shanghai Sute Corp., Shanghai, China) were used for all electrospinning experiments, together with an in-house coaxial spinneret. Fibers were collected on a flat piece of cardboard covered with Al foil.

2.2.1. Gliadin electrospinnability

Gliadin solutions with concentrations of 5, 10, 15, 20 and 25% (w/v) were prepared by adding appropriate amounts of gliadin powder to HFIP and stirring until homogeneous solutions were produced. The pump used to drive the sheath liquid was switched off for these experiments, and the liquids were pumped through the core channel only. Electrospinning was conducted under ambient conditions (22 °C ± 5 °C, and relative humidity of 58% ± 6%). After some initial optimization, the distance between the tip of the spinneret and the collector, the applied voltage, and the flow rate were fixed at 14 cm, 15 kV, and 2.5 mL/h, respectively.

2.2.2. Coaxial electrospinning

For the successful implementation of a coaxial electrospinning processes, only one of the two working fluids must be electrospinnable (Huang et al., 2006). Although the spinnable sheath fluid is traditionally required, many reports using a spinnable core and unspinnable sheath (commonly called "modified coaxial electrospinning") can be found in the literature (Wang et al., 2015). Specifically, pure solvents can be utilized as sheath fluids to help prevent clogging and ensure the production of high quality fibers (Yu et al., 2012).

In the traditional coaxial processes, an IBU solution in HFIP was used as the core fluid, with a gliadin sheath solution. In the modified process, HFIP formed the sheath fluid, and a mixed gliadin/IBU solution comprised the core. After some optimization, the core-to-sheath fluid flow rate ratios were fixed at 0.5:2.5 mL/h and 2.5:0.5 mL/h in the traditional and modified coaxial processes, respectively. The applied voltage was fixed at 15 kV, and the fibers were collected on aluminum foil at a distance of 14 cm from the tip of the spinneret (see Table 1). The compositions of the working fluids for the coaxial processes are also listed in Table 1.

2.3. Characterization

2.3.1. Morphology

The surface and cross-section morphology of the electrospun products were assessed using a Quanta 450 FEG field emission scanning electron microscope (FESEM; FEI Inc., Hillsboro, OR, USA). The samples were gold sputter-coated under a nitrogen atmosphere before examination. Images were then recorded at an excitation voltage of 20 kV. The samples of cross-sections were prepared by immersing a strip of non-woven mats into the liquid nitrogen for over 20 min, followed by