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Controlled engineering of highly aligned fibrous dosage form matrices for controlled release

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ABSTRACT

In this study, complex drug-cellulose acetate (CA) composite films were designed and fabricated possessing pre-determined grid spacing for inter-connected fibrous films. Ibuprofen (IBU) was selected as the active ingredient and grid spacing was varied between 300 and 500 μm (fiber diameter ~ 35 μm) for various geometries. Process parameter impact on fiber morphology and deposition was investigated. FTIR confirmed IBU encapsulation and XRD analysis indicated the drug was dispersed (amorphous) in films. Inter-connected grid void geometry was shown to impact water contact behavior, and drug release mechanism was shown to be Fickian diffusion. Furthermore, drug release rate depended on geometry of engineered structures. The findings suggest a spatial design approach for modulated drug release from bespoke drug delivery dosage forms.

1. Introduction

Oral drug dosage forms contribute towards a large portion of therapeutic delivery. Most oral tablets are manufactured by compressing drug and excipient materials together [1]. While this may be ideal for bulk preparation, this is not suitable for bespoke formulation preparation [2]. From an engineering perspective, micron-scale accuracy, regulation, complex structure engineering and spatial resolution provide opportunities to address personalized delivery [3].

Electrohydrodynamic printing (EHDP) is an emerging controlled deposition method which operates on similar principles to electrospinning. The transition between the two processes is achieved by reducing the distance between nozzle and collector [4,5]. Well-aligned electrospun fibers have also been collected using centrifugal methods [6], contributing towards greater fiber manufacturing precision albeit limited to equally spaced interconnected voids.

Although 3D fibrous films comprising stacked and aligned fibers have been generated, in this study, inter-connected grid void spacing (and geometry) was varied for standalone films; giving rise to variable dosage form designs using identical excipients. The effect of process parameters on deposition and end structures was evaluated. The impact of geometry on drug release behavior was evaluated.

2. Materials and methods

2.1. Materials

Cellulose acetate (CA, $M_w = 3 \times 10^4$g/mol) and model drug ibuprofen (IBU, ≥98%) were obtained from Sigma-Aldrich, USA. Acetone and N, N-Dimethylformamide (DMF) were purchased from Sinopharm Chemical Reagent, China. Phosphate Buffer Saline (PBS) tablets were supplied by SangonBiotech, China. Deionized water was produced using a Millipore Milli-Q, USA. All reagents were of analytic grade. CA powder (22%w/w) was dissolved in a co-solvent system comprising acetone and DMF (1:1, v/v) under mechanical stirring (VELP-ARE, Italy) for 12 h to ensure complete dissolution. IBU (5%w/w of CA) was dissolved tin the resulting solution by mechanical stirring (4 h), according to an earlier protocol [7].

2.2. EHD printing

The EHDP set-up is shown in Fig. 1a, and consists of stainless steel nozzle (outer/inner diameters = 0.9/0.7 mm, respectively), syringe pump (KDS100, USA), high voltage power supply (Glassman-FC, USA) and a controllable X-Y-Z movement stage.

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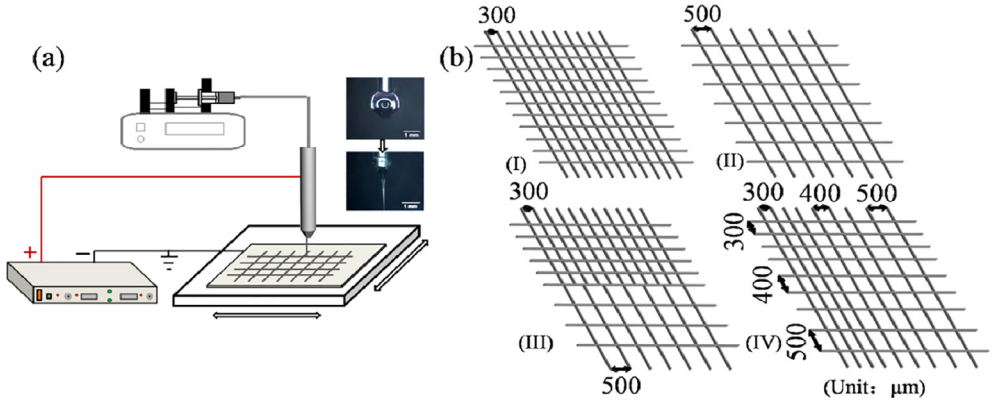

Fig. 1. Illustration showing (a) EHDP set-up; (b) pre-determined print designs.

Following infusion into the stainless steel nozzle, a stable and continuous jet-mode was achieved at optimum conditions (flow rate = 0.3 ml/h, voltage = 2 kV, collector distance and speed = 2 mm and 100 mm/s, respectively) (Fig. 1a). Precise movement of the X-Y-Z stage was afforded using PC software (Adtech, China), and various geometries (possessing 20 layers, overprints) were prepared (Fig. 1b).

2.3. Characterization

Printed fiber diameter was measured using ImageJ software (National Institute of Health, USA) directly from optical micrographs (OM, Phenix-BMC503, China). Mean diameter was determined by measuring 30 randomly selected fibers obtained at each parameter. Film morphology was investigated using scanning electron microscopy (SEM, ProX-Phenom, Netherlands) and scanned at an accelerating voltage of 15 kV. Prior to this samples were sputter-coated with gold for 90 s. Film composition was analysed using Fourier Transform infrared spectroscopy (FTIR, IR-Affinity-1, Shimadzu, Japan). Spectra were recorded between 400 and 4800 cm^{-1} at a resolution of 4 cm^{-1}. XRD patterns of pure IBU, CA and composite films were obtained using X-ray crystal diffractometer (Gemini-AOhra, UK). Water contact angle on regions of patterned films was measured using an interface tension meter (SL200KB, CO. Ltd., USA).

2.4. In vitro drug release

Phosphate buffered saline (PBS, pH = 7.4) was used for release studies. Each test sample comprised pre-weighted film (1×1 cm^2, 20 layers) and 10 ml PBS in a HZ-8801 K thermostatic oscillator (Taicang, China) at 37 ± 0.5 °C for 6 h. Characteristic UV

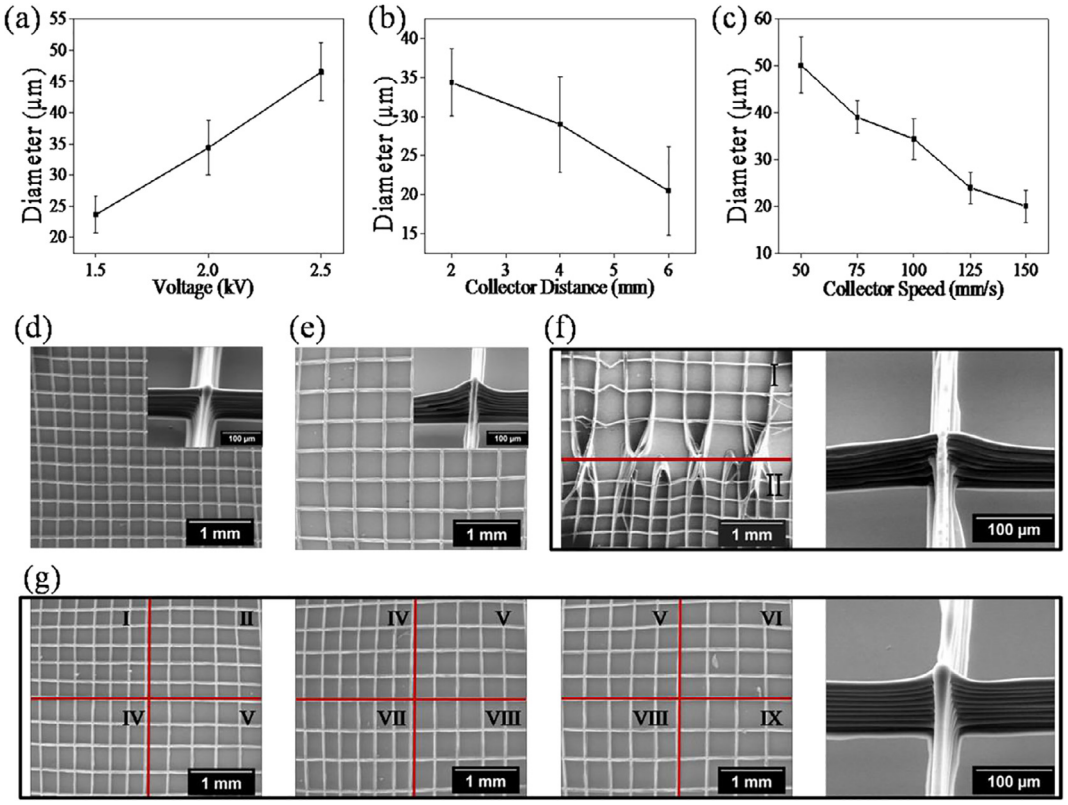

Fig. 2. Effect of EHDP parameters on fiber diameter: (a) applied voltage; (b) collector distance; (c) collector speed. Electron micrographs of IBU-CA films with various grid geometries: (d) F_{300}; (e) F_{500}; (f) $F_{300-500}$; (g) $F_{300-400-500}$.