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Development of random and ordered composite fiber hybrid technologies for controlled release functions

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HIGHLIGHTS

- One-step simultaneous engineering of random and ordered composite fibers into one system is demonstrated.
- Complex constructs hosting bioactive elements were engineered using 3D printing and electrospinning.
- Both sustained and rapid release is shown from hybrid systems.
- Dissolution rate, hydrophilicity, mechanical properties and external auxiliary magnetic field modulate drug release.
- Hybrid composite fiber systems demonstrated good biocompatibility and anti-bacterial function.

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ABSTRACT

Fibrous technologies (such as membranes, films, patches and filters) and their enabling engineering platforms have gained considerable interest over the last decade. In this study, novel fibrous constructs from a unique engineering platform were developed based on hybrid electrohydrodynamic (EHD) technology; incorporating functional and bioactive materials within random and aligned fibrous formulation geometries. Complex constructs were engineered using 3D printing (polycaprolactone, PCL, for sustained delivery) and electrospinning (polyvinylpyrrolidone, PVP, for rapid release) in an intercalating material layer-by-layer format using a side-by-side technological approach. Here, structure generation proceeded with deposition of ordered PCL fibers enabling well-defined void size and overall dimension, after which randomly spun PVP fibers formed a construct overcoat (as a membrane). Differences between polymer dissolution rate, hydrophilicity, mechanical properties and functional material hosting (and linked external auxiliary magnetic field trigger) provided opportunities to modulate antibiotic drug (tetracycline hydrochloride, TE-HCl) release. In vitro cell studies using human umbilical vein blood vessel cell line demonstrated device biocompatibility and Escherichia Coli (E. coli) was selected to demonstrate anti-bacterial function. Overall, a new hybrid engineering platform to prepare customizable and exciting multi-faceted drug release constructs is elucidated.

1. Introduction

Strategies and methods to modulate drug release behaviour have evolved significantly over the last few decades; from polymeric system to nano-functionalized pharmaceutics [1,2]. Specifically, a variety of systems have been developed to meet the needs of selected active release behaviour (i.e. immediate, pulsatile, delayed, sustained and biphasic releases [3–5]). Amongst these, sustained drug release systems are currently the most explored; with recent efforts focusing on enhancing drug concentration in blood (within therapeutic window) or target tissues therefore displaying prolonged activity [6,7]. While this provides a sustained active release period, rapid release features are often neglected, which becomes problematic if an active needs to be delivered immediately, providing a quick biological response.

Electrospinning (ES) has great potential in generating fibrous materials for drug delivery applications [8]. Using such filamentous

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structure, a host of drugs such as antibiotics and anticancer agents can be delivered [9]. Electrohydrodynamic (EHD) continuous jetting is based on digitally-controlled deposition of materials (often layer by layer) to create well-ordered freeform geometries, unlike random structures obtained when using ES [10]. EHD continuous jetting methods currently deployed in the engineering of pharmaceuticals permit simple, accurate, cheap, structured and tailored developments of drug delivery dosage forms.

Polyvinylpyrrolidone (PVP) is a synthetic, biocompatible and non-toxic polymer which has been widely used as a pharmaceutical excipient (for dosage form development) [11,12]. Polycaprolactone (PCL) is a hydrophobic polymer with desirable physicochemical properties, which has been used in diffusion-controlled delivery systems [13].

Fe_3O_4 nanoparticles (NPs) are rapidly emerging as opportunistic healthcare materials [14]. Recent explorations have shown their potential in cell separation, diagnostics and advanced therapy regimes [15]. In addition, co-encapsulation of Fe_3O_4 NPs with an active embedded into a polymeric matrix system affords trigger based drug release mechanisms (using an external auxiliary magnetic field (AMF)). In this instance, the functionality of the external trigger is dependent on NP loading within the formulation, strength of the applied field and geometrical features of the drug delivery system [16]. This approach is valuable since it has shown to improve pharmacokinetics of retarded active release systems as and when needed [17].

In recent times multi-step or two tiered drug release systems have gained popularity and these have focused on external triggers, materials and engineering of new and complex structures [18,19]. However, methods to design and develop such drug delivery systems (combining both rapid and sustained mechanisms) remain limited. To accommodate this several approaches have been undertaken including controlled layering or core -shell structures [20]. Conventional methods (e.g. wet granulation) have also been used to encapsulate or host multiple actives.

In this study, EHD continuous jetting and ES techniques are arranged in a side-by-side hybrid-engineering platform to fabricate mechanically and biologically improved constructs for drug delivery applications through a layer-by-layer materials approach. A non-core shelled delivery system is engineered. In addition to space, process stages and time benefits the developed system enables greater loading capacity, simultaneous entrapment of therapies where formulations are non-compatible, ease of operation [9] and the ability to alter specific components as required (specific drug and tailored drug loading capability) Multi-layered and well-aligned PCL fibers were used as the construct base (mechanically enforcing) and electrospun PVP membranes provided an overcoat layer. The well-established difference in dissolution and degradation rate between these polymers provided a two-tier active (TE-HCl) release mechanism. TE-HCl, which belongs to a group of broad-spectrum antibiotics and is commonly used to treat and control bacterial skin infections, was used as the model active compound [21–24].

2. Materials and methods

2.1. Materials

Polyvinyl pyrrolidone (PVP, $M_w = 1.3 \times 10^6$ g/mol) and Poly ε-caprolactone (PCL, mean $M_w = 8 \times 10^4$ g/mol) were purchased from Sigma-Aldrich, St Louis, USA. Tetracycline hydrochloride (TE-HCl) was purchased from Amersco, USA. Fe_3O_4 NPs (mean particle diameter ~ 20 nm) were purchased from HWRK Chem, China. Glacial acetic acid, absolute ethyl alcohol and phosphate buffer saline (PBS, pH 7.4) were supplied by Sinopharm Chemical Reagent, China. All chemicals and reagents were analytical grade.

2.2. Solution and suspension preparation

For EHD continuous jetting, PCL polymer solution (20% w/w) was prepared using acetic acid. To ensure complete dissolution, initial mixtures were mechanically stirred for 5 h at the ambient temperature (24 °C). Fe_3O_4 NPs were incorporated into selected PCL solutions and a second suspension was prepared which hosted both Fe_3O_4 NPs (0.5% w/w, of the final composition) and the model active TE-HCl (0.5% w/w, of the final composition). The drug suspension was stirred for 6 h to ensure complete dissolution. Both mixtures were placed in mild bath sonication (2 h), prior to EHD engineering, which resulted in near homogenous suspensions. TE-HCl release from constructs were evaluated with and without external stimuli (AMF).

A PVP/TE-HCl solution was prepared by adding both drug and polymer to ethyl alcohol at 15 and 0.5% w/w, respectively, (of the overall formulation) followed by mechanical stirring (1 h). Upon complete dissolution, a known quantity of the solution was magnetized through addition of Fe_3O_4 NPs (0.5% w/w of the final composition). The mixture was dispersed for 2 h by mild bath sonication to ensure a homogenous system.

2.3. Complex construct engineering

A schematic diagram showing the hybrid EHD system (EHD continuous jetting and ES) is shown in Fig. 1. The hybrid system, providing a patterned PCL fiber platform with randomly orientated PVP fibrous mesh overcoat, comprised an X-Y-Z motion stage controlled using mechatronics. This enabled precise programmable movement during construct engineering. Two high-voltage power supplies capable of generating ~30 kV (Glassman high voltage Inc. series FC, USA) were individually connected to EHD continuous jetting and ES nozzles, both of which possessed an inner diameter of 0.5 mm. PCL and PVP/TE-HCl formulations were loaded separately into 5 ml syringes and were subsequently mounted into the precision syringe pumps (KD Scientific KDS100, USA). A conductive glass collector was mounted onto the programmable X-Y-Z motion stage as the ground electrode. The applied voltage for EHD continuous jetting was set in the range 2.0–2.2 kV, and the applied voltage for ES was maintained at 9.0 kV. The deposition distance were set at 5 mm and 6 cm, for EHD continuous jetting and ES, respectively. To maintain a stable cone-jet for the process, solution feed rate for EHD continuous jetting and ES were selected as 0.2 and 0.8 ml/h, respectively.

Fabrication proceeded by patterning of a 3D PCL based scaffold (first) with precise designated filamentous layers (20 layer overprints). The next step involved the deposition of a PVP membrane comprising randomly orientated fibers *via* ES for 2 min. All experiments were performed at the ambient temperature (25 °C) and relative humidity (40–60%).

2.4. Material characterization

Construct surface morphology was characterized using optical (Phenix BMC503-ICCF, China) and scanning electron microscopy (SEM, FEI Quanta 650, Netherland). For SEM analysis, samples were applied with a thin layer of platinum for 60 s using a sputter coater (108auto, Cressington Scientific Instruments Ltd., UK) at a current intensity of 25 mA to prevent sample charging.

All data was exported for analysis and graphs were plotted using Origin software (OriginLab, USA). Fiber diameters were quantified using a statistical distribution that involved 50 fibers (50 layer overprints) for each experimental condition. Error bars were plotted to represent the mean ± standard deviation.

Construct hydrophobicity was assessed using an optical contact angle & interface tension meter (SL2000KB, Kino Industry Co., Ltd,