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Hollow polycaprolactone composite fibers for controlled magnetic responsive antifungal drug release

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ABSTRACT

Hollow magnetic fibers for trigger based drug release were synthesized using one-step co-axial electrospinning (COX-ES). This was achieved by encapsulating the antifungal active 'ketoconazole' (KCZ) and iron oxide (Fe_3O_4) nanoparticles (NPs) in composite form within the core shell polymeric matrix material (polycaprolactone, PCL) during the COX-ES process. Dimethyl silicone oil was used as the inner core (liquid) of co-flowing solutions, which subsequently perfused out of the two-phase electrospun microstructures to form hollow fibers. Resulting drug-loaded magnetic hollow fibers were characterized using optical microscopy, scanning electron microscopy and Fourier Transform Infra-Red. The tensile strength and magnetization properties of composite fibers were also assessed. KCZ drug concentration in electrospinning solutions strongly influenced resulting fiber morphology, drug loading efficiency and release. Expedited drug release during a slow-sustained phase was demonstrated through the application of an auxiliary magnetic field. Variations in tensile strength (~1.3–6.3 MPa) were due to composite fiber components compromising polymer chain integrity. *In-vitro* cell studies (using human cervical carcinoma cell lines) demonstrated fiber biocompatibility. The present study demonstrates the potential application of magnetic hollow fibers for controlled treatment of fungal infections and antimicrobial indications.

1. Introduction

Electrospinning (ES) is a cost-effective and versatile technique for fabricating fibers in the nanometer and micrometer range using a variety of materials (*i.e.* polymers, metals, ceramics and their composites) [1,2]. Several advantages drive the engineering selection of ES over conventional dry or wet spinning methods, such as ease of use, facile control on fiber diameter and potential to mass produce (*e.g.* up-scale) [3,4]. Fibers possess high surface area to volume ratios, and when prepared through ES and its peripheral technologies; fiber surface is tunable and its controlled structural alignment can yield enhanced mechanical properties. Numerous applications of electrospun fibers have been demonstrated, specifically for drug delivery, tissue engineering, environmental filters, sensors and medicated dressings [5–7].

Two main methods exist for the fabrication of hollow fibers; template synthesis and coaxial electrospinning (COX-ES). The COX-ES process (the use of two or more concentrically aligned nozzles) enables the fabrication of complex micro- and nano-fibers [8]. During this process at least two different solutions (variations in miscibility, viscosity and phase) are spun simultaneously to produce core-shell morphologies. The process is favorable where encapsulation and layering are crucial for either functional application or to protect the engulfed material from environmental damage. Specifically for fibers, a host of materials (*e.g.* powders, nanoparticle suspensions, catalysts, proteins (including Type I collagen), gelatin, liquid crystals and monomers) have been encapsulated within a polymeric core-shell matrix structure [9–11]. Furthermore, COX-ES has also been utilized to enhance surface properties of existing polymeric systems to deliver more suitable interfacial outcomes. For example, the surface wettability of nanofibers has been modified through COX-ES to increase cellular interaction for biological scaffolds. However applications also extend into more divergent fields such as microfluidics, photonics and even energy storage [12,13]. The ability to generate complex structures in one-step and as an on-demand process using the

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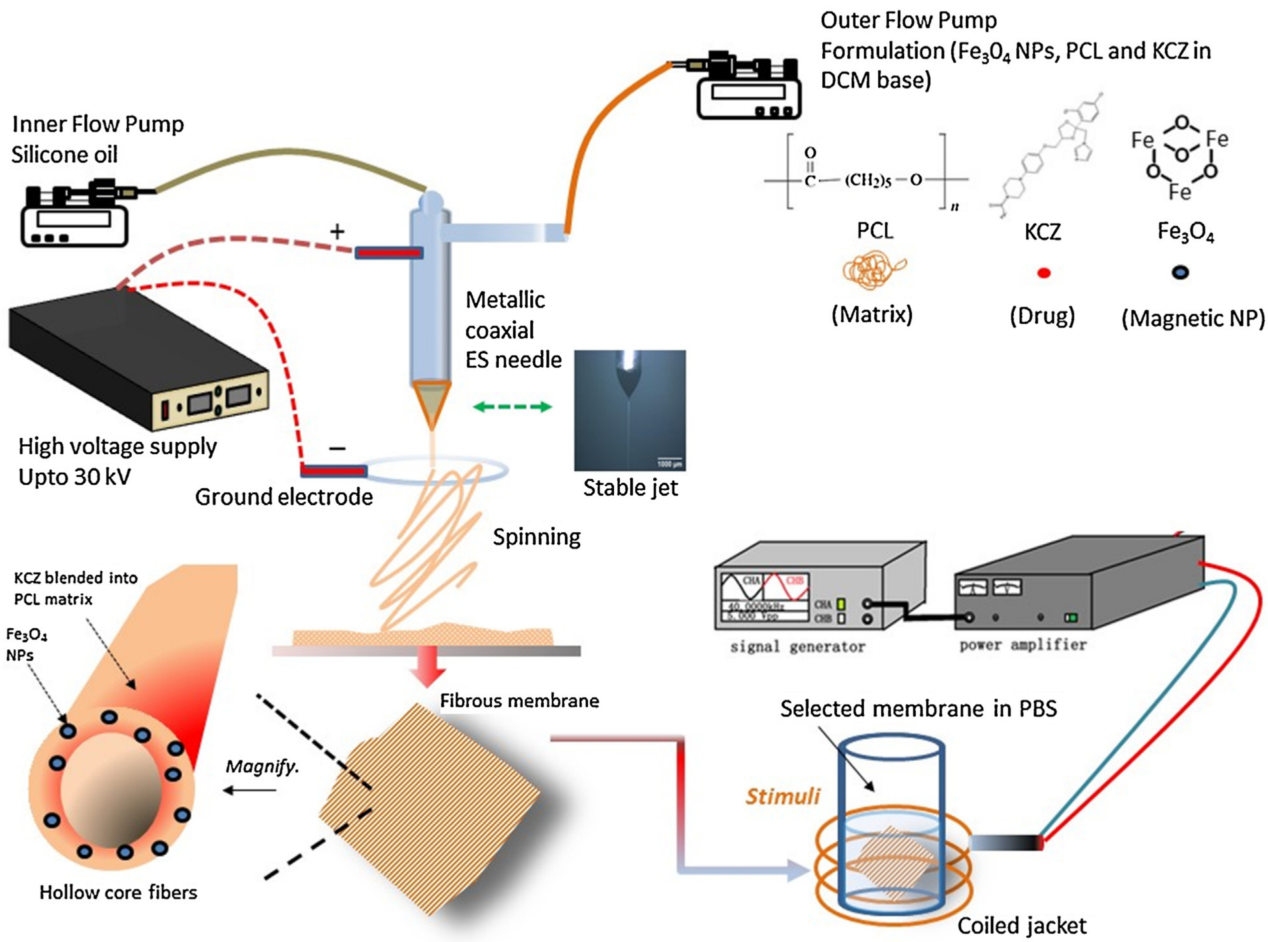

Fig. 1. Schematic diagram of the co-axial electrospinning set-up for KCZ loaded magnetic hollow fibers.

COX-ES format is also applicable for advanced functional materials, therefore with the potential to deliver advanced multi-functional technologies (*e.g.* healthcare engineering).

Nano-magnets are emerging materials with promising potential in all fields of engineering. Specific features (*e.g.* supermagnetic behavior) of Fe_3O_4 nanoparticles (NP's) have been exploited in photonics, electricity and sensitivity [14,15]. However, Fe_3O_4 NPs agglomerate due to dipole–dipole interactions [16]. This effect can be partially eliminated by encapsulating Fe_3O_4 NPs into an organic material. Once such strategy has involved the use of polymeric fibers as a matrix material [17]. Once embedded into the fiber matrix, Fe_3O_4 NPs retain their intrinsic properties; some of which have been utilized to reduce ES process instability (therefore increasing uniform fiber production) [18,19] for a variety of applications such as tissue engineering, composite reinforcement and data storage [20]. More recent uses of such Fe_3O_4 NPs composite materials include specific cell separation, diagnostics and advanced therapy regimes, such as trigger based drug release using an external magnetic field [21–23].

Ketoconazole (KCZ) is an active drug agent and is classed as a broad spectrum antifungal. KCZ has been widely utilized to treat superficial and internal fungal indications including; tinea corporis, onychomycosis, colpitis and psoriasis [24–27]. KCZ has been formulated into several dosage forms, although its accumulation and safety *in-vivo* remains contentious. Several side effects have been observed and relate directly to the uncontrolled dosing of KCZ in clinical application [28,29]. In this regard sustained release of KCZ (systematic) is highly desirable which will reduce unwanted side effects. In contrast, the concentration of KCZ must also reach the therapeutic window to elicit the desired response, which otherwise would render the regimen as a poor therapy. PCL is a biocompatible, bioresorbable and low-cost synthetic polymer. It is an FDA approved polymer and has been clinically used as a sustained drug release delivery matrix and suture material since the 1980s. However, the hydrophobicity and mechanical properties of solid PCL have hindered its progression within this remit [30,31].

Recent studies [32,33] have shown magnetic hollow drug loaded fibers to possess both magnetism and mechanical properties, ideally suited for controlled drug delivery of actives such as KCZ. It is envisaged that drug loading (*via* COX-ES) and release from PCL fibers will reduce side effects due to sustained matrix type delivery. In addition the utilization of hollow fibers increases the surface area [34,35] for interaction (as opposed to solid matrix type) and thus facilitates release from two faces of tubular constructs which possess thinner walls (by same volume when compared to non-hollow structures). In this study, hollow fibrous PCL mats containing KCZ and Fe_3O_4 NPs were prepared (*via* COX-ES), analysed and investigated for their external field triggered controlled release and *in-vitro* suitability.

2. Experimental

2.1. Materials

Poly (ε-caprolactone) (PCL, $M_w = 8 \times 10^4$ g/mol) was purchased from Sigma-Aldrich, St Louis, USA. Fe_3O_4 NPs (mean particle size of ~20 nm) were purchased from HWRK Chem, China. Ketoconazole (KCZ, 99.7%) was provided by Zhongtian Instrument Chemical