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Axon mimicking hydrophilic hollow polycaprolactone microfibres for diffusion magnetic resonance imaging

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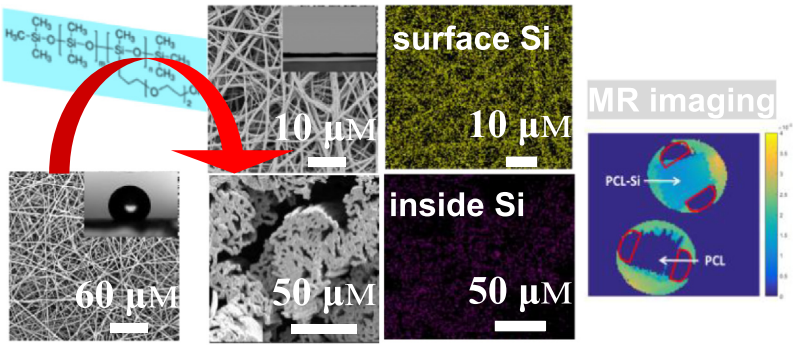
HIGHLIGHTS

- An inclusion of polysiloxane-based surfactant (PSi) into PCL solution improved the hydrophilicity of electrospun PCL fibres.
- Electrospun PCL-PSi fibres remained hydrophilic over a time period of up to 12 months.
- EDX analysis confirmed Si distribution on fibre surface and cross-section, which is responsible for the wettability of PCL-PSi fibres.
- Hollow PCL-PSi microfibres were only produced via co-electrospinning of a miscible combination of shell and core solutions.
- Phantoms were constructed from hollow PCL and PCL-PSi fibres, and water was detected by dMRI only from the latter.

GRAPHICAL ABSTRACT



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ABSTRACT

Highly hydrophilic hollow polycaprolactone (PCL) microfibres were developed as building elements to create tissue-mimicking test objects (phantoms) for validation of diffusion magnetic resonance imaging (MRI). These microfibres were fabricated by the co-electrospinning of PCL-polysiloxane-based surfactant (PSi) mixture as shell and polyethylene oxide as core. The addition of PSi had a significant effect on the size of resultant electrospun fibres and the formation of hollow microfibres. The presence of PSi in both co-electrospun PCL microfibre surface and cross-section, revealed by X-ray energy dispersive spectroscopy (EDX), enabled water to wet these fibres completely (i.e., zero contact angle) and remained active for up to 12 months after immersing in water. PCL and PCL-PSi fibres with uniaxial orientation were constructed into water-filled phantoms. MR measurement revealed that water molecules diffuse anisotropically in the PCL-PSi phantom. Co-electrospun hollow PCL-PSi microfibres have desirable hydrophilic properties for the construction of a new generation of tissue-mimicking dMRI phantoms.

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1. Introduction

The mobility of water molecules within tissue depends on the microstructure of the tissue. Brain white matter and cardiac muscle are highly anisotropic fibrous tissues with diameters ranging from 0.1–20 μm [1–5]. In both water diffuses more freely along the dominant fibre orientation and is hindered to different degrees in other directions, leading to diffusion anisotropy [5–8]. In brain grey matter, which has random microstructures consisting of neuronal cell bodies, neuropil, glial cells, and capillaries, the mobility of water molecules is measurably similar in all directions and is termed isotropic diffusion [9,10]. The anisotropy of water diffusion in tissue and the sensitivity of water diffusion to the underlying tissue microstructure form the basis for exploiting diffusion magnetic resonance imaging (dMRI) as a non-invasive tool to infer the microstructures of various tissues including brain and heart.

There is an emerging area of research on the development of polymeric materials composed of core-shell structured microfibres that can mimic the microstructure of brain and cardiac fibrous tissues for application in tissue engineering and drug delivery [11–14] and for brain tumour models [15]. We were the first to use co-electrospun core-shell structured microfibres to construct brain white matter, grey matter and cardiac tissue mimicking phantoms for the calibration and validation of dMRI [5,16,17]; this has now been extended to tumour cell-mimicking phantom composed of hollow microspheres [18]. More recently, hollow polypropylene (PP) filaments generated by melt spinning have been also used to mimic white matter axons and to construct an MR brain phantom [19].

Among polymers for biomedical applications, poly(ε-caprolactone) (PCL) is most commonly used for electrospinning for the fabrication of nanofibres as scaffolds, drug delivery systems and medical devices [20,21] because it has low toxicity, relatively good mechanical properties and can be processed easily, compared with other biodegradable polymers, such as poly(lactide) (PLA), poly(glycolic acid) (PGA), and poly(lactide-*co*-glycolide) (PLGA) [22,23]. For instance, in our previously developed brain and cardiac phantoms and Rao's tumour model, PCL was used as the shell material in the co-electrospinning process [5,15–17,24].

However, PCL is intrinsically hydrophobic, resulting in poor wettability, lack of cell adhesion and uncontrolled biological interactions with the material. There has therefore been long-standing interest in the development of hydrophilic electrospun PCL fibres. Both physical (blending/coating with hydrophilic polymers [25]) and chemical methods (plasma treatment [26–30], sodium hydroxide treatment [31,32], grafting or their combination [33], and block copolymers containing PCL [26,30,34]) have been employed to improve the wettability of PCL fibres. Among these methods, physical blending of PCL with hydrophilic polymers appears to be the most straightforward. In this work, we investigate the feasibility of using poly[dimethylsiloxane-*co*-[3-(2-(2-hydroxyethoxy)ethoxy) propyl] methylsiloxane] (abbreviated as PSi, Fig. 1), a non-ionic surfactant composed of polyoxyethlyene chains attached to siloxane chains, to enhance the hydrophilicity of PCL fibres.

2. Materials and methods

2.1. Materials

Polycaprolactone (PCL, number averaged molecular weight Mn = 70 k–90 k), and Polyethylene oxide (PEO, viscosity average molecular weight Mv = 900 k) were obtained from Sigma-Aldrich (Dorset, UK). The additive PSi, was also obtained from Sigma-Aldrich (Cat No. 480320). According to the supplier, PSi has a viscosity of 75 cSt, however the exact values of *m* and *n* in Fig. 1 are not provided. The solvents chloroform ($CHCl_3$) and *N*,*N* dimethyl-formamide (DMF) were also purchased from Sigma Aldrich (Dorset, UK). Deionized water or chloroform was used to dissolve the PEO.

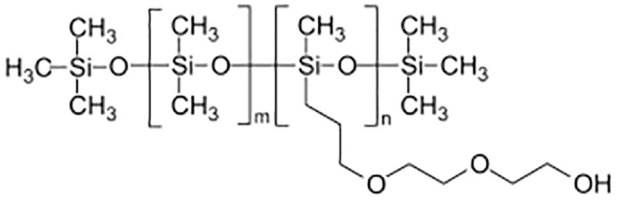

Fig. 1. Molecular structure of PSi, a siloxane-based surfactant.

2.2. Electrospinning of PCL-PSi fibres

PCL microfibres were fabricated using a setup schematically shown in our previous work [35].

The solutions and process parameters for electrospinning/co-electrospinning are given in Table 1. In brief, a mixed solvent of $CHCl_3$ and DMF (w/w = 8/2) was used to dissolve PCL at a polymer concentration of 9 wt%. In order to investigate the morphology size and hydrophilicity enhancement of PSi on PCL fibres, 12 different compositions of PCL polymer and PSi surfactant mixtures (from 100/0 to 78/22, w/w PCL/PSi) were prepared. A high-voltage power supply was employed to tune the applied voltage between 0 and 30 kV. A 10 mL plastic syringe with a stainless-steel needle (inner diameter 1.19 mm) mounted on a syringe pump was used to feed PCL solution to the needle tip with a controllable feed rate. The fabricated fibres were then collected on a grounded collector. All experiments were conducted using 2 mL/h flow rate, 15 cm working distance (between the spinneret and fibre collector), 10 kV applied voltage for ~10 min in a fume cupboard under ambient conditions.

2.3. Co-electrospinning of shell-core PCL-PSi -PEO microfibres

In a typical procedure for co-electrospinning, a mixing solution of 9 wt% PCL in $CHCl_3$/DMF with 1 wt% PSi was used as the shell solution and PEO in deionized water or chloroform acted as the core solution. The co-electrospinning was carried out on a lab-scale electrospinning setup described in our previous publication [35]. All experiments were conducted in a fume cupboard at ambient conditions. To investigate the effect of core flow rate on the morphology of co-electrospun fibres, the shell flow rate was set at 3 mL/h. For PEO/water and PEO/$CHCl_3$ core solution, the flow rate was varied from 0.25 to 4.0 mL/h and from 0.25 to 1 mL/h, respectively. Other co-ES parameters were as follows (unless stated otherwise): applied voltage of 16 kV, working distance of 16 cm. The resultant fibres were then collected on a grounded static

Table 1
Solutions and process parameters used for electrospinning and co-electrospinning.

	Solution	Process parameters
Electrospinning	9 wt% PCL in $CHCl_3$ + DMF (8/2 w/w) with 0–22 wt% PSi	10 kV applied voltage 2 mL/h flow rate 15 cm working distance
Co-electrospinning	Shell 9 wt% PCL in $CHCl_3$ + DMF (8/2 w/w) with 1 wt% or 0.4 wt% PSi	16 kV applied voltage 3 mL/h shell flow rate 16 cm working distance
	Core 4 wt% PEO in distilled water 2.5 wt% PEO in $CHCl_3$	0.25 to 4.0 mL/h core flow rate 0.25 to 1 mL/h core flow rate