International Journal of Pharmaceutics 505 (2016) 133–138

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Controlled release of a hydrophilic drug from coaxially electrospun polycaprolactone nanofibers

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ARTICLE INFO

Article history:
Received 12 February 2016
Received in revised form 17 March 2016
Accepted 19 March 2016
Available online 21 March 2016

Keywords:
Modified coaxial electrospinning
Controlled drug release
Core-shell fibers
Polycaprolactone
Ampicillin
Zero order drug release

ABSTRACT

A recent approach for controlled release of drugs is the production of core-shell fibers via modified coaxial electrospinning where a shell solution which is not fully electrospinnable can be used. In this study, this technique was used for achieving the controlled release of a model hydrophilic drug (ampicillin) which is known to have a low compatibility with the polymer (polycaprolactone). A partially electrospinnable shell fluid (4% (w/v) polycaprolactone (PCL) solution) and a fully electrospinnable core fluid (10% (w/v) PCL, 2% (w/v) ampicillin solution) were used in order to create ampicillin-loaded PCL nanofibers covered by a PCL shield. Scanning electron microscopy and optical microscopy images proved that the membranes have core-shell structured nanofibers. Fourier transform infrared spectroscopy demonstrated that some compatibility might be present between ampicillin and PCL. Finally, drug release studies showed that the drug release kinetics of core-shell products is closer to zero-order kinetics while the drug release kinetics of single electrospinning of the core resulted with serious burst release. Together, these imply that the application area of modified coaxial electrospinning in controlled release could be expanded to polymers and drugs with low compatibility.

1. Introduction

Membranes that are produced from randomly assembled electrospun polymer nanofibers have potential applications in various fields. Biosensors, filtration, pharmaceutics, tissue engineering and drug delivery are some examples for those fields (Barhate and Ramakrishna, 2007; Bui et al., 2011; Kaur et al., 2012a, b; Manickam and McCutcheon, 2012; Nagy et al., 2012; Rodoplu and Mutlu, 2012; Rodoplu et al., 2013). For drug delivery applications, several controlled drug release profiles (immediate, sustained, delayed, etc.) can be obtained by using electrospun nanofibrous membranes as drug carriers (Nagy et al., 2010; Yu et al., 2009). Among them, sustained drug release has attracted considerable attention as it gives rise to desired duration and dosage of drug delivery in target tissues (Xiang and McHugh, 2011).

For the production of drug-loaded nanofibrous membrane, the model drug and the polymer should be dissolved together and the resulting mixture should be electrospun via single electrospinning. Nevertheless, the initial burst release is indispensable for such membranes because of the drug distribution on the surface of the nanofibers, large nanofiber surface areas and amorphous status of the drugs inside the nanofibers (Chunder et al., 2007; Moghe and Gupta, 2008). This is not preferred in sustained release. One process to eliminate the burst release is post-treatment of membranes. It includes the processes applied after electrospinning. Cross-linking or chemical modifications are the ones generally used for electrospun membranes. Unfortunately, both types of post-treatments have disadvantages like toxicity and reduction of biocompatibility (Taepaiboon et al., 2007; Wang et al., 2005). Coaxial electrospinning is another way of eliminating the burst release where drugs are encapsulated in the core part of the core-shell structured nanofibers (Wu et al., 2011).

Coaxial electrospinning is superior to post-treatments as it reduces the complexity of the process while eliminating the potential harm that could be caused by post-treatment steps. However, the shell solution used in traditional coaxial electrospinning was chosen to be highly electrospinnable and have enough viscosity in order to overcome the interfacial tension between core and shell solutions (Moghe and Gupta, 2008).

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http://dx.doi.org/10.1016/j.ijpharm.2016.03.032
0378-5173/

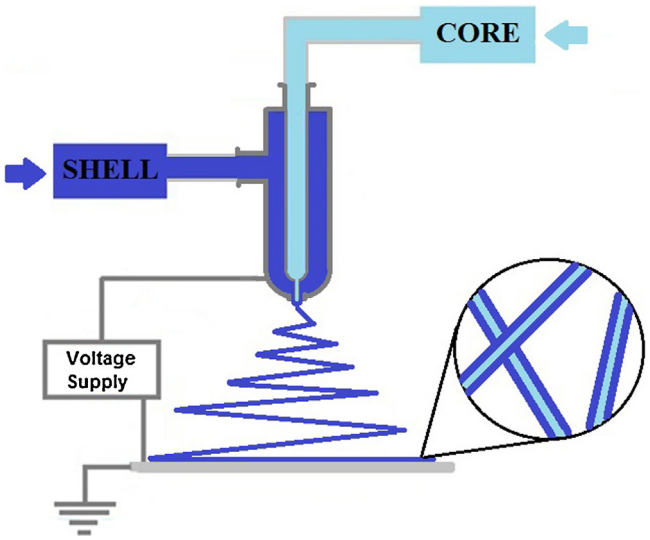

Fig. 1. Schematic illustration of formation of core-shell structure.

Recently, a modification was made on traditional coaxial electrospinning. This modification proved that dilute polymer solutions or organic solvents can also be used as shell fluids despite being unspinnable. Firstly, when the organic solvents were used as shell fluid, control over nanofiber diameters was achieved (Yu et al., 2010, 2011). Next, sustained drug release membranes were produced by using dilute polymer solutions as shell fluid. In drug release studies, a hydrophobic model drug (ketoprofen), which is miscible in the solvents and had good compatibility with the chosen polymers (zein and cellulose acetate) were used (Yu et al., 2013a,b). Compatibility implies the interactions between the drug and the polymer which do not modify the chemical structure of the polymer or the drug. Every drug has different chemical and physical properties. As a result, it is not possible to produce a drug release membrane from a particular polymer which will be convenient for carrying all kinds of drugs (Liu et al., 2004).

In this research, modified coaxial electrospinning was used for controlled release of a hydrophilic model drug (ampicillin) which has a low compatibility with the chosen polymer (polycaprolactone). The results of this research demonstrated that, the application area of modified coaxial electrospinning could be expanded for drugs and polymers with low compatibility where the drug is not fully miscible with the solvent.

2. Materials and methods

2.1. Materials

Polycaprolactone (MW: 80,000 Da), PBS tablets and methanol was obtained from Sigma Aldrich (USA). Ampicillin sodium salt was purchased from AppliChem (USA). Chloroform was obtained from Merck (Germany).

2.2. Coaxial electrospinning

For coaxial electrospinning, polymer solutions were fed into a stainless steel co-axial nozzle (Inovenso, Turkey) at flow rates controlled by two syringe pumps. The nozzle used during the process had an inner diameter of 0.7 mm and an outer diameter of 1.2 mm. It has two inputs from where core and shell fluids can be fed separately. After the solutions reached the nozzle tip, they were subjected to high electric field and it resulted with fine fibers due to stretching caused by electrostatic repulsion. Before electrospinning, core and shell solutions were prepared separately. The core fluid was a 10% (w/v) PCL solution containing 2% (w/v) ampicillin and the shell fluid was a 4% (w/v) PCL solution. The solutions were drawn into syringes after being produced and syringes were placed into syringe pumps. The setup is illustrated in Fig. 1.

Two membranes were produced via coaxial electrospinning: Core/shell 1 and Core/shell 2 (CS1 and CS2). For production of CS1 membranes, the core and shell flow rates were both kept 0.5 ml/h. For CS2 membranes, the core flow rate was kept 0.5 ml/h and the shell flow rate was kept 0.6 ml/h. By single electrospinning of the core, core membranes (CR) were produced. Core flow rate was kept 1 ml/h while the shell solution was not fed during the production of CR membranes. For single electrospinning of shell solution, the shell flow rate was made 1 ml/h and core solution was not fed (Table 1). The parameters resulting with a stable electrospinning process was determined after series of optimization processes with respect to flow rates, applied voltage and tip to collector distance.

2.3. Characterization of the fibers

The morphology of the membranes was observed under environmental scanning electron microscope (FEI-Quanta 200 FEG, USA). The samples were sputter-coated with Au prior to the examination. The average fiber diameter of the samples was determined by measuring their diameters from SEM images at 50 different places using Image J software (NIH, MD, USA).

The core-shell structures of the nanofibers collected on microscope slides were observed under polarized light microscope with high resolution (Nikon Eclipse, LV100, Japan).

The compatibility between components of the membranes was investigated by Attenuated total reflectance Fourier transform infrared (ATR-FTIR) analysis. It was performed with an FTIR spectrometer (Perkin Elmer Spectrum, 100, USA) with a collected spectrum in the range of 650–4000 cm^{-1}.

2.4. Release study

In vitro drug release profile of ampicillin from the electrospun membranes was detected by measuring the concentration of

Table 1
Electrospinning parameters used for production of membranes.

Sample Name	Composition		Flow Rate (ml/h)		Distance (cm)	Applied Voltage (kV)
	Core Fluid	Shell Fluid	Core Fluid	Shell Fluid		
CR	10% (w:v) PCL 2% (w:v) ampicillin	Not Present	1	–	9	12
CS1	10% (w:v) PCL 2% (w:v) ampicillin	4% (w:v) PCL	0.5	0.5	9	12
CS2	10% (w:v) PCL 2% (w:v) ampicillin	4% (w:v) PCL	0.5	0.6	9	12