Journal of Drug Delivery Science and Technology 29 (2015) 132–142

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Research paper

Dipyridamole embedded in Polycaprolactone fibers prepared by coaxial electrospinning as a novel drug delivery system

Alexandros Repanas*, Birgit Glasmacher

Institute for Multiphase Processes, Leibniz Universität Hannover, Hannover 30167, Germany

ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form
29 June 2015
Accepted 5 July 2015
Available online 7 July 2015

Keywords:
Biomaterials
Dipyridamole
Polycaprolactone
Coaxial electrospinning
Controlled drug delivery

ABSTRACT

Numerous clinical trials have indicated that an anti-platelet treatment can reduce the risk of recurrent stroke events. Dipyridamole (DIP) is a pharmaceutical compound known to induce platelet aggregation inhibition. Drug delivery systems (DDSs) made of biodegradable polymers can be created using electrospinning, which is a versatile and cost-effective technique that can produce fibrous structures, capable of sustained drug release. A novel DDS made of Polycaprolactone (PCL) with encapsulated DIP was prepared by coaxial electrospinning. The main aim of the current study was to evaluate how different concentrations of PCL in the core and shell solutions and different core concentrations of DIP, affect the fibers' structural and physical properties. Results indicated that the electrical conductivity of the solutions was influenced mainly by the concentration of DIP and less by PCL. Moreover, the average fiber diameter was altered by the concentration of both PCL and DIP, which consequently had an impact on the surface hydrophilicity. Finally, the fibers' encapsulation efficiency and the cumulative drug release were studied and correlated to the concentrations of the drug and the polymer. The obtained data was fitted to a known kinetics model in order to evaluate their release mechanism, which was Fickian diffusion in all cases.

1. Introduction

Over the last decade, electrospinning has received worldwide attention in the biomedical research community as a cutting-edge technology for the fabrication of scaffold materials in the micro- and nanoscale [1]. Electrospinning involves the application of an electrical field to generate polymeric non-woven fiber mats from polymeric blends, melts or emulsions. It is a cost-efficient, versatile, top-down approach to generate 3D scaffolds of different shape and size. Furthermore, a typical setup of an electrospinning apparatus consists of three basic elements: a high voltage power supply (AC, DC or AC/DC), a solution reservoir connected with a spinneret and a grounded metal collector [2,3]. The solution properties, such as the choice of solvents and polymers, as well as the processing parameters, namely the applied voltage or the solution flow rate are very important for the morphological, physical and biomechanical properties of the generated fibers [4]. Moreover, electrospinning technology has shown great promise in the fields of tissue engineering and controlled drug delivery, due to the wide range of materials that can be employed [5–8].

There are various electrospinning protocols and techniques, with their respective advantages and disadvantages. The most common electrospinning approach is the blend or single jet electrospinning, where all the constituent polymers and chemical compounds, are mixed together using one solvent. Blend electrospinning has some limitations especially with regard to drug delivery applications. The effectiveness of sensitive pharmaceutical molecules, proteins or even DNA are often reduced due to the possible loss of bioactivity, caused by denaturation in the presence of organic solvents, used in the technique. Non-specific distribution within the fiber body can also occur, since the majority of the bioactive molecules are electrically charged and can migrate towards the fiber's surface due to electrostatic repulsion. This can ultimately lead to burst release of the entrapped substances when the fiber mats are placed into an aqueous medium [9].

In contrast to conventional electrospinning, coaxial

Abbreviations: DIP, Dipyridamole; PCL, Polycaprolactone; DDS, drug delivery system; TFE, 2,2,2-trifluroethanol; PBS, phosphate buffer solution; SEM, scanning electron microscopy; EE, encapsulation efficiency.

* Corresponding author. Leibniz Universität Hannover, Institute for Multiphase Processes, Callinstrasse 36, 30167, Hannover, Germany.

E-mail addresses: repanas@imp.uni-hannover.de (A. Repanas), glasmacher@imp.uni-hannover.de (B. Glasmacher).

http://dx.doi.org/10.1016/j.jddst.2015.07.001
1773-2247/

electrospinning involves using two concentrically arranged nozzles that are connected to the high voltage power source [5]. This set-up results in fibers having a core–shell structure that can be used as carriers of pharmaceutical substances and other sensitive biological molecules, in order to protect them from the surrounding environment and control their release kinetics [10,11].

Cardiovascular diseases are the main cause of death worldwide and account for more than 80 million patients only in the USA [12]. Patients who have survived a severe cardiovascular event such as a myocardial infarction, often face the risk of recurrent strokes [13]. Numerous clinical trials have indicated that medical treatment with anti-platelet agents can significantly reduce the chances of such recurrent stroke events [14]. Dipyridamole (DIP) is an antiproliferative and antithrombotic pharmaceutical agent which has been used in patients with chronic cardiovascular disease [13].

Polycaprolactone (PCL) is a hydrophobic, semi-crystalline polymer that has been approved for biomedical uses by the Food and Drug Administration (FDA). It does not present any solubility problems in most organic solvents and has a low melting point (59–64 °C) [15]. PCL has numerous advantages, such as good miscibility with other polymers, mechanical stability and elongated degradation rate that can last up to four years. Additionally, it can be easily electrospun and therefore, can be used for long term sustained delivery of pharmaceutical agents for various applications [16–19].

The aim of this work was to fabricate a drug delivery system (DDS) made of fibers from PCL, in order to provide sustained delivery and reduced burst release of DIP. In this regard, the coaxial electrospinning method was chosen in order to confine most of the drug in the core of the electrospun fibers. Furthermore, the effect of the polymer's concentration, both in core and shell solution, as well as the effect of DIP's concentration on the fibers' structural and physical properties was investigated. Moreover, the effects of the aforementioned parameters on encapsulation efficiency of the fibers were studied. Additionally, the cumulative release of DIP from the electrospun fiber mats *in vitro* was monitored throughout a period of ninety six days and analyzed. Last but not least, the release kinetics of DIP were evaluated, fitting the obtained data to the theoretical model described by Peppas et al. in order to study the release mechanism [20].

2. Materials and methods

2.1. Materials

Polycaprolactone (PCL) (Mn = 70,000–90,000) and Dipyridamole (DIP) (≥98.0%) were purchased from Sigma–Aldrich. 2,2,2-trifluroethanol (TFE) was purchased from abcr GmbH & Co.KG. A phosphate buffer solution (PBS, pH = 7.4) was prepared using bidistilled water. All materials and reagents were used as received without any further purification.

2.2. Polymer solution preparation

Both core and shell solutions were dissolved in TFE. DIP was used only in the core solution at concentrations ranging from 5 mg/mL to 20 mg/mL. PCL concentration in the core solutions ranged from 50 mg/mL to 200 mg/mL and in the shell solution from 100 mg/mL to 200 mg/mL Table 1 summarizes the concentrations of the materials used. Moreover, each specimen was given a short code. The upper and lower limits of the concentrations of PCL and DIP were selected based on previous preliminary experiments, taking into account the ease of electrospinning of the solutions and the solubility of the materials used in TFE (data not shown). All polymeric solutions were constantly stirred for 12 h at room temperature in order to achieve homogenous mixtures. Part of each polymeric solution was then transferred into 10 mL syringes (Omnifix, B. Braun), while the rest of the solution was used for the electrical conductivity experiments.

2.3. Electrospinning

A custom electrospinning set up equipped with a coaxial nozzle was used. The core solution flow rate for all samples was kept stable at 1 mL/h, while the shell solution flow rate was 3 mL/h in order to achieve a stable process. Moreover, the applied voltage was kept constant at 25 kV in order to achieve continuous flow with no jet breaks. The distance between the tip of the nozzle and the collector was kept constant at 25 cm. This resulted in an electrical field of 1 kV/cm. For the core solutions, disposable blunt-tipped needles (Nordson EFD) of an inner diameter of 0.4 mm were used, whereas the inner diameter of the coaxial spinneret nozzle for the shell solution was 1.35 mm. A grounded, square aluminum collector (15 * 15 cm^2) covered with aluminum foil was used to collect the samples. Electrospinning was performed under constant conditions of temperature and relative humidity (T = 22 ± 5 °C, Rel. Humidity = 35 ± 4%). The duration of electrospinning time per sample was 30 min. Finally, the samples were collected on the surface of the aluminum foil, removed from the collector and left to dry for 12 h under vacuum.

2.4. Characterization of the electrospun fiber mats

2.4.1. Electrical conductivity

The electrical conductivity of all the different polymeric solutions was measured using a conductometer (SevenMulti, Mettler Toledo AG). Two mL of each different polymeric solution was measured at 25 °C. All measurements were taken in quintuplicate.

2.4.2. Scanning electron microscopy (SEM)

Square strips of 3 * 3 mm^2 were carefully cut from each electrospun fiber mat and they were sputter coated with Au/Pd for 45 s, before being placed inside the SEM instrument (S3400N, Hitachi) under high vacuum. An accelerating voltage of 15 kV, a 7.2 mm distance between the edge of the electron gun and the surface of the samples and magnification rates of 500×, 1000×, and 4000× were used for the morphological and structural analysis of the fibers. In order to determine the average diameter of the electrospun fibers, pictures obtained at 4000× magnification were processed using the image analysis software ImageJ (National Institutes of Health). Measurements were taken at 50 different fibers from each picture.

2.4.3. Static water contact angle assay

Square strips of 5 * 5 mm^2 were cut from each of the different electrospun specimens in order to investigate the static contact angles of water droplets on the surface of the fiber mats, using an optical contact angle apparatus (FM40 Easydrop, Krüss). Measurements were taken at 0 s after a single droplet of bidistilled water (1 μL) got in contact with the surface of the samples. The angles were calculated by the software of the device. All measurements were performed in quintuplicate at room temperature.

2.4.4. In vitro drug release and encapsulation efficiency

For the encapsulation efficiency measurements, square strips of 10 * 10 mm^2 were carefully cut from each of the different electrospun specimens, subsequently immersed in 1 mL of TFE and constantly stirred for 1 h at room temperature to fully dissolve the scaffold. Using a UV–Vis spectrometer (LIBRA S22, Biochrom), the absorbance of DIP was measured at 291 nm. A standard calibration