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Polyvinyl alcohol composite nanofibres containing conjugated levofloxacin-chitosan for controlled drug release

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ABSTRACT

A range of biodegradable drug-nanofibres composite mats have been reported as drug delivery systems. However, their main disadvantage is the rapid release of the drug immediately after application. This paper reports an improved system based on the incorporation of drug conjugated-chitosan into polyvinyl alcohol (PVA) nanofibers. The results showed that controlled release of levofloxacin (LVF) could be achieved by covalently binding LVF to low molecular weight chitosan (CS) via a cleavable amide bond and then blending the conjugated CS with polyvinyl alcohol (PVA) nanofibres prior to electrospinning. PVA/LVF and PVA-CS/LVF nanofibres were fabricated as controls. The conjugated CS-LVF was characterized by FTIR, DSC, TGA and ^{1}H NMR. Scanning electron microscopy (SEM) showed that the blended CS-PVA nanofibres had a reduced fibre diameter compared to the controls. Drug release profiles showed that burst release was decreased from 90% in the control PVA/LVF electrospun mats to 27% in the PVA/conjugated CS-LVF mats after 8 h in phosphate buffer at 37 °C. This slower release is due to the cleavable bond between LVF and CS that slowly hydrolysed over time at neutral pH. The results indicate that conjugation of the drug to the polymer backbone is an effective way of minimizing burst release behaviour and achieving sustained release of the drug, LVF.

1. Introduction

Controlled slow release systems for drugs have been widely explored due to their advantages compared to other methods of drug administration [1,2]. The advantages include reducing the side effects by delivering the drug at a controlled release rate, improved therapeutic efficiency, continuous sustained release of small amounts of drug instead of several large doses and improved of patient compliance [3]. In the past decade several drug delivery systems have been investigated for a controlled release of drugs from nanoparticles [4] and biodegradable nanofibres [5]. Nanofibres are made by a variety of methods such as melt blowing, drawing, phase separation, self-assembly and electrospinning [6–8]. Electrospinning is a simple and convenient technique to fabricate nanofibres from a large variety of polymers [9,10]. In the process of electrospinning, the polymer solution in a syringe is fed through the spinneret at a constant pump rate. When a high voltage is applied, the electrostatic field charges the solution drop at the nozzle of a spinneret and forms the electrified jet that can be attracted by the collectors with the opposite electrical charge. As it travels to the collector the solvent is evaporated, the solid polymer nanofibre is deposited as a nonwoven mat on the surface of the collector [11].

Electrospun nanofibres have gained considerable attention as potential drug delivery systems in the last decade [12,13]. Various biodegradable nanofibres have been investigated for controlled release of drugs [14–16]. However, the major drawback of drug loaded nanofibres is the undesired burst release behaviour of the drug [17–20]. For example, ciprofloxacin loaded nanofibres of PVA have been reported [20] with high initial burst release (80%) of the ciprofloxacin content in the first 40 h. The burst release of salicylic acid (SA) from PVA nanofibres with different SA concentration has also been reported [21]. The release profiles showed very high burst release within the first hour with 40–65% of the total drug released. Such burst release behaviour of these drugs may be due to a large proportion of the drug being on the nanofibres' surface and/or rapid drug diffusion out of the polymeric matrix because of fast polymer degradation [20,22,23].

It is important, therefore, to devise systems which overcome the initial burst release. One approach for achieving a controlled release of drug is covalent conjugation of drugs to the polymer backbones [24–26]. This requires the presence of functional groups on both the drug and polymer. For example, docetaxel (DTX) was covalently attached to low molecular weight CS via a cleavable amide linker. Prolonged slow release of DTX was obtained in simulated intestinal fluid

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(pH 7.5) which resulted in higher bioavailability along with prolonged circulation time in the blood stream than the intravenously injected DTX [27]. In another study, composite nanofibres of poly(lactide-*co*-glycolide) (PLGA) and poly(ethylene glycol)-*g*-chitosan-ibuprofen (PEG-*g*-CS-IBU) conjugates were fabricated by covalently linking IBU to the amine groups of CS via an amide bond [28]. There it was observed that presence of conjugated CS-IBU in the matrix reduced the burst release due to the cleavable amide bond between CS and ibuprofen. Another report includes synthesis of doxorubicin conjugated stearic acid-*g*-chitosan polymeric micelles (DOX–CS–SA) [29]. The release profile showed that release behaviour of DOX is pH-dependent where the release rate of DOX increased with the reduction of the pH for release medium from 7.2 to 5.0.

PVA is widely used in biomedical applications due to its well-known characteristics of biocompatibility, biodegradability, water solubility, nontoxicity, swelling capability in an aqueous medium, and appropriate mechanical properties [30–32]. It has been reported that by incorporating a second polymer component such as CS into the PVA solution, leads to an improvement in biocompatibility and mechanical properties (e.g. solubility) of the nanofibres. Chuang et al. [33] fabricated PVA/CS blended membranes for cell culture. They observed that the PVA/CS blended membrane was more favourable for the cell culture with better spreading of cultured cells than the pure PVA membrane.

The aim of this work was to design a controlled drug delivery system by conjugating the carboxylic groups in LVF to the amine groups of CS [34,35], followed by mixing the conjugated system with PVA prior to electrospinning in order to reduce the burst release of drug from highly water soluble PVA nanofibres [20,21]. The release profiles of PVA/CS-LVF (conjugated) electrospun composite mats were measured and compared to the control PVA/LVF and PVA-CS/LVF (non-conjugated) electrospun composite mats.

2. Materials and methods

2.1. Materials

PVA (MW 85,000–124,000, 98–99% hydrolysed), low molecular weight CS (deacetylation ≥75%), LVF (98.0%) and acetic acid were sourced from Sigma-Aldrich. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) crosslinker was supplied by Pierce, Dimethyl sulfoxide (DMSO) from Fisher Chemical and sodium hydroxide from Chem Supply. All other chemicals were of reagent grade.

2.2. Methods

2.2.1. Synthesis of CS-LVF

The conjugation of LVF and CS was based on carbodiimide chemistry (Fig. 1) [34,35]. CS (1 g) was dissolved in 0.1 M acetic acid solution (500 mL). A mixture solution of LVF and EDC (1:1 M ratio) was prepared by dissolving LVF and EDC in 10 mL anhydrous dimethyl sulfoxide (DMSO). Then, the mixture solution was added dropwise to the CS solution under continuous stirring for 12 h. The conjugated CS was then coagulated by adding 1 M NaOH. CS-LVF was collected by centrifugation (15 min, 16,000 g), washed by DI water and then dried at room temperature for 24 h.

2.2.2. Preparation of composite electrospun mats

Electrospun mats were prepared containing 1 wt.% of LVF, and 5 wt.% of CS-LVF (with respect to PVA). For polymer solutions 20 mg LVF, 100 mg CS-LVF were added to two separate vials containing 20 g of 10 wt.% PVA (dissolved in water) and stirred continuously until a homogeneous solution was obtained. A solution of 10 wt.% PVA-CS (9:1) was also prepared with 1 wt.% LVF (with respect to PVA-CS).

The basic setup used for electrospinning is shown in Fig. 2. The setup contained a spinneret needle (23 G Terumo), syringe pumps (model NE-1000 New Era Pump Systems, Inc., Farmingdale, NY, USA), a high voltage supply (Spellman high voltage DC power supply, USA) and a 5 mL syringes (Terumo). The electrospinning distance was varied between 0 and 300 mm (optimised distance of 150 mm) and the applied voltage varied between 0 and 40 (optimised value of 12 kV). Electrospun mats were collected for 10 h at 0.6 mL/h pump rate on a drum collector (100 mm diameter) driven by a 12 V motor rotating at 60 mms^{-1} and a moving horizontal oscillating speed of 10 mms^{-1}.

2.3. Characterization

IR spectra were collected in the transmission mode using a Thermo Nicolet 6700 FTIR Spectrometer. DSC analysis of samples was carried out at a heating rate of 10 °C/min under a nitrogen purge of 40 mL/min using a Netzsch STA 449 F1 Jupiter DSC Thermal Analyser. TGA was performed using a Netzsch STA 449 F1 Jupiter TGA Thermal Analyser at a heating rate of 10 °C/min under a nitrogen purge of 40 mL/min. ^{1}H NMR spectra of the samples were recorded on a Bruker Av400 NMR spectrometers. Scanning electron microscopy (SEM) analyses were carried out using a Philips XL30 field microscope. Fibre diameters were measured using microstructure measurement software. For each sample, 100 measurements were taken to obtain an average fibre diameter. A Varian UV–Vis spectrophotometer was used to measure the LVF concentration at 290 nm.

2.4. In vitro drug release

The electrospun mats were cut into 50 mm squares, weighed and then placed in 5 mL of phosphate buffer saline solution (PBS, 100 mM, pH 7.4 and pH 5.0) and shaken continuously for 3 days at 150 rpm at 37 °C. At each measurement time point 1 mL of release medium was removed and replenished with 1 mL of fresh buffer. The amount of LVF released at each time point was determined by UV spectrophotometer.

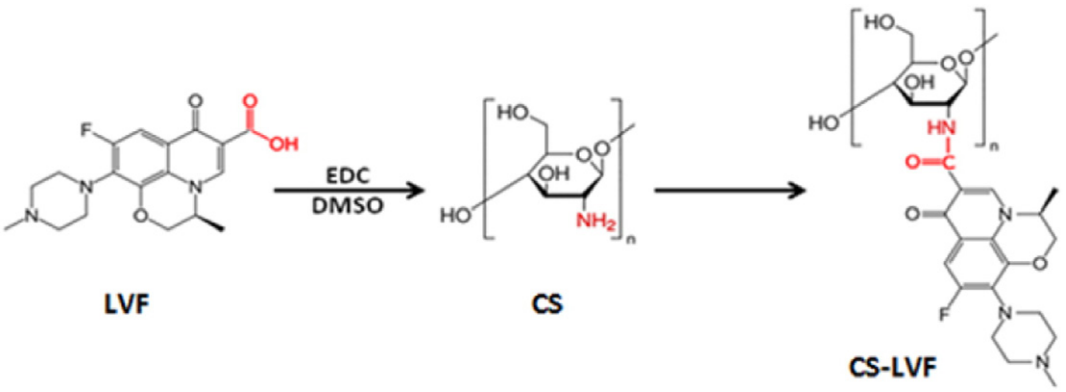

Fig. 1. Preparation of CS-LVF.