Electrospun Nanofibrous Wound Dressings for Controlled Drug Delivery

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ABSTRACT

Electrospun nanofibres have attracted much attention in wound care owing to their unique properties such as high surface area and porosity. Many current studies on nanofibres have demonstrated their feasibility over existing forms. However, the mainly supportive role of nanofibres in wound healing prevented them to become more useful in large area or chronic wounds, which are major medical challenges. In order for wound dressings to help regulate processes involved in wound healing, functional elements such as drugs can be incorporated into nanofibres. This study focuses on how to control drug release from nanofibres such that the optimal dosage can be achieved at the right timing to enhance therapeutic effects, using a hydrophilic model drug as an example. Electrospun PVA was chosen as the drug carrier, and was modified via crosslinking treatments to vary the fibre degradation rate. In addition, hydrophobic PCL layers were also added to the drug-carrying PVA to further limit drug release. Through these comparisons, the effects of fibre degradation and hydrophilicity of drug release control can be demonstrated. The results obtained in this study can be used as a guide for improving nanofibre drug carriers to achieve desirable release behaviors.

Keywords: nanofibres, wound dressing, drug delivery, biomedical, electrospinning, release profiles

1 INTRODUCTION

The human skin is the largest and one of the most important organs responsible for interactions with the environment, and therefore any breach in the skin must be repaired in a timely manner. Accordingly, wound care is one of the most significant topics in medical field, with a $13 billion market as of 2008 [1]. While the native wound healing process in the human body is able to repair most minor injuries, larger wounds and burn injuries remain a significant concern. Moreover, non-healiing wounds such as those suffered by elderlies and diabetic patients add complication to the challenge due to the lack of stimulations for native healing processes to occur. In the US, there are 6.5 million patients suffering from chronic wounds [2]. As a result, much effort has been put towards developing would healing aids that can encourage tissue regeneration in a more timely manner, ranging from fibrous dressings, injectable scaffolds from hydrogel, and artificial skin composed of a multi-layer structure such as Integra [3].

Among the various material structures used today, electrospun nanofibres attract much attention, owing to the large surface area, and interconnected porosity. Nanofibrous polymeric structures also closely match the blueprint set out by nature, such as the collagen nanofibres that compose the extracellular matrix (ECM) in native tissues. Indeed, many existing studies have shown that the desirable surface properties of nanofibrous scaffolds have translated to superior cell attachment and proliferation compared to their microfibrous counterparts as well as other forms such as sponges [4]. From a manufacturing point of view, electrospinning is a highly customizable process that is compatible with a wide range of polymers, which enable a great degree of control over fibre properties such as diameter, orientation, hydrophilicity, degradation, crystallinity, and more. In addition, fibres are highly connective with superior tensile properties

compared to other forms, which enables formation of many higher order structures such as wound pads, sutures and more [5, 6].

However, even with optimized material and fibre properties, electrospun wound dressings play mainly a supportive role because the wound healing process is mainly controlled by various signalling factors that stimulate cell activities involved in the process [7]. In order to provide use for large surface wounds and non-healing injuries, many have examined incorporation of various drugs and signalling molecules into nanofibres to help regulate processes involved in wound healing, including antibacterial and anti-inflammatory agents, painkillers, and growth factors [8]. Each drug, however, has optimal therapeutic dosage and retention time in the body, which translates to a design constraint for nanofibre carriers in that drug release must be controlled. For example, a patient may require quicker release of antimicrobials at the initial stage of wound healing to prevent infection or prolonged inflammation period, or another paitent may require a more gradual release of a growth factor for encouraging angiogenesis that does not take place until granulation tissue is formed. The nanofibre, therefore, must be able to protect the drug from surrounding environment. This paper explores two nanofibre parameters that affect drug release behavior, including hydrophilicity and fibre degradation, and examines methods for controlling drug release through modification of these parameters.

2 MATERIALS AND METHODS

To demonstrate drug release control, FS-1, a hydrophilic model drug provided by our collaborator, was incorporated into the nanofibres fabricated in this study. FS-1 release can be detected spetrometrically via light absorbance.

2.1 Electrospinning

The polymers used in this study as drug carriers include polyvinyl alcohol (PVA) and polycaprolactone (PCL), all of which were purchased from Sigma-Aldrich. Electrospinning solutions of PVA were prepared by dissolving the polymer in distilled water at 7 – 10 wt% for PVA. PCL was dissolved in dichloromethane and dimethylformamide at a 1:1 ratio at 8-12 wt%. FS-1 was added to the PVA at a concentration of 20 mg/mL. Electrospinning was carried out using a Katotech Nanofibre Electrospinning Unit by applying a voltage of 15-25 kV with a solution flow rate of 0.005 – 0.03 mL/min. Barrier layers of PCL were added to the drug carrier by electrospinning PCL directly onto the drug-loaded PVA layer. To further control the degradation rate of PVA nanofibres, an aqueous solution of sodium tetraborate was sprayed onto the nanofibre membrane as a crosslinking agent.

2.2 Nanofibre Characterization

Nanofibre morphology was observed using a Hitachi S-3000N scanning electron microscope, while quantitative analysis such as fibre diameter measurement was performed using the image analysis software ImageJ. The degradation rate of the fibres were compared against each other by soaking 2 cm x 2 cm pieces of the nanofibre membrane in 1X phosphate buffered saline (PBS) solution, followed by removing after specific durations for drying and weight loss measurements.

2.3 Drug Release Studies

Electrospun nanofibres containing FS-1 were incubated in 1X PBS at 37°C for specific durations for drug release studies. An alloquot of the PBS solution from each sample was removed and analyzed spectrometrically by absorbance. The drug concentration in the known alloquot volume can then be used to determine the amount of drug released into the PBS solution from the carrier.

3 RESULTS AND DISCUSSIONS

Nanofibre morphologies of electrospun PVA and PCL are shown in Figure 1. The diameters of the PVA fibres (shown in Figure 1, left) ranged

from 150 – 300nm whereas those for the PCL fibres (shown in Figure 1, right) ranged from 260 – 420 nm. When the PVA fibre membrane was sprayed with sodium tetraborate solution, fibre diameter increased by an average of approximately 30% due to swelling from the water content in the crosslinking solution.

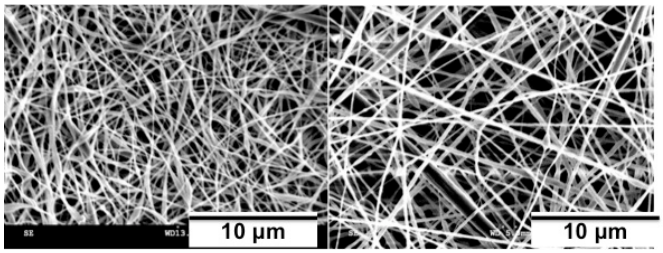

Figure 1: SEM images of electrospun PVA (left) and PCL (right) nanofibres.

The degradation profiles for PVA and PCL are shown as weight loss vs. time plots in Figure 2. Due to the water-soluble nature of PVA, complete dissolution of as-electrospun PVA nanofibres in PBS was observed within minutes. However, when the nanofibres were sprayed with the sodium tetraborate solution, degradation was significantly reduced such that complete degradation was observed after 3 – 4 days, although most of the weight loss occurred within the first 12 hours. The hydrophobic PCL, on the other hand, remained marginally degradable in PBS after 4 days.

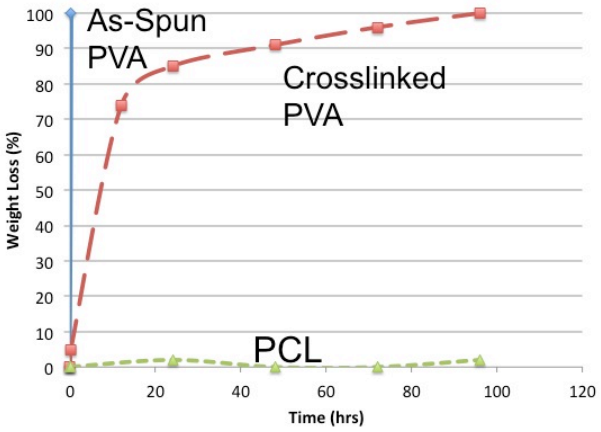

Figure 2: Degradation profiles of as-electrospun PVA, PVA crosslinked with sodium tetraborate, and PCL in 1X PBS.

From the fibre degradation profiles, it can be estimated that drug incorporation into the as-spun PVA will lead to a significant burst release due to the rapid fibre disintegration. When the PVA is crosslinked with sodium tetraborate, the duration of drug release can be extended, although burst release will still occur initially because most of the weight loss occurs within the first 12 hours. The FS-1 release profiles from as-spun and crosslinked PVA fibres are shown in Figure 3. Indeed, all of the loaded FS-1 had been released from the as-spun PVA nanofibres within the first PBS extraction time point at 15 minutes. Crosslinking the PVA allowed FS-1 release to be extended, with a burst release of most of the loaded drug in 4 hours, followed by a gradual release of the remainder over the next several hours. The FS-1 release was quicker than earlier prediction based on the degradation profile due to swelling mechanisms and surface effects that act simultaneously with fibre degradation, and therefore it is desirable to study these effects in future studies. However, the overall trend observed is similar to the prediction, which indicate that degradation is a major release mechanism for this system.

In addition to crosslinking, further modification to the drug release profiles can be performed by adding a hydrophobic barrier layer. By doing so, liquid diffusion into the FS-1 carrying PVA layer is delayed because diffusion path becomes more tortous, causing more difficulties in transporting drugs from the PVA phase to the bulk phase. Furthermore, degradation of PVA is also delayed as a result of the barrier layer. From Figure 3, it can be observed that addition of a PCL barrier layer to crosslinked PVA was effective in reducing the burst release of FS-1. The effects of the PCL barrier layer on reducing liquid diffusion and delaying fibre degradation are more pronounced when the thickness of the barrier increased from 250 to 400 µm, as observed in Figure 3.

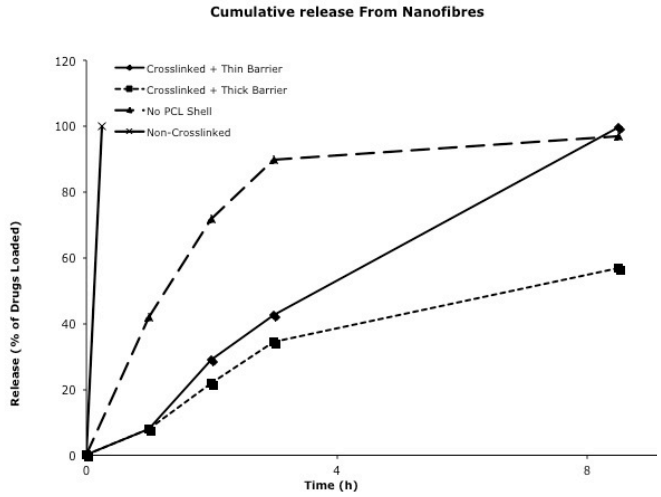

Figure 3: Drug release profiles of as-electrospun and crosslinked PVA nanofibres, and crosslinked nanofibres with PCL barrier layers.

4 CONCLUSION

This study examined the impact of nanofibre degradation profile and hydrophilicity on the release behavior of a hydrophilic model drug. By reducing the degradation rate of a water-soluble polymer by crosslinking, the duration of drug release was extended, while release behavior still follow the degradation profile to some extent, in that burst release was observed when majority of the weight loss take place. In addition, by adding hydrophobic barrier layers, burst release was further reduced as a result of increased diffusion tortuousity and delayed fibre degradation.

The results from this study also indicated that although fibre degradation played a significant role in drug release for a water-soluble polymer carrier, other mechanisms such as swelling and surface desorption also play a role. This conclusion was drawn from the discrepency between the observed drug release profile and the degradation behavior. As a result, it is desirable to further study these mechanisms in future work.

The fundamental studies on drug release mechanisms in nanofibres, such as the work performed in this study have nonetheless provided indication that drug release can be controlled by adjusting the parameters mentioned. Further development of these techniques will therefore be benefical in fabricating a new generation of wound dressing products that is able to more appropriately regulate processes involved in healing, as well as many others outside of wound healing applications.

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