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Bioactive Nanofibres for Wound Healing Applications

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Abstract

Electrospun nanofibres have become an exciting area in textile product development, due to their unique properties such as high surface area and porosity. Indeed, many studies on nanofibres have demonstrated their feasibility in various applications. For example, nanofibre scaffolds were shown to be promoters for tissue cell adhesion and encapsulators for drugs. In the past decade, numerous studies revealed the areas in which nanofibres can be useful, and capability for scaling-up nanofibre production, which established a starting step in the development of a new generation of textile products. However, many challenges faced today are complicated in nature and require a multidimensional approach to solve, necessitating multifunctional products. This review explored recent efforts in developing a new class of active textiles for wound care. The wound care sector is one of the most advanced in the medical industry, with a massive global demand from patients suffering from wounds, burns, and diseases such as diabetes. Ensuring satisfactory wound healing is often difficult due to the dynamic nature of the skin, requiring fulfilment of multiple objectives at different stages of the healing process. We demonstrated that by controlling how wound dressing release therapeutic agents, its mechanical responses to the wound and in aqueous environment, a wound dressing that can interact with different wounds can be developed.

Keywords: Nanofibres; Wound Dressing; Drug Delivery; Biomedical; Electrospinning; Active Textile

1 Introduction

In the recent century, the textile industry has undergone a significant transition, from serving the basic functions such as clothing, containers, and decorations, to specialized uses such as filtration, structural reinforcement, biomedical, protection, automotive, and more. While such advanced textiles are becoming increasingly important for supporting a variety of scientific and industrial activities, the demand on performance for textile products is ever increasing. One of the objectives in advanced textiles is to facilitate a paradigm shift from traditional, passive textile products into active textiles. In the context of our studies, passive textile products are those that mainly serve a supportive function, without the ability to interact with the surrounding

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environment, with typical examples including clothing and cotton wound dressings. On the other hand, an active textile product can be functionally engineered to suit specific environments, and stimulate surrounding elements to perform functions beneficial for the intended applications. Examples of active textile products include shape memory fabrics, heat regulating clothing, and vapour absorbing fabrics. The abilities of active textile products to perform specific functions and stimulate activities by surrounding elements enable such products to approach multidimensional challenges that are typical in a variety of applications, thereby producing a great impact in different industries and markets. An important example of such passive to active textile product shift can be seen in wound care, owing to the dynamic nature of the human body and the intricate healing process involved.

The wound care sector is one of the most advanced areas in the pharmaceutical industry, with a worldwide market worth $13 Billion in 2008 and was expected to grow to $17 Billion over the next four years [1]. Contributions to the large demand on wound care are from both acute wounds from surgeries or burns, and chronic wounds from venous and diabetic ulcers. In the US there are nearly 500 000 burn patients annually requiring medical treatment, as well as over 120 000 surgical procedures performed daily [2]. Also, roughly 6 million US patients suffer from chronic wounds annually [3]. The demand on wound treatment is much larger globally, especially considering the aging population in many countries. Injuries to the skin are significant burdens to the healthcare systems worldwide. Besides the direct cost from patient care, the loss of productivity associated with lengthy treatment processes, such as for diabetic ulcers, also hampers the economy [4]. The skin is the largest organ of the body. With a major role in maintaining moisture balance, temperature and protection from environmental insult timely repair of the skin is essential for the patient.

Currently, autografting remains the standard for treatment of complicated wounds such as large burns, however many patients lack available donor sites or risk generating chronic wounds and problematic healing. Skin replacement products, such as Integra developed by Yannas and Burke [5-7], and injectable scaffolds [8] have shown feasibility for partial and full-thickness wounds, whereas various hydrogel, foam, and fibre scaffolds were used for partial thickness wounds. However, for artificial skin products such as Integra, multiple surgical procedures are required during treatment, whereas injectable scaffolds suffer from the lack of structural integrity. Recently, electrospun nanofibres were introduced to tissue repair as a mechanically robust form of material that can be more effective for tissue cell activities than other forms due to its large surface area available [9]. In addition, nanofibres are also structurally similar to the extracellular matrices in tissue, composed of nanofibrous collagen. The potential for nanofibre use for partial thickness wounds have been shown in numerous studies, including our previous work on alginate nanofibres that showed enhanced fibroblast cell proliferation compared to a commercial alginate-based wound dressing [10]. Nanofibres can also be added to existing systems for enhanced performance for partial and full-thickness wounds.

With the main focus on its surface and mechanical properties, as-spun nanofibres could only serve as a platform for cell activities for relative benign wounds, or as structural supports in wound care products in the early studies. However, recent studies have shown that electrospinning is a highly versatile technique that enables control over nanofibre properties such as surface area, hydrophilicity, extensibility, strength and biodegradability. To fully harness the versatile nature of nanofibres and their properties, it is desirable to devise a new class of multifunctional nanofibres that can be customized for specific wounds, thereby overcoming multidimensional challenges that are typical in wound healing.

2 Active Wound Dressing

Wound healing is a dynamic process that involves an intricate sequence of events divided into four phases: homeostasis, inflammation, proliferation, and remodeling [11]. The sequence is controlled by signaling molecules, or factors, produced by cells. Many factors are speculated to be involved in the wound healing, and the processing of identifying and understanding of all factors involved is still ongoing. In treating benign wounds, wound dressing can serve as a platform for facilitating cell migration to the wound site such that the healing sequence can occur in a timelier manner. For large wounds, however, obtaining sufficient cell coverage can be difficult [12], and wound dressings that merely act as surface support are no longer effective. Furthermore, for non-healing wounds such as diabetic ulcers, parts of the healing sequence cannot take place due to lack of essential proteins such as insulin. In this case, a wound dressing that can interact with the wound by stimulating and managing cell migration and the sequence of healing events is highly desired. To address the dynamic nature of wound healing and the multidimensional objectives, the wound care market is transitioning into advanced, active wound dressings, such as growth factor enhanced dressings (Biovance, Covaderm, etc.) and swellable dressings (Tegagel, Kaltostat). In nanofibre wound dressings, several groups examined the incorporation of antimicrobial agents to prevent infections, and there are also several examples on growth factor incorporation in nanofibers, as discussed in our previous review [13]. In a simplified example we have previously shown that incorporation of poly-L-lysine into alginate nanofibres has aided cell attachment [10]. Building on the success of these earlier studies, our goal is to develop active wound management systems, via careful manipulation of nanofibre properties. To achieve our goals, material-wound interactions must first be understood, from which important nanofibre properties can be identified, and then strategies for controlling such properties can be formulated.

In general, nanofibre wound dressings must be biocompatible, non-irritating, and have suitable mechanical properties for the application. However, specific properties and material-wound interactions depend greatly on the type of wound considered. For example, heavily exudating wounds require more porous or swellable dressings to prevent excess fluid buildup, open wounds from surgical incisions and burns require antimicrobial, or growth factors, and materials that degrade faster and in some cases rapid exhibit rapid drug release profiles that can also be used since some of these dressings are changed daily. For closed wounds or for wounds where dressing change is not advisable, more durable materials and more gradual drug release profiles are required.

In this regard, the role of nanofibre became much more significant, and this review explores our current work in developing multi-functional nanofibres that can serve this active role. Besides performing the basic function of wound protection and moisture retention, the fibres must also protect incorporated therapeutic agents and release them in a desired and controlled manner without impeding the normal course of healing.

3 Materials and Methods

The polymers used in our study, including Polyvinyl Alcohol (PVA), sodium alginate, Polycaprolactone (PCL), and Polylactic-glycolic acid (PLGA) were purchased from Sigma Aldrich. These polymers were electrospun using a Katotech nanofibre electrospinning unit. Fibre morphology was confirmed using a Hitachi S-3000N scanning electron microscope, and the tensile behavior

was measured using a Katotech KES-G1 tensile tester. To obtain an average stress-strain curve, 10 specimens for each sample were measured. Biodegradability tests were performed by soaking nanofibres in 1x Phosphate Buffered Saline (PBS) solutions for varying lengths of time and measuring the weight loss after drying. To evaluate drug release control a water-soluble model drug provided by the BC Professional Firefighter and Wound Healing Laboratory at the Vancouver General Hospital was used. The release was measured spectrophotometrically by absorbance after incubating in 1x PBS solution at pH7.5 for defined lengths of time.

4 Wound Healing Management

Traditional textile wound dressing mainly protects the wound and retains moisture. A new generation of active textile dressings, however, must also participate in the management of the wound healing process. The key to successfully managing the wound healing process is to ensure that specific cell activities are stimulated at the right time, and that undesirable events such as infection are prevented. An active wound dressing therefore manages the interaction between the wound and the stimulating element, which can be drugs or signaling molecules. Management of interaction is most commonly achieved by controlling the rate and the manner at which the stimulating element is released into the wound. Therefore, an active wound dressing for effective healing management must enable tailoring to adopt appropriate release properties, which depends heavily on the element being released and the specific wound. For example, a fresh wound may require a relatively quick, or even burst release of antibiotics to prevent infection, whereas a surgical wound may require a more sustainable release of antibiotics or growth factors, and an epithelialized wound may require a stable release of matrix remodeling agents. Fig. 1 shows examples of desirable release profiles for several types of wound dressings that would be changed daily. It must be noted, however, that optimal release profile varies significantly from different drugs and conditions, and the profiles shown in Fig. 1 are generalized examples that serve as starting points for formulating objectives for our study. In addition to managing activities around the wound, the dressing must be able to provide protection for the loaded drugs or growth factors against structural damage, especially for signaling molecules in aqueous environment. Therefore,

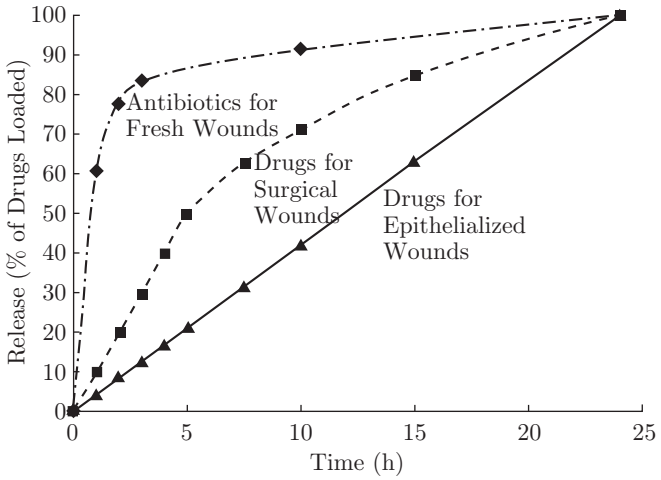

Fig. 1: Generalized examples of appropriate release profiles for different applications

drug protection and release control are the two primary objectives in wound healing management.

Controlling drug release rate from nanofibres requires an understanding and careful manipulation of the release mechanisms, which includes liquid-state diffusion in which drugs desorb from the dressing and diffuse towards the wound site by penetrating body fluid, solid-state diffusion in which drugs encapsulated within the fibre diffuse outwards, and release via fibre degradation. The relative impact of each mechanism on release rate depends highly on the material choice and geometry. Therefore, drug release rate can be controlled to match an ideal profile for a specific wound by adjusting the extent of activity for one or more of the three mechanisms. For example, hydrophilicity and swelling of the fibre affects the rate of drug desorption and thus outward diffusion of drugs to the wound. Fibre diameter and geometry affect drug diffusion rate within the fibre as well as the desorption rate on the surface. Fibre geometry can often be affected by drug loading, and a study of the effect of drug loading on fibre diameter and morphology has been demonstrated by Katti et al. [9]. Material choice and the molecular orientation affect the biodegradation rate of the fibre, and thus drug release via the degradation mechanism.

The flexibility in controlling nanofibre properties offered by the electrospinning techniques opens opportunities for tailored drug release properties for different types of wounds, by allowing one to manipulate each of the three drug release mechanisms. Some success on rate controlling had been achieved in recent work. For example, Srikar [14] and Gandhi [15] related the release of dyes and proteins to the nanofibre surface area and porosity according to the release model shown below, where G_t is the mass released at time t, M_{d0} is the initial mass of the loaded reagent, α is the nanoporosity factor defined by the initial mass of reagent on fibre surface over the total initial mass of reagent, and τ_r is the characteristic time dependent on pore size and effective diffusivity. Since this model only considers surface and pore properties, it is able to predict drug release via the liquid-state diffusion mechanism.

$$\frac{G_t}{M_{d0}} = \alpha \left[1 - \exp\left(\frac{-\pi}{8} \frac{t}{\tau_r} \right) \right]$$

In addition, several previous studies have shown that release rates vary by controlling nanofibre diameter, with quicker release observed from fibres with lower diameters [16, 17]. In these previous studies, drugs such as albumin and ibuprofen could be incorporated directly into organic solvents in electrospinning solution. However, some drugs, especially growth factors, are soluble or active only in aqueous medium. Previous studies included examples in which water-soluble drugs were incorporated as part of a W/O emulsion, which resulted in nanofibre implants with slow release rates in the week time scale [18], as well as examples in which antibiotics (Biteral) were coated on a hydrophobic PCL scaffold for preventing abdominal adhesion, which resulted in a quick release system in the hour scale [19], but there were no means to control the drug release profile. These studies demonstrated some control over the general time scale, between hours to weeks. However, to determine whether release rate control can be fine-tuned within each timescale, we examined direct incorporation of a water-soluble drug into water-soluble polymer, modified via post-processing to achieve different release profiles. As a first step to our release control studies, we will discuss two simple examples of dressings: quick release, and intermediate release.

Quick release systems are suitable for delivery of drugs like antibiotics, especially in the inflammation stage early in the wound healing process. This type of wound dressing is also desirable for open wounds such as those from surgical incision, or for situations where frequent replacement of dressing is required, such as in exudating wounds. The goal of a quick release system is to deliver

the desired drug, which can be antibiotics, growth factors or cell signaling agents, within time frames ranging from hours up to one or two days. Previous work by Bölgen et al showed that by adding Bilateral into a hydrophobic PCL nanofibre membrane, burst release of the antibiotic was observed with most of the drug released within 3 hours [19]. We electrospun a PVA solution containing a water-soluble model drug provided by the BC Professional Firefighter Burn and Wound Healing Laboratory at the Vancouver General Hospital. In its as-spun form, the PVA nanofibres underwent a burst release in which release was only detected for the first 30 minutes. To reduce degradation and swelling, the as-spun nanofibres were sprayed with a mist of aqueous sodium tetraborate solution to crosslink the fibre membrane surface. Care must be taken to avoid loss of drugs through interaction with the crosslinking solution. By reducing degradation and welling, release was sustained in the crosslinked PVA membrane for 24 hours, as shown in the release profile in Fig. 2. However, a burst release is still evident. Our current work in progress focuses on further control on the release profile through changing the crosslinking density, which further adjusts the swelling and degradation rate, as well as adjusting the thickness of the dressing, which change the solid-state diffusion rate.

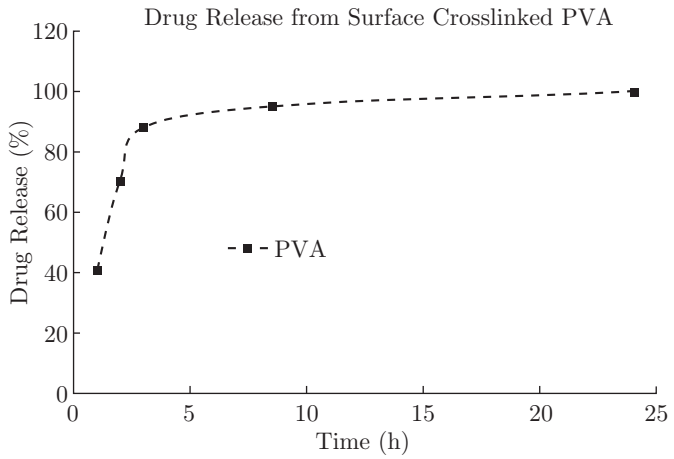

Fig. 2: Release profile of model drug from electrospun PVA crosslinked with sodium tetraborate

While a quick releasing dressing is suitable for antibiotics or frequent dressing change, a more prolonged release profile is desired for wounds in which frequent interruption is undesired, or when burst release of drugs is harmful to the patient. In these cases, more consistent release of drugs is required. To stabilize the release profile, we enclosed the crosslinked, electrospun PVA quick release system in an electrospun PCL protective layer. By adding a layer of PCL shell, liquid-state drug diffusion from PVA to the bulk liquid phase is greatly reduced due to the tortuous path introduced by the PCL layer. In addition, the degradation of PVA is delayed due to the PCL acting as a barrier against liquid diffusion. Fig. 3 compares the release profile of a PVA system without PCL encapsulation, and two PCL-PVA-PCL sandwich structure systems, with different average thicknesses of 250 μm and 400 μm. Indeed, by adding a PCL protective shell, the initial release at the first hour reduced by an order of magnitude, and the release of the sandwich structure remained more stable than the unprotected system. Moreover, by increasing the thickness of the shell from 250 μm and 400 μm, burst release and the release rate were further reduced. The comparison in Fig. 3 clearly outlined the effect of limiting drug diffusion from the PVA to the bulk phase. Further control of release rate can also be achieved by varying the porosity of the PCL layer.

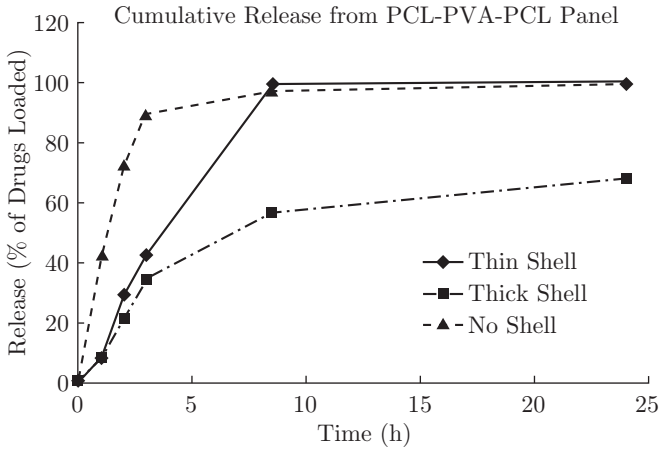

Fig. 3: Release profile of model drug from a PCL-PVA-PCL sandwich structure system

Our current study on the quick release and the slower release systems demonstrated that drug release rate from nanofibres can be controlled via post-processing treatments, by considering the three release mechanisms and manipulating the extent of each. Beginning with a polymer that is immediately soluble in water, we reduced degradation and swelling via crosslinking, allowing sustained release up to 24 hours. With a simple addition of a hydrophobic envelope to limit liquid-state diffusion, the initial release rate was reduced significantly, allowing more prolonged release profiles. In addition to the enveloped structure, core-shell structured nanofibres are an attractive area in drug delivery. In core-shell nanofibres, the shell polymer can serve many functions, most important of which is to protect the core and to reduce release rate through reducing liquid-state diffusion. The release properties of core-shell nanofibres depend more heavily on the material choice of the shell, whereas the material choice for the core more often relates to drug compatibility. In previous nanofibre drug release studies, shell materials with different swelling properties and degradation have yielded a wide spectrum of release durations, ranging from 2 hours using highly soluble polymer (PVA) [20], to 10 days (PDLLA) [21], to 60 days (PCL) [22], up to 3 months using marginally swellable polymers (PCLEEP) [23]. In addition, use of a crosslinkable polymer as the shell, such as PVA, can further modify the swelling rate, thereby fine-tuning the release behavior.

5 Mechanical Properties Control

The ability to control drug release rate from a wound dressing via manipulating the three release mechanisms enables a more active role in optimizing the wound healing process. However, the therapeutic function is only one part of an effective response in the dressing-wound interaction, as mechanical properties are also an important part of the response. Not only must a wound dressing interact with the wound, it must also be sufficiently durable for handling and application, and have similar mechanical response as the skin it is intended to repair. For nanofibre wound dressings, the most common mechanical properties being compared include tensile strength, stiffness and strain. The first important consideration is that the dressing must be able to withstand the load applied by cells, generated by cell attachment and associating shape changes, migration, and differentiation [24]. For fibroblasts and chondrocytes, Culture Force Monitor (CFM) measure-

ments showed that force exerted on its surroundings during migration is in the order of 0.1 nN per cell [24-26]. In addition, design objectives for nanofibre dressings can be identified by examining existing products. Unfortunately, obtaining reliable mechanical properties from native skin had been difficult because they depend greatly on the patient as well as the test method. For example, reported values for the Young's modulus for native skin ranged from 0.008 MPa [27] to 20 MPa [28]. Studies on existing wound dressing products provide a more consistent reference for design objectives. Artificial skin similar in structure to Integra has a tensile strength of 10 kPa, Young's modulus of 69 kPa, and maximum strain of 41% [29], whereas hydrogel scaffolds can have tensile strengths in the order of 50—100 kPa, and maximum strain of 600—800% [30]. However, unlike hydrogel dressings, which can be contained as a liquid and injected into the wound, or Integra, which is supported by a silicone topcoat, fibrous wound dressings are handled and applied as a textile and therefore must be more robust. Indeed, microfibrous dressings such as Biofix and Resolut LT have tensile strength in the order of 10 MPa. Mechanical properties of nanofibrous wound dressings depend mainly on the material choice as well as solution properties. Examples of tensile stress-strain behaviors for several common polymers used in nanofibrous wound dressing research are shown in Fig. 4. It is worth noting that natural polymers, which are sometimes more compatible with growth factors and cells, have significantly lower strain than synthetic polymers. Therefore, envelope or core-shell nanofibre designs with a natural polymer as the core for drug binding and a synthetic shell polymer, provide another merit of enhancing mechanical properties, in addition to enabling control over drug release.

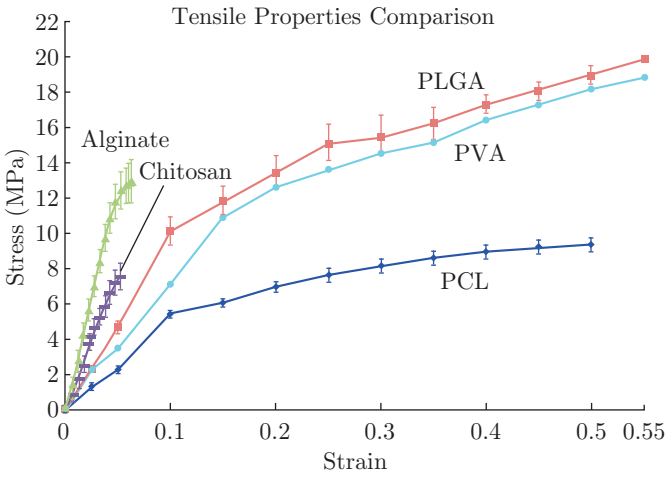

Fig. 4: Tensile properties comparison between polymers commonly used as nanofibre wound dressings

Given a specific polymer, mechanical properties can be further controlled via fibre orientation and crystallinity. While aligned nanofibres lead to superior tensile stress and strain in the axial direction, randomly oriented nanofibres are used for wound dressing because their isotropic properties are desired. Control over nanofibre mechanical properties for a specific polymer is usually achieved through changing the crystallinity of the polymer, via adjusting the polymer concentration or solvent. Higher crystallinity leads to higher tensile strength, Young's modulus, but lower strain. Many previous studies have shown that several-fold changes to tensile strength and strain can be achieved by adjusting polymer crystallinity [31-33]. In addition to varying the solution preparation and electrospinning processes, these previous studies have also shown that post-processing steps can add further control in mechanical response as well with the potential of these steps outlined in the work by Gandhi et al., who found that treatments such as anneal-

ing, methanol treatment, and carbon nanotube incorporation can individually increase tensile strength and Young's modulus up to three-folds, with a reduction in extensibility of up to 20% [31]. Indeed, carbon nanotube incorporation had become a popular method for strengthening nanofibres.

While the robustness of the dressing under load is considered, the structural integrity in body fluid must also be ensured. The ability to control biodegradability is therefore highly beneficial for developing an active wound dressing. Requirements on biodegradability depend heavily on the condition of the wound. The main objective in controlling biodegradability is to ensure that the dressing remains intact while managing a specific stage in wound healing, and then degrade to not obstruct new tissue formation. Like the tensile properties, biodegradability also depends on material choice, with more hydrophilic polymers being more degradable. As a result, polymers that are compatible with water-soluble drugs and growth factors are often highly degradable in aqueous environments. However, by incorporating envelope or core-shell designs, biodegradability of hydrophilic polymers can be significantly reduced by controlling liquid diffusion via a protective layer, such as the PVA in PCL envelope design. In addition to limiting liquid diffusion, further fine-tuning of the degradation rate can be achieved by crosslinking. Our study on alginate nanofibres has demonstrated the effect of crosslinking on biodegradability. In this study, we soaked as spun and crosslinked alginate nanofibres in 1X PBS solutions for specific lengths of time, followed by weight loss measurement. Without any crosslinking, sodium alginate nanofibres were immediately soluble in PBS solution. After crosslinking with 1M calcium nitrate tetrahydrate and washing in distilled water, the degradation rate reduced and remained intact in PBS solution after several days. Although calcium is a common crosslinking ion for alginate nanofibres, ion exchange with sodium can occur in PBS solution, and therefore to further enhance integrity, crosslinked calcium alginate nanofibres can be double crosslinked with glutaraldehyde or Polyethylene Glycol (PEG). The degradation properties of the crosslinked alginate nanofibres are shown in Fig. 5, presented as weight loss vs. time, where the control is the calcium crosslinked alginate nanofibre. As seen in Fig. 5, dual crosslinking with glutaraldehyde was effective in reducing degradation on the nanofibre whereas the degradation PEG dual crosslinked sample was statistically the same as the control. Our studies on alginate nanofibres and the PCL-PVA envelope design have therefore shown that both major and minor control of the degradation rate can be achieved through protective layers and crosslinking steps.

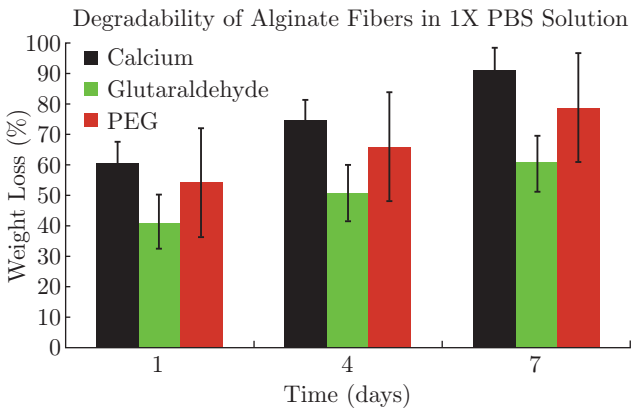

Fig. 5: Degradability comparison in PBS solution between crosslinked calcium alginate nanofibers, glutaraldehyde double-crosslinked and PEG double-crosslinked nanofibres

6 Manufacturing Nanofibre Dressings

The focus in developing active textile wound dressing is the interaction between the dressing and the wound, and we have presented our approach to impart optimal therapeutic and mechanical responses for interactions with different types of wounds. However, as pointed out by Place et al., transition from laboratory to clinical use is a critical aspect for biomaterials development, and one must avoid over-engineering textile products [34]. Here we will explore approaches to manufacture the active wound dressings considered in our studies. The objective in manufacturing is to form functional nanofibres into linear or planar assemblies. For planar assemblies, single or multiple jets of fibre can be electrospun on collectors that can be a drum or conveyor belt for continuous production, as shown in Fig. 6, ultimately leading to membrane structures desirable for wound dressings. The capability for spinning multiple jets in the planar setup allows for a simple method for fabricating sandwich-structured membranes. A continuous layer of the protective polymer can be electrospun from one set of nozzles (C in Fig. 6), while drug containing nanofibres can be spun from a second set of nozzles (B in Fig. 6), followed by deposition of a top layer of protective polymer at another set of nozzles (A in Fig. 6). In addition to enveloped structures, nozzles can be modified to electrospun core-shell nanofibres. Fig. 7 shows a co-axial spinneret designed in-house and Fig. 7 shows an example of core-shell nanofibres containing two PLGA solutions in different solvents as the core and shell solutions. Co-axial spinnerets can also be incorporated to planar electrospinning setups for manufacturing a continuous membrane of core-shell nanofibres.

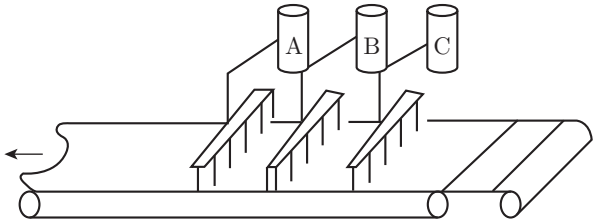

Fig. 6: Electrospinning setup for planar assemblies

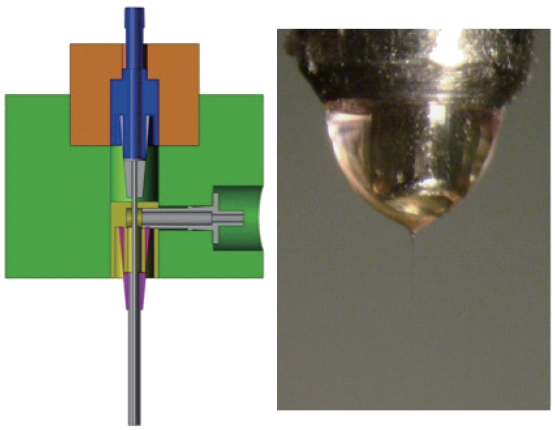

Fig. 7: Co-axial electrospinning nozzle (left), and core-shell nanofibre spinning (right)

Linear assemblies can be achieved by electrospinning onto a sharp disc collector or by orienting and attenuating a fibre jet at flight, as shown in Fig. 9 from our previous work on nanofibre yarns [35]. Both methods can lead to threads of aligned nanofibres, which can be subsequently twisted

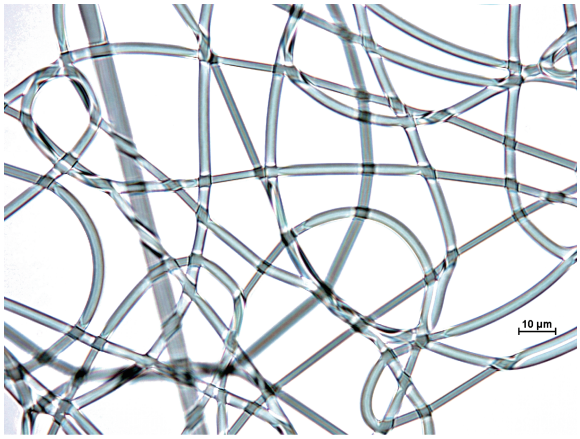

Fig. 8: Core-shell nanofibres with two PLGA solutions in different solvents as core and shell solutions

into yarns. The nanofibre-based yarns then serve as a basis for higher-ordered structures, as they can be woven into fabrics for wound dressing and garments, or braided into sutures and threads [36]. Indeed, the possibility for nanofibres to be formed into higher ordered structures such as nonwoven membranes, woven fabrics, and sutures is one of the advantages of nanofibre technology that cannot be satisfied by other forms of wound dressing, such as hydrogel and foam.

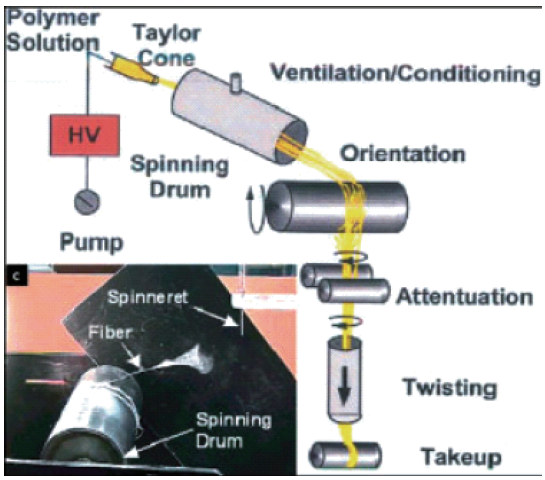

Fig. 9: Orienting and attenuating a jet of fibre before twisting into yarns

7 Summary and Future Prospects

As an example of a new generation of active textile products, we have presented our early work on nanofibre based wound dressings that can adapt to different wounds to actively facilitate wound healing management. The two important aspects behind the active role played by the nanofibre dressing are the therapeutic and mechanical responses. For therapeutic response, depending on the type of wound, whether it is open or closed, epithelialized or not, large or small, effective healing management requires different drugs released at specific rates with specific profiles. We assert that through manipulating the extent of each drug release mechanism, including liquid and solid state diffusion, and fibre degradation, drug release rates can be controlled to suit a

wide variety of wounds. For manipulating drug release mechanisms, we showed the feasibility of techniques such as crosslinking, and adding hydrophobic protective layers, using the quick release and slower release systems as examples. In devising optimal mechanical responses, we showed that tensile behavior depends on the material choice, and further control can be achieved through controlling fibre orientation and crystallinity, as well as several post-processing techniques. In addition, biodegradability plays an important role in the interaction with the wound, and can be controlled through material choice and crosslinking. By developing an active wound dressing using the techniques explored in this study, wound healing management can be optimized such that an effective dressing can be applied to a specific wound, with the necessary drug or growth factor released that can stimulate a particular cellular response needed for that stage in the wound healing process, followed by degradation of the fibre or replacement of the scaffold upon depletion of the drug or when the drug is no longer needed.

While the current study is an initial step in advancing textile technology toi more adequately address the current demands in wound treatment, there is still much room for improvement, which will be the focus of further studies. For example, we have shown how the duration of drug release can be controlled, and how burst release can be prevented, but it is possible to further fine-tune the release rate and profile in order to achieve more complex objectives such as several hours of delayed release, or a specific percentage of release within the first several days and then a steady release thereafter. The ability to fine-tune release profile can help optimize the wound healing process, which is the focus of our future studies. The ultimate goal in developing active wound dressing, however, is one that can interact not only with the wound, but also with the surroundings, by actively participating in wound management when stimulated by external changes. In addition, incorporation of multiple drugs is also desired for optimal therapeutic effect, such that the dressing can act on different stages in the healing process.

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