Electrospun fibers –
A new dawn for advanced wound care
By: Dr. Hennie Kotzé (PhD) – Senior Scientist, SNC
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1. Introduction

For effective wound healing to occur, an optimal environment for wound repair needs to be provided and maintained. Traditional wound dressings mainly maintain moisture and protect against further trauma. Modern advanced, interactive dressings however do not only interact with the wound surface but also modify the physiology of the wound bed. This is currently a topic of great discussion and ongoing research. The need to promote debridement of necrotic tissue and slough, enhance re-epithelialization and granulation, while simultaneously reducing the risk of infection and managing exudate levels is non-negotiable when designing dressings in the modern advanced wound care paradigm.¹

Dressings used in advanced wound care should possess a combination, or ideally all, of the following characteristics:¹

- Maintain a moist wound environment
- Debridement of necrotic tissue and/or slough
- Exudate control
- Non-toxic and non-allergenic
- Allow for gaseous exchange
- Barrier to protect from further trauma
- Easy to remove (low adherence)
- Infection control/ barrier to bacterial infection
- Thermal insulation
- Ease of application with reduced numbers of required dressing changes
- Comfortable and conformable
- Long shelf life, ideally without requiring refrigeration.

You might ask yourself why electrospun fibers are such attractive materials for use in wound care when there are numerous so-called “conventional dressings” already on the market. The answer lies in the inherent properties of electrospun fibers. Electrospun fiber dressings can possess most of the above-mentioned characteristics, which makes them ideal materials for use in advanced wound care. Properties like high surface-to-volume ratio, tunable porosity, the ability to control fiber size and morphology, as well as the ability to fabricate nanostructures from a variety of materials are what affords electrospun fibers these characteristics and makes them such attractive alternatives to conventional gauzes and foams.²³ Electrospun fibers can be prepared from natural or synthetic polymers, or a hybrid blend of both.⁴ The flexibility by which the porosity and fiber diameter can be controlled during the electrospinning process gives us the ability to design and tailor the properties of the material to suit a specific application.

Since there are many different types of wounds, each needing their own dressings with specific functional technical interventions (e.g. moisture control, thermal control, biofilm disruption etc.), it is important to note that there is no silver bullet approach when dealing with wound dressings. With
electrospun fibers however exists the possibility to allow for the design of dressings that approach wound healing from multiple fronts by combining some of the aforementioned characteristics, giving us the best opportunity for successful wound healing. By exploring the inherent properties of electrospun fiber materials further, the untapped potential of these fibers for application in advanced wound dressings will be highlighted.

2. Compositional and functional flexibility of electrospun fibers

One of the most important properties of electrospun fibers is its biomimicking ability. Polymeric fibers’ similarity to the nanofibrous structures that are present in human tissues and organs makes them especially important for the biomedical field. Electrospun fibers can be fabricated with micro to nanoscale topography and high porosity, which is comparable to that of the natural extracellular matrix (ECM) of human skin, making them ideal for use as scaffolds for tissue engineering.

Several polymers share structural and/or chemical similarities to materials within the human body, which instills favourable properties when fibers from these specific polymers are used for biological applications, as either scaffolds for tissue engineering or as dressings for wound care. Biomaterials, as these materials are known, are intended to interface with biological systems and are important as they can potentially be used to assess, treat, augment or replace tissues, organs or specific functions in the body.

Electrospun fibers have been applied directly as wound dressings. These dressings showed excellent oxygen permeability, controlled water loss via evaporation and increased fluid drainage ability. The potential of electrospun fibers is further maximized by incorporating the release of active compounds from the dressing material. The presence of micropores together with the biomimicking nature of electrospun fibers give these materials numerous advantages over conventional dressings. This will be discussed in more detail in the sections to follow.

2.1 Synthetic polymers & natural polymers

Electrospun fibers can be prepared from polymers that are either derived from natural or synthetic materials, or a hybrid blend of both. Natural polymers are materials that are derived from plant or animal-based sources and have been widely explored for biomedical applications, since they often exhibit good biocompatibility. These polymers have been shown to possess low immunogenicity, with some known to also exhibit intrinsic antibacterial activity. Some natural polymers have an added advantage of being biodegradable, with their degradation products generally being biocompatible and metabolically accessible with lower risk of cytotoxicity to the human body.

Natural polymers can be classified into three main categories, namely:

- Proteins (e.g. silk, collagen, gelatin, fibrinogen, elastin, keratin, actin)
- Polysaccharides (e.g. amylose, cellulose, chitin, chitosan, dextran, glycosaminoglycans, alginate)
- Polynucleotides (e.g. DNA, RNA).

Due to their chemical and structural characteristics, a broad spectrum of synthetic polymers have been extensively used in biomedicine as biomaterials for applications in tissue engineering and regenerative medicine. The physical and chemical properties of synthetic polymers can readily be modified by changing the polymerization conditions, using different monomer units or by the
formation of co-polymers. Consequently synthetic polymers can be tailored to be either biodegradable or non-biodegradable. The degree of biodegradability of these synthetic materials can therefore be modified to have specific degradation behaviour suitable to the required application.

Synthetic polymers that are commonly used for medical device applications include:\(^4,13\)

- Poly(lactic acid) (PLA)
- Poly(ε-caprolactone) (PCL)
- Polyurethane (PU)
- Poly(vinyl alcohol) (PVA)
- Poly(ethylene oxide) (PEO)
- Co-polymer blends, such as poly(lactic-co-glycolic acid) (PLGA).

The sheer number of different polymer combinations available, natural and/or synthetic, that can be electrospun provides us with an impressive toolkit to design new materials or modify existing materials that can be tailored for specific wound care applications.

2.2 Design of required functionality

The ability to design and incorporate different functionalities into electrospun fibers makes them ideally suited for use in the biomedical field. Electrospun fibers have been used as carriers for DNA and drug delivery systems, as scaffolds in tissue engineering as well as in the development of wound dressings. It is the combination of both physical and mechanical properties that allow these materials to, for instance, be able to curb bacterial colonization and infection, while potentially simultaneously imparting controlled drug release from the porous electrospun material. In the next sections, each of the properties of electrospun fibers will be looked at in more detail to get a better understanding of the extent to which these materials could change our understanding of what a good wound dressing is, or rather, should be.

2.2.1 Infection control and semi-permeability

When the skin barrier is compromised, the exposed tissue is vulnerable to infection, which is a significant problem in wound care as the injury diminishes the body’s natural resistance to infection. The microporous structure of electrospun fibers is a valuable barrier that can restrict the entrance of foreign bodies, such as bacteria, via a “sieve” effect, thereby promoting wound cleanliness and minimising infection from the external environment.\(^9\) During wound healing it is important for certain gases and fluids to continuously exchange between the wound microenvironment and the external environment. Electrospun fiber materials are semi-permeable, due to their unique microporous structure, and therefore allow for the exchange of gases (oxygen, carbon dioxide and water vapour) and fluids (exudate). This allows the dressing to maintain the appropriate oxygen and moisture level for wound healing to occur, while simultaneously acting as a physical barrier against the entrance of foreign bodies.\(^14,15\)

2.2.2 Moisture control

Electrospun fibers have a very large surface area to volume ratio and can consequently absorb and retain a significant amount of fluid relative to their own mass. Compared to traditional film dressings
that show only minimal water absorption of around 2-3%, electrospun fibers can absorb water in the range of 18-213%. Electrospun fiber nonwovens have been shown to also provide good control over the water vapour transmission rate (WVTR). The high porosity and large surface area of the electrospun fibers assist hemostasis, and when more hydrophilic polymers are used the high surface area results in improved absorption compared to conventional dressings, and so pooling of exudate is also avoided.\textsuperscript{16-19}

2.2.3 Accelerated healing

Successful wound healing is dependant on the ability of the wound care technique to establish and maintain a moist environment in the wound, facilitating much needed proliferation and cell migration. Electrospun fiber dressings are ideally suited for this task as they can regulate and maintain the ideal moisture levels needed for efficient wound healing. Furthermore, electrospun fibers also leads to faster healing and regeneration of the skin by providing a better guide to skin cells for self-repair.\textsuperscript{14,15} Electrospun fibers are also ideal materials that mimic the ECM while simultaneously acting as a temporary skin substitute facilitating accelerated wound healing in the process. Electrospun fibers have also been shown to mimic the fibrous matrix of a scab, and in doing so, mimics the body's natural defence mechanism.\textsuperscript{20}

2.2.4 Inclusion of active/ bioactive agents

Electrospun fiber nonwovens are excellent candidates for the delivery of therapeutic agents in the local wound environment.\textsuperscript{13} The active agents can either be incorporated prior to electrospinning (drug encapsulated fibers) or during a post-treatment step after electrospinning (post-functionalized fibers).

Methods for incorporating active agents into the electrospun fiber structure include:\textsuperscript{21,22}

- **Drug encapsulated fibers:**
  - Mixed directly into the polymer solution (blending).
  - Incorporated into the core region by a polymer layer (core/shell) through coaxial electrospinning.
  - Incorporated into nanoparticles and encapsulated into the electrospun fiber structure.

- **Post-functionalized fibers:**
  - Adsorption onto the electrospun fiber surface.
  - Chemical functionalization onto the electrospun fiber surface.
  - Incorporated into nanoparticles, decorated within the electrospun fiber structure (results in unique active agent releasing profiles, together with added advantage of high loading capacity).

When therapeutic agents are used for local treatment during wound healing, it is independent of systemic circulation and can therefore stimulate new tissue healing, reduce pain, decrease bioburden on the wound as well as increase vascular perfusion. By tailoring the fibers to possess specific degradation characteristics and modifiable drug delivery profiles, electrospun fibers have
been shown to be superior to polymeric films and particles when it comes to delivery of therapeutic agents.\textsuperscript{14,15}

Examples of therapeutic agents that have been incorporated in electrospun fibers for wound healing are:\textsuperscript{13}
- Antimicrobial agents
- Antioxidants
- Anti-inflammatory drugs
- Anesthetics
- Enzymes
- Growth factors.

2.2.4.1 Infection control

Roughly 75\% of the mortality following burn wounds is due to infections caused by bacterial contamination during the wound healing process. Although the systemic administration of antibiotics is effective for the treatment of infections, the development of antibiotic resistant strains is possible. Systemic poisoning is also of concern due to the high concentrations of antibiotics needed for efficient treatment of infection in the wound bed.\textsuperscript{23,24} Significant effort has therefore been put towards the development of appropriate topical delivery systems for antibiotics, which leads to higher concentrations of the antibiotic at the wound bed during infection, while simultaneously preventing systemic toxicity.\textsuperscript{25,26} Effective treatment involves the release of drug quantities higher than the minimum inhibitory concentration (MIC) needed to kill all bacteria over a number of days. The incorporation of antibiotics into electrospun fiber materials has been shown to be effective in this regard, as they can be tailored to have ideal release profiles with an initial moderate burst release followed by a slow, sustained release over a number of days.\textsuperscript{27}

Silver nanoparticles (Ag-NPs) can be used in conjunction with antibiotics and have been shown to have synergistic (ceftazidime), additive (ampiclox, kanamycin, streptomycin, polymyxin B) and antagonistic (chloramphenicol) effects against pathogens. The inverse size-dependence of Ag-NPs (increase in activity with decrease in size) towards pathogens is due to the size-dependent release of silver ions in solution. Due to their small size, nanoparticles are able to penetrate biological membranes, thereby allowing them access to cells.\textsuperscript{28}

2.2.4.2 Growth factors

Growth factors are naturally occurring substances, usually proteins or steroid hormones, that are capable of stimulating cellular growth, proliferation, healing and differentiation. These characteristics make growth factors attractive alternatives to facilitate and promote accelerated wound healing and skin regeneration, with the added potential of limiting scar formation.\textsuperscript{29} An effective delivery system is however needed to effectively utilise the wound healing properties of growth factors. The efficacy of these growth factors are dramatically hindered due to elimination by exudate, as well as degradation \textit{in vivo}. The controlled release from the appropriate scaffold protects the growth factors against \textit{in vivo} degradation.\textsuperscript{30,31} Electrospun fiber dressings can allow for the tailored loading and release of growth factors from the dressing. Furthermore encapsulation of the growth factor in the electrospun fibers can also protect the growth factors from degradation. By
modifying the electrospun scaffold, it is possible to delay burst release as well as control the release of the active thereafter.27

2.2.4.3 Biofilm disruption

Once biofilm formation in the wound is established, it can be very difficult to control and remove. This can result in the prolonging of the inflammation phase, sometimes indefinitely, resulting in delayed wound healing. Several biofilm management strategies are available to help suppress biofilm propagation and include physical interventions (wound debridement), wound dressings and the use of antimicrobial therapies. Wound debridement, although able to control bacterial growth, is not always sufficient, and additional antimicrobials are often required. These may include topical antiseptics, topical antibacterials and systemic antibiotics. Ionic silver, iodine and honey have also been shown to be effective in the suppression of biofilm in the wound.32 It is however important to note that although these therapies can control bacterial growth, it might be to the detriment of the host tissue. Many antimicrobial therapies have been shown to be effective to target planktonic bacteria, which make them beneficial for wound healing. Biofilm-producing microorganisms however, remain a challenge. Photodynamic therapy as well as silver-containing dressings have shown potential to successfully eliminate planktonic, biofilm and multidrug-resistant bacteria.33 Glucose oxidase, in combination with other enzymes, has also been shown to have effects on biofilms.

Antibiofilm strategies, which prevents biofilm formation, are also available. Most notable of these are:33

- Lactoferrin
- Ethylenediaminetetraacetic acid (EDTA)
- Dispersin B
- Gallium
- Acetylsalicylic acid.

Incorporation of these agents into electrospun fiber dressings can potentially overcome some drawbacks suffered by these agents by allowing them to be administered at the wound bed, with the dressing acting as a barrier for further infection from the external environment.

2.2.4.4 Mopping up matrix metalloproteinases (MMPs)

The presence of matrix metalloproteinases (MMPs) in the wound bed is of utmost importance for healing as they play a vital role in regulating ECM degradation while simultaneously facilitating deposition essential for re-epithelialization. Furthermore they allow for cell migration and tissue remodeling to occur. Excessive expression of MMPs in chronic wounds may however be detrimental to wound healing and could also inhibit successful wound closure. The removal of MMPs from the wound bed is therefore important and currently dressings containing highly absorbent polymers are used. Polyacrylate containing dressings have been shown to bind MMPs due to the presence of high density ionic charges.34,35 Electrospun fiber dressings are perfect candidates for control of MMPs as they can be designed to be highly absorbent as well as being functionalized with the appropriate compounds to bind and remove MMPs.

2.2.4.5 Conformability
Conformability is defined as the ability to conform to the 3-dimensional topography of a wound. This is one of the properties associated with the flexibility and resiliency during topical application. Fabric conformability, as stated by the theory of textile structures, is directly related to the fiber fineness; therefore, finer materials will fit more easily around complicated 3-dimensional shapes than thicker materials. Consequently, electrospun fiber dressings that are ultrafine are more suited for topical application, by providing better conformability, better coverage, as well as increased protection against the entrance of foreign bodies such as bacteria.\textsuperscript{14,15}

2.3 Combination of individual properties

The unique ability of electrospun fiber dressings to combine the previously discussed individual properties into a single material allows for the creation of an active wound management system that grants electrospun fiber dressings superior capabilities when compared to conventional gauze or foam dressings. Electrospun fiber dressings allow us to do away with the need to have different dressings or treatment regimes throughout the wound healing process; instead it is possible to use a single dressing to accomplish numerous tasks during wound healing. Being able to specifically design electrospun fiber materials to combine the required characteristics, being it infection control, semi-permeability, thermal control, moisture control, ECM mimicking ability or the incorporation of actives, into one material, we now have a tool like no other that allows us to accomplish with one dressing that would usually take numerous dressings or treatments to achieve effective and efficient wound healing.

If we take an acute surgical wound as an example, where infection control from the external environment as well as the protection of the wound from further trauma is important. Electrospun fiber dressings allow us to protect the wound from infection while simultaneously acting as a protective barrier against further trauma, with the added advantage of being able to load the material with growth factors that can facilitate accelerated wound healing. For non-healing wounds such as diabetic ulcers, an imbalance in the body’s natural biochemistry can block the wound healing sequence to effectively take place. For such wounds it is possible to design the appropriate electrospun fiber dressing that not only protects against further infection, but can be functionalized by the incorporation of additives which can stimulate and manage cell migration to allow effective wound healing to occur.

These are just two examples of how the combination of properties of electrospun fibers can be utilized to facilitate successful wound healing. Slowly but surely it is being realized that electrospun fiber dressings are potentially the long awaited “holy grail” of wound care with an all encompassing holistic approach for wound healing.

3. The future of advanced wound care

Electrospun fibrous materials for use as wound dressings in advanced wound care is a very exciting prospect. The inherent properties of electrospun fibers, their biomimicking nature, microporous structure and compositional and functional flexibility, makes them ideally suited for treatment of a wide variety of wounds. Coupled with the ease by which the fibers can be functionalized to incorporate active materials, it is easy to see how valuable electrospun fibers are for wound care. Realizing the potential of electrospun fibers will allow us to produce a wide range of wound dressings that will dramatically alter the advanced wound care space. With the potential to outperform conventional “advanced” dressings in almost every aspect, being it exudate control, infection control, ease of application or the controlled release of actives, electrospun fiber dressings will soon be at the forefront in advanced wound care.
References:

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