Designing electrospun nanofiber mats to promote wound healing – a review

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Current strategies to treat chronic wounds offer limited relief to the 7.75 million patients who suffer from burns or chronic skin ulcers. Thus, as long as chronic wounds remain a global healthcare problem, the development of alternate treatments remain desperately needed. This review explores the recent strategies employed to tailor electrospun nanofiber mats towards accelerating the wound healing process. Porous nanofiber mats readily produced by the electrospinning process offer a promising solution to the management of wounds. The matrix chemistry, surface functionality, and mat degradation rate all can be fine-tuned to govern the interactions that occur at the materials–biology interface. In this review, first we briefly discuss the wound healing process and then highlight recent advances in drug release, biologics encapsulation, and antibacterial activity that have been demonstrated *via* electrospinning. While this versatile biomaterial has shown much progress, commercializing nanofiber mats that fully address the needs of an individual patient remains an ambitious challenge.

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1 Introduction

Chronic wounds are a global healthcare problem. In the United States alone, 1.25 million patients suffer from burns and an additional 6.5 million patients endure chronic skin ulcers most commonly caused by pressure, venous stasis, or diabetes mellitus. In 2011, the CDC estimated that 25.8 million people—8.3% of the U.S. population—suffer from diabetes.[1] An estimated 15% of people with diabetes mellitus will develop lower extremity ulcers and up to one fourth of diabetic patients with foot ulcers will eventually undergo amputation. Annually in the U.S., approximately 100 000 lower extremity amputations are performed on diabetic patients.[2]

Though the two most common treatment options for chronic ulcers are potentially successful, neither ensures recovery. The first option, negative pressure wound therapy, only effectively treats very small chronic wounds, while the second, hyperbaric

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Nathan P. Birch is a Ph.D. candidate in Chemical Engineering at the University of Massachusetts Amherst where his current research focuses on biopolymer polyelectrolyte interactions for wound healing and drug delivery applications. Currently his research focuses on chitosan–pectin interactions, which yield nanoparticles, and hydrogels. Birch recently received a Ciba Travel Award in Green Chemistry and Engineering to present at the 246th ACS National Meeting and Exposition in Indianapolis, IN. Previously, he received a B.S. in Chemical Engineering and a minor in Polymer Science and Engineering from Michigan Technological University.

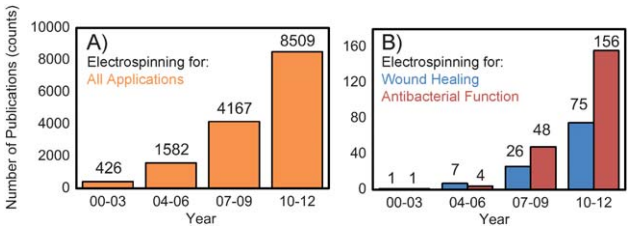

Fig. 1 Over the past dozen years, the number of electrospinning publications exhibit an upward trend. Plotted is the growth of publications on nanofibers electrospun (A) for any application and (B) specifically to address the topic of this review: wound healing or antibacterial activity. The SciFinder Scholar database was used to determine the total number of unique results from searching (A) "electrospinning" and (B) "electrospinning" plus "wound healing" or "antibacterial". The total counts is displayed above each bar; data analysis was conducted on May 14, 2013. While not included in the graph, currently, there have been 1224 publications on electrospinning with 9 and 20 publications dealing with wound healing and antibacterial applications, respectively.

oxygen therapy does not ensure success after one year of treatment.[3] Successful alternate treatments are desperately needed and engineered drug delivery vehicles, especially electrospun fiber mats, offer a promising solution.[4]

A wound dressing is a protective barrier used to assist in many aspects of the healing process. In comparison to typical bandages, which do not meet all the requirements of wound care, electrospun fiber mats could potentially provide an excellent environment for healing. Thus, there has been an increase in research focused on developing electrospun nanofiber mats that accelerate wound healing and prevent bacterial infections, Fig. 1.

Nanofibers generated using the electrospinning process exhibit high levels of porosity, gas permeation, and offer a high surface-to-volume ratio. These properties promote cell respiration, skin regeneration, moisture retention, removal of exudates, and hemostasis.[5] Additionally, by electrospinning a bioabsorbable polymer, patient comfort can be increased because the need to change the bandage is reduced.[6] By incorporating therapeutic or antimicrobial agents, functionalized electrospun mats could potentially serve as a personalized bandage that will contour to virtually any wound surface.[7] In this applications review, we present the five stages of wound healing, the electrospinning process, and strategies towards engineering electrospun nanofiber mats into advanced nanobiomaterials.

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2 Wound healing process

Naturally, when the skin is damaged, the body responds *via* a complex process known as wound healing.[8] Recent literature and numerous review articles provide detailed accounts of the wound healing process.[9–13] Therefore, in the following sections, we aim to present only the quintessential elements of (Section 2.1) how to categorize wounds and (Section 2.2) the stages of the wound healing process.

2.1 Categorizing wounds

Wounds—acute *versus* chronic—can be primarily categorized by their healing time. A wound that heals normally is an acute wound, while a wound that is arrested in a phase of healing is known as a chronic wound. Most often, chronic wounds are arrested in the inflammatory phase; high levels of matrix metalloproteinases (MMPs) cause degradation of the extracellular matrix (ECM) and of certain growth factors. The lengthened healing process associated with chronic wounds can cause a number of cells, particularly fibroblasts, present in the wound to become less active due to senescence (aging).[10]

The type of wound—cut *versus* burn—also affects the natural response of the body. After a cutting injury, hemostasis is achieved quickly, within the first 15 minutes.[11] In contrast, when an injury is caused by a burn, wounding can continue for up to 4 days after the initial trauma. The prolonged injury period, along with the increased extent of damage, causes a heightened inflammatory response commonly leading to extensive and sometimes hypertrophic scarring.[12]

2.2 Five stages of wound healing

During the ideal healing process, the wound progresses through (i) wounding, (ii) hemostasis, (iii) inflammation, (iv) proliferation, and finally (v) maturation (Fig. 2). These phases may overlap in some instances, not all phases will be reached in chronic wounds.

The wounding phase (Fig. 2A) marks the beginning of the wound healing process. During this phase, the skin is punctured leaving dead and devitalized tissue.[8] Immediately, fluid begins to leak from blood and lymphatic vessels, filling the injured site. Bacteria start to invade the open wound.

Within 15 minutes, local hemostasis is achieved at the wound site, (Fig. 2B).[11] Injured blood and lymphatic vessels rapidly undergo vasoconstriction,[10] preventing blood flow into local tissue indicated by visible blanching.[11] Thrombocytes

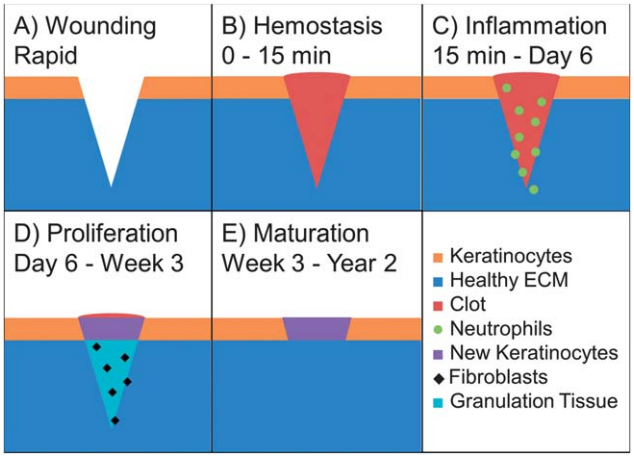

Fig. 2 The schematic provides the major elements, which occur during the five stages of wound healing. (A) During wounding, existing keratinocytes and the healthy extracellular matrix (ECM) are damaged. (B) Hemostasis is characterized by the formation of a clot that becomes the provisional ECM. (C) Neutrophils infiltrate the wound during the inflammation phase. (D) In the proliferative phase, new keratinocytes migrate into the wound as do fibroblasts, which produce granulation tissue. Finally, (E) as the wound matures the underlying ECM eventually returns to normal. Time duration for each phase of the wound healing process are also noted.

migrate to the wound site and fibronectin is cleaved into fibrin. Platelets, fibrin, fibronectin, vitronectin, thrombospondin, and various blood cells[10] join to form a clot. In later wound healing stages, the clot serves as a provisional ECM for cell migration.[11]

Fig. 2C displays the inflammation phase, which follows hemostasis and can last for up to 6 days after the wounding incident.[11] Vasodilation, accompanied by an increase in capillary permeability, is induced by chemical signals released from injured tissue and mast cells.[10] Polymorphonuclear cells, are the first inflammatory cells to arrive at the wound site; these cells are responsible for producing growth factors and removing cellular debris, foreign particles, and bacteria.[9,11]

Monocytes migrate to the wound site, where they transform into macrophages[11] to remove necrotic tissue and foreign particles.[9] Macrophages also stimulate fibroblasts to produce collagen and influence reepithelialization. The macrophage population reaches a peak 4 to 5 days after wounding and remain at the site for multiple weeks.[11] Lymphocytes, particularly $CD4^+$, $CD8^+$, and dendritic γδ epidermal T cells (DETCs), arrive approximately 6 days after injury[10] to facilitate later stages of the wound healing process.[11]

The proliferation phase, Fig. 2D, is characterized by reepithelialization, which occurs 24–48 hours after wounding. Keratinocytes migrate from the surrounding tissue and nearby hair bulges to the wound boundary. A wedge of keratinocytes, moving in from the edges across the wound, releases enzymes to begin the degradation of the provisional ECM.[11] The wedge continues until it contacts another wedge, leaving a stratified layer of keratinocytes in its wake. This migration is partially stimulated by the contact the cell has with fibrin and might also be motivated by connexins.[11] Keratinocyte migration does not depend on the number of platelets present but is slowed by the presence of neutrophils and macrophages, especially in diabetic wounds.

During the second day of healing, endothelial cells begin migrating into the wound as part of angiogenesis—the physiological process wherein new blood vessels develop from preexisting vessels. The migration is driven by cytokines, the presence of an ECM, and the absence of neighboring endothelial cells. MMPs stimulate the degradation of the basement membrane and the ECM. The endothelial cells migrate through the ECM, form tubules, and eventually form new capillaries. Laminin production is stimulated in endothelial cells to produce a new basement membrane.[11]

Approximately 4 days into the wound healing process, collagen-based granulation tissue replaces the fibrin-based provisional ECM. Granulation tissue contains fibroblasts, collagen, blood vessels, and macrophages and is similar to healthy ECM, except for the absence of elastin. In response to fibronectin, cytokines, and growth factors, the fibroblasts migrate along the fibronectin into the provisional ECM from the surrounding tissue. In addition to the existing fibroblasts, new fibroblasts are produced in response to macrophage products from nearby mesenchymal cells. All fibroblasts present in the provisional ECM regulate the growth and function of other cells within the matrix.[11] T cells, specifically DETCs, stimulate fibroblasts to produce type I collagen, fibronectin, and α5 integrin.[11] The net collagen deposition is needed to form the granulation tissue from 3 to 21 days after wounding.

As new granulation tissue is being generated, the wound undergoes contraction, 4–14 days after wound formation. Wound closure tends to occur at a rate of 0.6 to 0.75 mm per day and is aided by DETCs.[9] Approximately 4 to 6 days after wounding, some fibroblasts are converted into myofibroblasts, which produce actin and decrease wound closure time.[11]

In the maturation phase, tissue remodeling begins with the replacement of granulation tissue with scar tissue approximately 3 to 6 weeks after the wound incident and can continue for months, Fig. 2E.[11] Over time, the proportion of type I collagen increases, while the proportions of type III collagen, proteoglycans, and water decreases. During remodeling, collagen fibrils increase in diameter, exhibit increased interfibril binding, and rearrange.[11] Mast cells may be involved in the collagen remodeling process as well.[9] In early phases of wound healing, collagen fibrils are arranged haphazardly, which results in a high level of collagen, and low relative tissue strength. Collagen fibrils become significantly more ordered after one year of recovery. As the scar matures, redness decreases as the capillary density decreases. The level of scar tissue is greatly influenced by the presence of immune cells and the level of inflammation that the wound has undergone. For example, the lack of immune cells has been linked to an absence of scar formation, as well as, a lower level of fibrogenic growth factor and a higher level of hyaluronic acid.[9] Scar formation increases in the presence of neutrophils, macrophages, and T cells,[9,14] while a large number of mast cells causes hypertrophic scarring.[9]

3 Commercial treatments *versus* electrospun nanofiber mats

Armed with the knowledge that the wound healing process is complex, it should come as no surprise that currently, no single treatment modality can address all aspects of the healing process. Hence, a plethora of options are available. As far as we are aware, clinical "head-to-head" trials between commercial treatments and electrospun nanofiber mats have not yet been conducted. However, the unique structure-to-function relationship of nanofiber mats can be discussed with regard to the properties offered by conventional treatment options. While in Sections 4 and 5 of this review we will discuss the specifics of electrospun materials, here, we briefly discuss why nanofiber mats hold promise as a commercially viable alternative to the current strategies.

Plain gauze is the most widely used material because it is inexpensive and readily available. However, it has numerous shortcomings, which have inspired the development of other approaches: foams, hydrogels, films, biologic dressings, and hydrocolloids.[15] Conventional foams and hydrogel dressings can adsorb only minimal exudates with moderate success[15] and lack the additional features of more advanced dressings.[16] For instance, the nanostructure of an electrospun fiber mat allows for an incredibly high surface area, better gas transport, and more efficient exudate absorption than traditional films and foams.[5]

Current biologic dressings fall into one of three categories: composite grafts with epidermal and dermal components, dermal replacements, and epidermal grafts. However, they all suffer from the major disadvantages of cost and availability.[19] On the other hand, recent advances have made electrospun materials commercially viable for some applications.[20]

Traditional antibacterial ointments have to be reapplied often to maintain moisture.[15] But, by properly choosing the electrospinning technique and post-processing steps, a prolonged and improved release profile of antibacterial agents can be achieved. Additionally, the frequency of dressing change could be lowered.[5,16]

To date, no commercial strategy has replicated the complex biological functionality and biophysical properties offered by the native ECM. However, nanotopology has been noted as key determinant of cell proliferation and migration.[4,18] Due to the morphology of fiber mats fabricated by the electrospinning process, they are being proposed as a better ECM analog than current technologies.[4,5,17] Thus, unsurprisingly, electrospun nanofiber mats have been demonstrated to support the adhesion, proliferation, and differentiation of various cells. Additionally, they have served as a delivery platform for drugs, growth factors and other biomolecules that may further improve cell function and tissue regeneration. In order to match the innate structural advantages of electrospun fiber mats, traditional wound dressings would have to undergo extensive lithography or imprinting. In terms of transport and materials availability, nanofiber mats can be spun directly onto the open wound of a patient.[21] In sum, the advantages that nanofiber mats have to offer, *i.e.*, structural, functional, falling cost, and ease of use, add more incentive to fully explore their potential as wound healing scaffolds.

4 Electrospinning

Early exploration into electrodynamics laid the foundation to our current mechanistic understanding of the electrospinning process. Gilbert (1500s) reported that in the presence of charged amber, spherical droplets of water could be pulled into a conical shape.[22] Three hundred years later, the excitation of a dielectric liquid by an electric field was reported by Lamor.[23] Significant progress was documented in patents published in 1902[24,25] and 1934.[26–28] Electric fields were applied to polymer solutions using a systems approach featuring multiple spinnerets, a moving collection target, and a collector composed of parallel electrodes. These systems pioneered the design resembling modern laboratory and industrial electrospinning set-ups. While there have been numerous significant lulls in electrospinning research over the past five hundred years, current interest in this inexpensive nano- and macro-fiber fabrication technique continues to be on the rise.[29]

4.1 Electrospinning process

A conventional electrospinning apparatus includes a high voltage power supply, a grounded collector, and a spinneret, Fig. 3. Electrodes connect the collector to the spinneret, which completes a circuit to produce an electric field. A precursor solution—typically a polymer, sol–gel, or melt—is loaded into the spinneret and advanced at a low feed rate allowing for the formation of a pendent drop held at the tip of the spinneret *via* surface tension. As the voltage is increased, the repulsive electrical forces pull the pendent drop into a conical shape known as a Taylor Cone.[30,31] Once the voltage reaches a critical value, the electrical forces overcome the surface tension forces and a liquid jet emerges from the Taylor Cone, which reaches the collector in 18 nanoseconds.[32] During travel, the polymeric solution enters a bending instability where the liquid jet is stretched and whipped forcing the solvent to evaporate before fibers are collected on the target. A polymer solution with an insufficient viscosity will experience an additional instability during travel known as the Rayleigh instability, which can cause inconsistent fiber morphology, *i.e.*, beading.

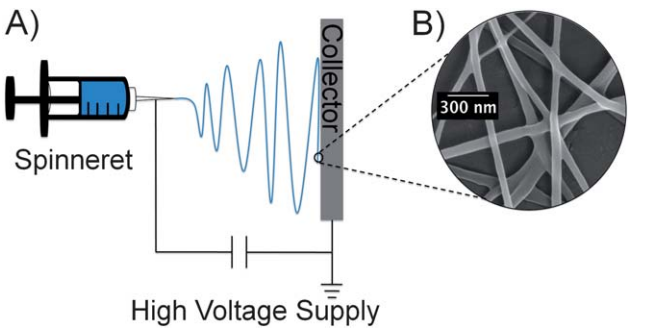

Fig. 3 (A) The schematic displays an electrospinning apparatus, which is composed of a spinneret, a high voltage supply, and a collector. Usually, an advancement pump is used to regulate the flow rate of the polymeric solution. (B) The scanning electron micrograph displays the nanofiber morphology present in an electrospun non-woven mat, a 300 nm marker is displayed.

4.2 Electrospinning variables

Fabrication of fibers *via* electrospinning is dependent on the precursor solution, processing variables, and ambient conditions. The extent of chain entanglement within a polymer solution is directly related to the ability to electrospin fibers. Only once the polymer concentration is above the critical concentration, can fiber spinning ensue.[33–35] Other properties of the precursor solution—conductivity, surface tension, viscosity, and polymer concentration—can be optimized by appropriate polymer and solvent selection. Different solvents and salts can be used to adjust the conductivity and surface tension of the system.

Controlling particular electrospinning apparatus parameters directly influences the resultant mean diameter and arrangement of the accumulated fibers. An increase in voltage or a decrease in feed rate will facilitate a reduction in fiber diameter.[36] The separation distance needs to be sufficient for solvent evaporation but close enough to enable the desired fibrous morphology.[37] Ambient parameters—temperature and humidity—should be controlled and monitored through the process since they affect fiber formation. For example, an increase in temperature will decrease the average fiber diameter, due to a decrease in solution viscosity. While an increase in humidity will increase the average fiber diameter due to polymer swelling.[38–40] Fiber alignment can be achieved through the manipulation of the electric field profile and appropriate collector selection.[41] Rotating drums,[42] parallel electrodes,[43] and an array of counter-electrodes[44] are example collectors, which have been implemented to generate a controlled arrangement of fibers.

5 Nanofiber mats for wound healing

Electrospinning enables the fabrication of scaffolds, which can be easily altered *in situ*—during the electrospinning process—or post-fabrication to be suitable for a specific biomedical application. The rate at which drug(s) are released from a mat can be controlled through polymer selection, which dictates the degradation rate of the mat[45] or *via* the placement of the drug within, or on the surface of the fibers.[46] Details concerning polymer selection, as well as numerous methods towards tailoring the location of the active agent within the electrospun mat are provided.

5.1 Polymer selection enables appropriate wound healing

When engineering mats for wound healing applications the appropriate polymer matrix, natural, synthetic, or a rational combination of polymers, should be selected that match the desired scaffold properties.[47] Natural polymers are derived from renewable sources and are intrinsically biocompatible and biodegradable. Polysaccharides, such as chitosan,[35,48–51] cellulose,[52–55] and hyaluronic acid,[56,57] as well as proteins, collagen[42,58,59] and silk[60–63] have been electrospun for localized drug delivery.[47] Many of these polymers have specific properties that promote wound healing. For instance, chitosan exhibits both antibacterial and hemostatic activity. Synthetic polymers commonly used for wound healing applications include poly(ethylene oxide) (PEO),[64–66] poly(lactide) (PLA),[67–71] poly(caprolactone) (PCL),[72] and poly(vinyl alcohol) (PVA).[73] Mats composed of these polymers display higher mechanical properties than natural polymers. Additionally, synthetic polymers are compatible with a wider range of solvents, which can facilitate the spinning process.[74] Often, wound healing scaffolds depend on spinning the biopolymers in conjunction with a synthetic polymer in order to fine-tune the mechanical, degradation, and/or morphological features of the porous fiber mats towards the needs of the individual patient.

5.2 Electrospinning technique tailors the active agent location

Strategically designed electrospun mats are enabled by implementing a variety of electrospinning and post-processing techniques. Depending on the desired release rate, active agents can be incorporated within or decorated on the outside of the fibers, Fig. 4. Implementing solution blending or core/shell electrospinning can additionally provide active agents that are housed inside the fibers. Typically, modification of nanofiber mats after electrospinning yields fibers with the active agents close-to or on the outer surface of the fibers.

5.2.1 Blend electrospinning yields a dispersed active agent. Blending,[75] consists of suspending a drug,[76] an active agent,[77] or a precursor agent (*e.g.*, silver ions[78]) that can be reduced to an active agent (*e.g.*, silver nanoparticles) into the electrospinning solution, Fig. 4A. The as-spun mats can contain the agent dispersed throughout or at the surface[79,5] of the fibers. This technique requires the traditional electrospinning apparatus and can be used to incorporate a multitude of polymers and wound treating agents.[80]

Ojha *et al.*[65] demonstrated that polymer/agent blend fibers can accumulate the agent along the surface of the fibers, which

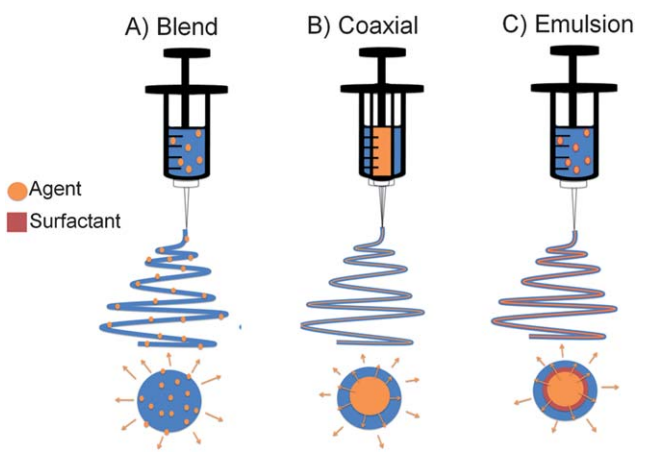

Fig. 4 Schematic displays the spinneret loaded with a bioactive agent for (A) blend, (B) coaxial, and (C) emulsion electrospinning. Coaxial electrospinning requires the use of a concentric spinneret configuration. (A) Blend electrospinning often yields fibers that contain the active agent dispersed throughout the fibers, whereas (B) coaxial and (C) emulsion electrospinning lend well to the synthesis of a core/shell morphology. The cross-section of an individual fiber produced *via* the three methods is displayed.

occurs *in situ* as the solvent is being evaporated. As a result, these blended fibers exhibit a high initial release of drug known as a burst release.[81] Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of agents where a burst release would be favorable. A PLGA electrospun mat containing ibuprofen was shown to reduce pain immediately and prevent the response of fibroblasts to major pro-inflammatory stimulators due to a burst release of medicine characteristic of polymer/agent blend fibers.[6]

A high initial release of an antibiotic is desirable at the site of a wound to eliminate bacteria, while a subsequent slow release of drug aids in preventing an infection. Jannesari *et al.*[73] electrospun composite PVA/poly(vinyl acetate) (PVAc) nanofiber mats containing ciprofloxacin HCl, whose initial burst release rate was doubled when the drug content was increased from 5 to 10 weight percent (wt%). By blending the hydrophobic polymer, PVAc, into the fibers, the hydrophilic model drug would be more likely to migrate to the surface of the fibers during solvent evaporation. Additionally, the PVAc mats were better engineered for wound healing because they demonstrated a slower sustained release rate and were more flexible.

5.2.2 Coaxial electrospinning controls active agent release. When a burst release is not desired or the bioactivity of the agent is sensitive to harsh solvents, encasing the agent in a polymeric shell is necessary. Coaxial electrospinning[82–86] produces core/shell fibers by using a "coaxial" or concentric needle arrangement, which features an inner and an outer channel to separate two or more solutions, Fig. 4B. In the context of synthesizing wound healing mats, an outer polymer shell can be used to encase the active agent. To do this, the active agent is fed through the inner channel. The outer shell provides a protective barrier from the electric field, as well as from harsh solvents, which might be needed to electrospin the polymer located in the outer channel of the syringe.[87] Additionally, non-spinnable material such as inorganic nanomaterials can be electrospun into the core of the fiber by placing a polymer in the outer channel to carry the non-viscous material through the process.[88]

While the addition of an inner channel increases the processing parameters that need to be optimized, this electrospinning technique is superior for obtaining controlled drug release *via* eliminating a burst release. Su *et al.*[89] compared the release rates of heparin encapsulated in the core of poly(L-lactide-*co*-ε-caprolactone) (PLCL) fibers and fibers composed of heparin blended with PLCL. The composite fibers showed a high initial release while heparin, once located in the core of the fiber, demonstrated a stable sustained release over two weeks. It was deduced that the release from the core/shell fibers was governed by a coupled diffusion/degradation mechanism.

5.2.3 Emulsion electrospinning enables active agent loading. Another route towards achieving a core/shell morphology is to employ an emulsion as the precursor solution,[90–94] Fig. 4C. Here, a surfactant is used to separate the distinct phases. This type of electrospinning allows for the incorporation of protein, DNA, and peptides by preventing their exposure to harsh organic solvents.[94] Yang *et al.*[93] demonstrated the use of emulsion electrospinning as a carrier for therapeutic proteins *via* electrospinning an emulsion consisting of a water phase containing the model protein, bovine serum albumin, and an organic phase using the polymer, poly(DL-lactide). In addition to keeping the encapsulated protein bioactive, the initial burst could be reduced through lowering the volume ratio of aqueous to organic phase.

Water-in-oil (W/O) emulsions have been electrospun wherein the oily phase consists of a polymer dissolved in an organic solvent and the water phase contains the active agent. This system is ideal for the delivery of a hydrophilic drug because a hydrophobic shell is needed to protect the drug from dissolving instantaneously in the blood stream.[92] For example, by spinning from an emulsion pre-curser solution, TCH (a hydrophilic antibiotic) was successfully encapsulated within the core of poly(ethylene glycol) PEG–PLA nanofibers.[95] As characteristic of emulsion electrospinning, these fibers showed a stable release rate, elimination of an initial burst release, and protection of the active agent incorporated.

5.3 Post-processing of electrospun mats enhances wound healing properties

The surface of an electrospun mat might lack the properties needed for a specific bio-application. As a result, as-spun fibers can be modified post-spinning *via* electrostatic attachment,[96] dip-coating,[97,98] layer-by-layer assembly,[99] or by performing surface chemistry,[100–102] Fig. 5.

Coating consists of submerging a fabricated electrospun mat into a solution in order to transfer desirable properties to the mats. Chitosan has been used to coat PVA electrospun fibers by submerging the fibers in a 1.0 wt% chitosan solution for 1 hour at 30 °C.[97] In addition to using this facile process, another advantage of coating is that chemically, the chitosan coating more closely resembled glycosaminoglycans in the ECM than their control (chitosan–PVA blend fibers). In order to provide immediate hemostatic activity, Spasova *et al.*[98] also chose chitosan to coat their wound healing electrospun PLA and PLA–PEG mats.

Performing chemical modifications to functional groups located on the surface of the fibers can enable the attachment of biofunctional molecules or tune the degree of hydrophilicity of the mat. The addition of a biofunctional molecule can promote certain biological activities such as cell proliferation and migration.[101] This is specifically important in treating diabetic ulcers, where the natural wound healing process is

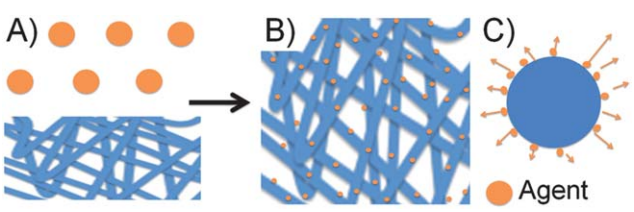

Fig. 5 Post-production, (A) as-spun mats can be modified with functional agents (*e.g.*, polymers, drugs, biomolecules) to (B) alter their surface chemistry and functionality. (C) A cross-section of an individual fiber post-modification displays that the new functional units are located on the surface of the fiber.

compromised, thus leading to chronic wounds and in some cases amputation. EGF, the epidermal growth factor, was chemically immobilized to functional amine groups on the surface of PCL and PCL–PEG block copolymer blended fibers to treat diabetic ulcers.[102] *In vivo* wound studies demonstrated an increase of keratinocyte-specific genes as a result of the EGF conjugated fibers. Thus, the incorporation of a growth factor facilitated gene expression, which in turn accelerated wound healing.

Through the attachment of biomolecules onto the surface of fibers, the mat can be functionalized to make use of the body's natural enzymes. A MMP-responsive release dressing was electrospun as a local gene delivery system to treat diabetic ulcers, which display high levels of MMPs.[100] Linear polyethyleneimine (LPEI) was chemically attached through an MMP-cleavable peptide linkage to amine groups, which were already present on the surface of PCL–PEG nanofibers. The mat was further modified through the electrostatic attachment of negatively charged DNA to the positively charged LPEI. The ability to release DNA in the presence of MMP makes this system ideal for local gene therapy of diabetic ulcers.

5.4 Antibacterial nanofiber mats can reduce chronic wound biofilms

Prevention of an infection is essential to complete wound repair. The addition of antibacterial agents—inorganic, organic, or metallic—into electrospun mats has continually been an important research focus (Fig. 1), especially as antibiotic resistant bacteria strains increasingly emerge. A wide range of biocidal nanofibers is imperative to effectively treat both the Gram-positive and the Gram-negative bacteria present during wound healing and for the prevention of hospital-acquired infections.

Metals have been incorporated into electrospun mats as antibacterial agents; the most common of these agents is silver.[51,78,79,96,103] Silver displays a wide spectrum of biocidal activity and a low bacterial resistance as compared to other antimicrobials agents. In wound healing, silver decreases surface inflammation and promotes surface calcium, stimulating epithelialization. In order for silver to be incorporated, a reducing method must be utilized to prevent cytotoxicity. This can be achieved by using an aqueous route instead of an organic agent.[103] Nguyen *et al.*[79] took advantage of the ability of PVA to be a reducing agent for silver nanoparticles/PVA blended fibers. Once electrospun, a heat treatment process was employed to draw silver nanoparticles to the surface of the fibers where they can be the most effective. The use of PVA as a reducing agent allowed for a faster, simpler and more economical process than conventional methods. Silver has additionally been reduced *in situ* while electrospinning a number of other polymer mats.[104,105] The bactericidal efficacy of silver nanoparticle (AgNP)-coated electrospun fiber mats has been demonstrated for the first time by Schiffman *et al.*[96] Here, polysulfone (PSf) fiber mats were electrospun and then surface-modified using an oxygen plasma treatment, which allowed for the facile irreversible deposition of cationically charged polyethyleneimine (PEI)–AgNPs *via* electrostatic interactions. Time-dependent bacterial cytotoxicity studies indicate that the optimized PSf–AgNP mats exhibit a high level of inactivation against both Gram-negative bacteria, *Escherichia coli* (*E. coli*), and Gram-positive bacteria, *Bacillus anthracis* (*B. anthracis*) and *Staphylococcus aureus* (*S. aureus*). Although silver, like many other metals, displays excellent antibacterial properties, it can also cause irritation and bind to DNA preventing replication, both of which can hinder the healing process.

Inorganic materials, specifically titania, have been incorporated within electrospun bandages. Pure and iron (Fe)-doped titania nanofibers, spun from ceramic–polymer precursor solutions, demonstrated photoactivated antimicrobial activity against *E. coli* using multiphoton infrared spectroscopy for 3 seconds.[106] Titania also exhibited antibacterial efficiency against *Pseudomonas aeruginosa* (*P. aeruginosa*) and *S. aureus* when loaded into polyurethane (PU) electrospun fibers.[107] Testing performed in solution on titania mats doped with 0.4 and 1.6 $\mu g\ mL^{-1}$ of zinc (Zn)[108] demonstrated an inhibition of *E. coli* and *S. aureus* growth, respectively.

Carbon-based nanomaterials are cytotoxic to bacteria.[109–111] Of this class of materials, single-walled carbon nanotubes (SWNTs) exhibit the highest toxicity and they can kill microbes on contact.[112,113] For the first time, Schiffman *et al.*[75] has demonstrated that even at a low weight percent loading of incorporated SWNTs, their antibacterial activity is retained. Four different weight percents of well-characterized, small diameter (0.8 nm) SWNTs were incorporated into electrospun polysulfone (PSf) mats. Electrospun PSf–SWNT mats were observed to be flexible and composed of continuous, cylindrical, and randomly oriented fibers. Loss of bacteria (*E. coli*) viability was observed to directly correlate to increased SWNT incorporation within the mat, ranging from 18% for 0.1 wt% SWNTs to 76% for 1.0 wt% SWNTs. Time-dependent bacterial cytotoxicity studies indicated that the antimicrobial action of the PSf–SWNT mats occurs after a short contact time of 15 minutes or less.

Alternatively, researchers have been inspired by nature for antibacterial agents. Plant-based antimicrobials, shikonin and alkannin, loaded into polymeric fibers demonstrated biocidal activity against both *S. aureus* and *E. coli.* The fiber mats additionally provided aid in both the inflammation and proliferative phases of wound healing.[114,115] Fusidic acid, a protein synthesis inhibitor derived from fungus, was blended into PLGA fibers to prevent the growth of bacteria.[69] The drug release from these fibers was dependent on the severity of the wound. Both lightly and heavily infected wounds were treated *via* bioburden-triggered drug release of fusidic acid from PLGA mats. Lysostaphin (Lst), a cell lytic enzyme with specific bactericidal activity against *S. aureus*, was immobilized on the surface of cellulose, cellulose/chitosan, and cellulose/poly(methyl methacrylate) (PMMA) electrospun fiber mats.[116] In addition to cleaving the pentaglycine cross-bridges in the peptidoglycan layer of the cell walls of *S. aureus*, Lst loaded nanofibers also displayed low toxicity towards keratinocytes, which are cells imperative in the proliferative phase of wound healing. Motivated by the findings by Zodrow *et al.*,[117] cinnamaldehyde (CA), an essential oil derived from cinnamon bark, was delivered from electrospun nanofiber mats. A Schiff base reaction was employed to reversibly conjugate CA (0.5 and 5.0%) to chitosan. Chitosan and chitosan-CA

derivatives were electrospun with PEO into nanofiber mats, all of which had an average fiber diameter of ~50 nm. At physiological conditions the Schiff base was reversed, thus releasing CA-liquid and CA-vapor from the chitosan-CA nanofiber mats. CA release was correlated to time-dependent bacterial cytotoxicity against two Gram-negative bacteria, *E. coli* and *P. aeruginosa*. Fig. 6 displays that due to their chitosan content alone, after 180 minutes of incubation, the control mats inactivated 47 ± 4.4% *P. aeruginosa*. However, by statistically increasing the availability of the CA to interact with the bacteria, the antibacterial activity of the mats increased. A very high inactivation against this opportunistic human pathogen, 81 ± 4.1%, was achieved by the nanofiber mats, which were spun with the 5.0 wt% chitosan-CA derivative. Their findings indicate that potentially chitosan-CA nanofiber mats could serve as therapeutic wound dressings to treat nosocomial pseudomonas infections.

5.5 Emerging nanofiber mats that strategically target multiple facets of wound healing

The next generation of electrospun mats will be functionalized to fulfill multiple components of the wound healing process. The current aim is to develop systems that not only target various components of the wound healing process (*i.e.*, anti-inflammatory and antibacterial activity) but also provide an adjustable and controlled release of multiple drugs.[119] The amount and progression (be that simultaneous or a stepwise release) of drugs will be determined by the stage of the healing wound.

Fibers with a core/shell structure offer a simple way to deliver more than one active agent. Using coaxial electrospinning, Su *et al.*[46] fabricated core/shell poly(L-lactide-*co*-caprolactone) (PLLACL) fibers to encapsulate both rhodamine B (RHB) and bovine serum albumin (BSA). To study the effect of drug placement on release rates, three different systems were fabricated: (i) two drugs in the shell, (ii) two drugs in the core, and (iii) one drug in the shell and one in the core. The drug encapsulated within the core displayed a slow release rate, unlike the burst release exhibited when the drug was placed in the shell. Certainly, the core/shell thickness ratio can be adjusted to tailor release rates.

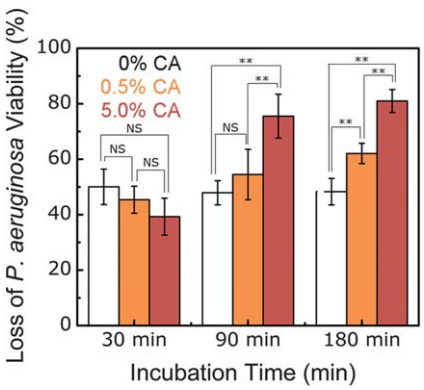

Fig. 6 Recently, Rieger and Schiffman[118] blend electrospun chitosan/polyethylene oxide (PEO) nanofiber mats (control), as well as PEO blended with two synthesized chitosan–cinnamaldehyde (CA) derivatives (0.5% and 5.0% CA). CA release was correlated to time-dependent bacterial cytotoxicity against two Gram negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* (shown above). Asterisks (**) denote that a statistical increase in cytotoxicity occurred whereas "NS" indicate that the change is not significant. Figure from ref. 118.

Core/shell morphology is also favored when fabricating multifunctional fibers because the encapsulated agent is protected from post-spinning functionalization. To treat diabetic ulcers, Choi *et al.*[82] electrospun core/shell basic fibroblast growth factor (bFGF)/PCL–PEG block copolymer fibers using a coaxial apparatus. EGF was conjugated to the exposed amine groups on the surface of the fibers, thus further functionalizing them. The nanofiber mats demonstrated biphasic release profiles, which supplied a cascade of growth factors to increase collagen and keratin expression leading to a decreased healing time.

Recently, triaxial electrospinning of nanofiber has been demonstrated in an effort to improve the biocompatibility, mechanical properties, and the incorporation of drugs into mats for biomedical application. By using three concentric needles, Lui *et al.*[120] have electrospun biodegradable nanofibers, which have an outer and inner gelatin layer, as well as a middle layer composed of PCL. Most core/shell morphology nanofibers can only meet one or two of these objectives, showing advantages for a three-layer structure.

Spinning two types of polymer fibers, each containing an active agent, onto the same collector, is another approach to develop multi-component mats. Simultaneously, two solutions of poly(L-lactic acid) (PLLA) were spun using separate spinnerets, which were connected to the same target to fabricate a wound healing bandage.[71] One solution contained lidocaine, an anesthetic, while the other carried the antibiotic mupirocin. The resulting mats demonstrated altered kinetics when compared to electrospun mats containing only one of the active agents. Lidocaine shows a higher burst release, while mupirocin shows a sustained release rate.

Encapsulation of an active agent in micro/nanoparticles, which were then electrospun, has been proposed as an effective means to produce multifunctional fibers. PLLA/polyvinylpyrrolidone (PVP) blended fibers were used to encapsulate the model hydrophilic and hydrophobic drugs, bovine serum albumin (BSA) and benzoin, respectively. This was accomplished by loading BSA into chitosan microspheres, which were then suspended into the polymer solution along with benzoin.[121] By loading one drug into microspheres, each agent had distinct release rates that could be adjusted by changing the polymer blend ratio. Song *et al.*[122] also investigated the use of particles to encapsulate an active agent. RHB was enveloped inside mesoporous silica nanoparticles (MSNs) and incorporated into a PLGA/fluorescein (FLU) polymer/drug blended solution. The release rates were found to be independent of each other, which is in agreement with the previous example. The loading percent of MSNs was directly related to the release of RHB and even at high loading levels, RHB was released at a slow sustained rate.

6 Perspective

In the quest to develop an ideal wound healing dressing, there exists a consensus that the material should be antibacterial,

nontoxic to mammalian cells, nonantigenic, permeable for gaseous exchange, and resistant to shearing forces; while also being elastic and flexible to conform well to the underlying topography. From the perspective of the patient, other essential properties for a dressing include reducing pain and healing time, as well as increased long-term aesthetics. To ensure that commercialization is a success, the dressing should be inexpensive and have a long shelf life.[123,124]

However, due to the complexity of the healing process no panacea exists. In part because different wounds have different needs from a wound dressing. Heavily exuding wounds require an exceptionally absorbent dressing, while a dry wound should receive a high water content dressing for rehydration. Nanofiber mats electrospun from biopolyelectrolytes, such as hyaluronic acid[56] hold promise for these wounds.

A cavity wound must be packed with a flexible and suitable dressing.[13] Nanofiber mats can be directly spun as a conformal coating onto practically any surface, thus, a good option for cavity wounds.[5,21] If a wound is contaminated with bacteria, as is the case for diabetic foot, pressure, and venous leg ulcers, then the bandage needs to be able to disrupt the biofilm.[2] Section 5.4 discusses numerous case studies where antimicrobial nanofiber mats have delayed the onset of biofilm formation, however future research aimed to inactivate specific microbes would further these wound dressings for individualized health care.

As a value-added product, wound healing scaffolds do not require the same economics of scale needed for many other industries. While electrospun materials are commercially viable for some applications,[20] increasing the production of bioactive electrospun nanofiber mats beyond the bench scale still remains an obstacle. However, this is not unique to nanostructured dressings as commercially available dressings are also currently expensive and limited.[19]

Without a doubt, significant advances over the past dozen years have been made to tailor nanofiber mats towards wound healing applications. However, there are numerous additional factors—clinical, psychosocial, educational, and professional/organizational—that may also delay the clinical implementation of nanofiber mats.[125]

Most relevant to this review is the need for the scientists and engineers who designed the nanostructured wound dressings to work with clinicians to increase educational best practices. For example, if a nanofiber mat is engineered to stay on a cavity wound for a longer duration of time than the current commercial treatment, this procedure must be well communicated to the clinician to ensure that when the randomized controlled trials (RCTs) are conducted, there will be an improved interpretation of results. Well-designed RCTs are the "gold standard" method of evaluating effectiveness of a wound dressing[125] and still remain essential before the commercialization of highly specified electrospun nanofiber mats tailored for wound healing.

7 Conclusions

The continued development of antimicrobial resistance, globalization, and industrialization reinforces the need to engineer alternate treatments, which can successfully heal chronic wounds. Scaffolds composed of electrospun nanofibers have demonstrated an impressive versatility. Matrix chemistry, surface functionality, and mat degradation rate can be tuned in conjunction to govern the interactions that occur at the interface between the materials' surface and biology. With the addition of more RCTs in clinical settings, tailored electrospun nanofiber mats can offer a broad impact to the nanomedicine community.

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