# Electrospun Nanofibers as Dressings for Chronic Wound Care: Advances, Challenges, and Future Prospects

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Chronic non-healing wounds show delayed and incomplete healing processes and in turn expose patients to a high risk of infection. Treatment currently focuses on dressings that prevent microbial infiltration and keep a balanced moisture and gas exchange environment. Antibacterial delivery from dressings has existed for some time, with responsive systems now aiming to trigger release only if infection occurs. Simultaneously, approaches that stimulate cell proliferation in the wound and encourage healing have been developed. Interestingly, few dressings appear capable of simultaneously impairing or treating infection and encouraging cell proliferation/wound healing. Electrospinning is a simple, cost-effective, and reproducible process that can utilize both synthetic and natural polymers to address these specific wound challenges. Electrospun meshes provide high-surface area, micro-porosity, and the ability to load drugs or other biomolecules into the fibers. Electrospun materials have been used as scaffolds for tissue engineering for a number of years, but there is surprisingly little literature on the interactions of fibers with bacteria and co-cultures of cells and bacteria. This Review examines the literature and data available on electrospun wound dressings and the research that is required to develop smart multifunctional wound dressings capable of treating infection and healing chronic wounds.
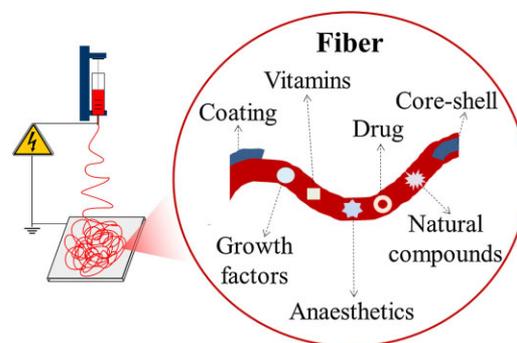
1. Introduction

Chronic non-healing wounds, such as diabetic foot ulcers, pressure ulcers, and venous leg ulcers exhibit a pathologically delayed healing process, remaining open or partially healed for several weeks or months. The microenvironment of a healing wound is complex and involves a large number of molecules, which require a cascade of events for wound closure to occur.[1] Chronic wounds are characterized by the presence of persistent inflammatory stimuli, which interrupt the physiological healing mechanisms. This causes the continuous attraction of macrophages and neutrophils to the wound bed, with the secretion of inflammatory cytokines, which in turn increase the production of metalloproteinases (MMPs), which disrupt the healing process.[2] Moreover, wounds can become contaminated by a complex population of many different bacteria coming from different sources (external environment, surrounding skin, and endogenous sources). In chronic wounds, the immune response to the presence of bacteria further prolongs tissue inflammation, consequently delaying healing. Pathogens enter chronic wounds leading to development of infection through the formation of a biofilm. Within the biofilm, bacteria are isolated from the

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immune system and can develop high resistance against antibacterial agents, which in turn leads to higher risk for systemic infection.[3]

Currently, chronic wounds are treated with a broad variety of dressings tailored to the requirements of the wound (dry or exuding, clean or infected, superficial or deep). The simplest dressings, such as gauzes and bandages, provide protection of the wound from mechanical trauma and bacterial infiltration and allow gaseous and fluid exchange; they are used as a support for more complex dressings or for the treatment of superficial, shallow, and non-infected wounds. Most chronic wounds require a specific control of the moisture levels. Various dressings, including hydrocolloids and alginates, capable of maintaining or providing suitable levels of moisture are available. More advanced devices are able to reduce the bacterial load in the wound bed by releasing antimicrobial agents, such as iodine or silver. Although these dressings have significantly improved wound management, a device capable of effectively healing chronic wounds while tackling infection does not exist.

The manufacture of polymeric nanofibrous meshes is central to the development of many wound dressings. These structures are made of ultra-fine fibers with diameters ranging from several micrometers down to few nanometers. Several intrinsic properties of nanofibrous meshes, such as high-surface area and nanoporosity, make these structures particularly interesting for wound healing applications. Various techniques, including phase separation or self-assembly, can be used for the fabrication of the meshes, but electrospinning is most frequently chosen because it is a simple, cost-effective, and versatile process. Based on the application of a high voltage to the selected polymer solution or melt, nanometric filament formation is induced as the polymer is drawn toward a collector (Figure 1b). After a certain time, a nanofibrous structure made of polymeric non-woven or aligned fibers can be collected.[4] The electrospinning process has been known since 1900 when it was patented for the first time by Cooley,[5] but it is only over the past 10 years that it has been used for medical applications, in particular for the fabrication of tissue engineering scaffolds.

Electrospun scaffolds have been shown to promote cell migration and proliferation, thus being suitable structures for supporting three-dimensional tissue formations.[6] However, for wound healing applications, these structures need to be specifically adapted to satisfy essential requirements. Electrospun scaffolds in the form of two-dimensional non-woven meshes have been shown to promote hemostasis, fluid absorption, cell respiration, and gas permeation when implanted onto open wounds.[7,8] Ideally, the meshes should be able to actively initiate the healing processes, while reducing the bacterial contamination and treating infection only if necessary. Since the dressing is

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designed to be removed once the wound has healed, the mesh should promote cell migration and proliferation within the wound bed while preventing tissue ingrowth within the fibrous structure.

Different strategies are currently used by researchers to create electrospun meshes with the ability to assist the healing processes while preventing wound infection (Figure 1c). Various synthetic and natural polymers can be combined to develop materials that actively support and supplement the deposition of healthy tissue. Different techniques have been developed for the loading of fibers with growth factors, vitamins, and other biomolecules known to encourage the healing processes. Coaxial electrospinning is frequently used to fabricate core–shell fibers, constituted by a polymeric external shell and an internal solution containing drugs or other biomolecules. There is also significant focus on incorporating drugs, silver nanoparticles, and plant-derived compounds, including essential oils and honey, which exhibit antimicrobial properties. Finally, the real-time detection of the wound bed environment, including pH or temperature, as
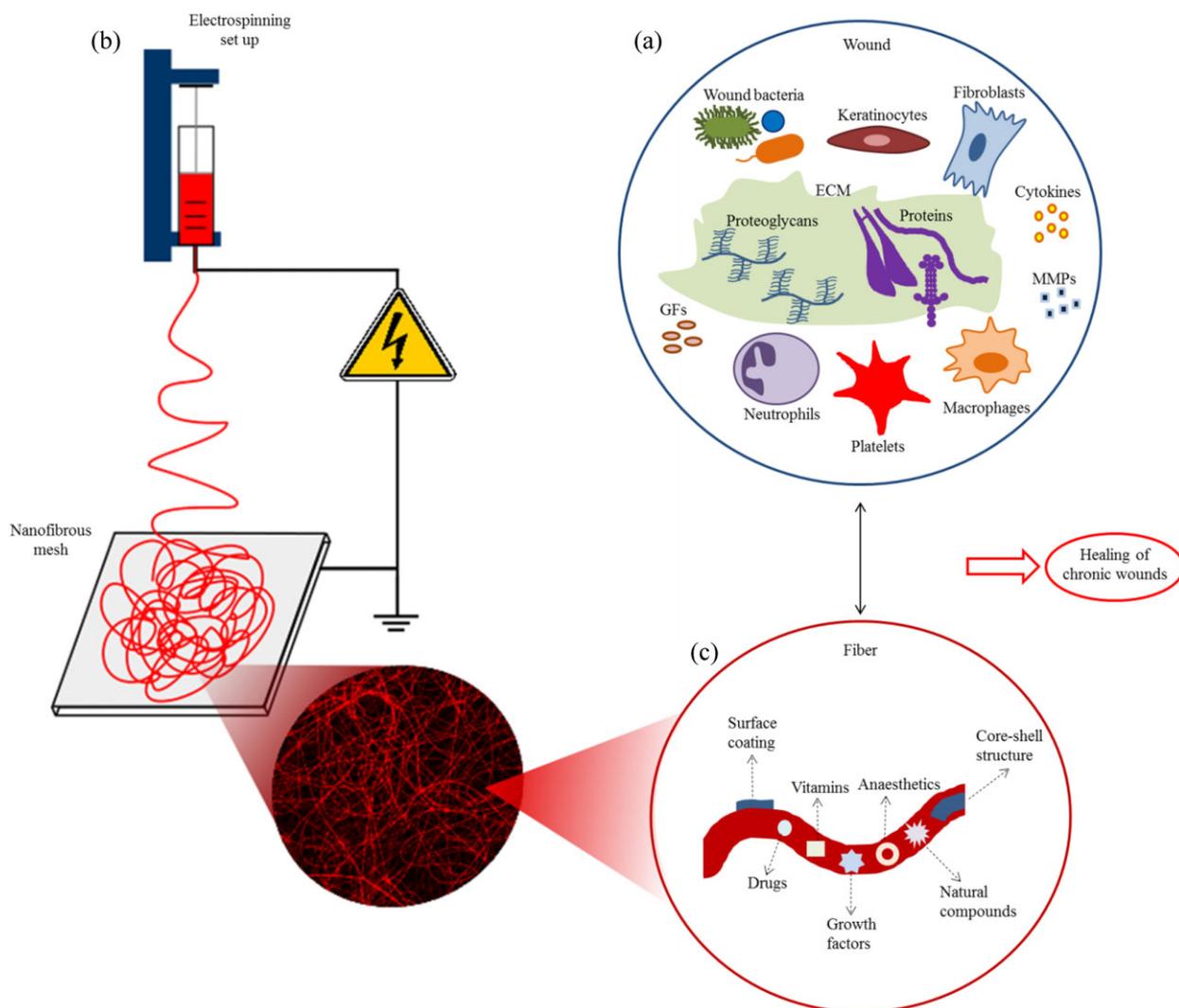
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Figure 1. Schematic showing a) the principal biomolecules present in the wound bed and involved in the healing process; b) the fabrication of nanofibrous meshes by electrospinning process; and c) the main approaches to provide electrospun fibers for the necessary properties for wound healing applications.

indicators of the status of the wound has been explored.[9] The integration of different types of biosensors within wound dressings has been proposed as the future of smart devices, capable of real time sensing and monitoring the wound.

Although electrospun materials have been used for tissue engineering for a number of years, there is surprisingly little literature on the interactions of fibers with bacteria and co-cultures of cells and bacteria. The knowledge of the mechanisms of adhesion and growth of bacteria onto the fibers could lead to tailoring either physically or chemically the properties of fiber surfaces to specifically address microbial behavior. The effects induced by electrospun meshes on skin cells and bacteria in co-cultures, in order to simulate the microbiological

environment that wound dressings have to face once used on patients, should be further explored.

In this Review, the main challenges associated with chronic wound management are described and currently available wound dressings presented; the advances in the fabrication of electrospun meshes as wound dressings are highlighted, focusing on the most recent strategies for developing effective innovative systems. Current challenges and future prospects in the field are also discussed.

2. Chronic Wounds

The skin is the largest organ of the body and it is composed of different types of tissue (connective, nervous, muscular,

and epidermal).[10] These tissues constitute a multifunctional organ responsible for providing sensation, thermoregulation, biochemical, metabolic and immune functions, and physical protection.[11] The skin has inherent properties for promoting wound healing and preventing infections of wound beds,[12,13] such as low moisture content, acidic pH, high salt and lipid content, and the presence of over 20 antimicrobial peptides.[10] The natural microflora of the skin is part of a set of defensive mechanisms through which the skin prevents pathogen contamination and infection development. However, these same bacteria are a potential source of infection when the skin's normal microbiological balance is disrupted.[14] Exposure of subcutaneous tissues and their natural moist, warm, and nutritious environment is perfect for colonization and proliferation of both native and external microbes.[15,16]

Healing of acute or surgical wounds occurs through a cascade of sequential processes that result in the anatomic and functional restoration of the skin. These processes can be divided into four stages: coagulation, inflammation, cell proliferation and repair of the matrix, epithelialization, and remodeling.[17] Chronic wounds fail to heal through these natural physiological processes. Chronic wounds are classified in a number of ways: those which have not healed after a fixed period of time (anywhere between four and six weeks to up to three months[18]); those that do not show a 20–40% reduction in area after two to four weeks of treatment. The most prevalent chronic wounds are diabetic foot ulcers, pressure ulcers, venous leg ulcers, and arterial leg ulcers. In most patients, the origins of delayed healing include dysfunction in the diabetic fibroblasts, immunological defects due to genetic defects or cancer, malnutrition, obesity, drug abuse, alcoholism, and smoking.[17]

Several differences in the molecular environments of chronic and acute wounds have been shown to be involved in the pathophysiology of chronic wounds. In particular, chronic wounds exhibit higher protease activity, reduced growth factor activity, and elevated levels of pro-inflammatory cytokines, if compared to acute wounds.[17,19]

Mast and Schultz[19] provided a detailed description of the pathophysiology underlying impaired healing in chronic wounds. Although different wound types have different origins or causes, all chronic wounds seem to be characterized by one or more persistent inflammatory stimuli (repeated trauma, ischemia, or low-grade bacterial contamination), which impair the physiological progression toward healing.[19] When the skin barrier is disrupted and bacterial colonization occurs, endotoxins from bacteria, platelet products, and fragments of extracellular matrix (ECM) molecules attract neutrophils and macrophages to the wound. These inflammatory cells are responsible for the secretion of inflammatory cytokines, which increase the production of MMPs while reducing the production of tissue inhibitors of metalloproteinase (TIMPs). The uncontrolled activity of MMPs degrade the ECM, thus reducing cell migration and new connective tissue deposition; moreover MMPs degrade growth factors, which are essential mediators within the cascade of mechanisms constituting the healing process. Chronic wounds often fail to heal because tissue inflammation is continuously stimulated and never overcome, and consequently the repair stage of the healing process is impaired.[19]

Chronic wounds are highly exposed to the risk of bacterial infection because the longer the wound remains opened and unhealed, the more likely it will be colonized by microorganisms coming from different sources (external environment, surrounding skin, and endogenous sources).[18] Moreover, the devitalized tissue often found in non-healing wounds facilitates the colonization and proliferation of a wide range of pathogens. Chronic wounds are contaminated by a polymicrobial population of aerobic and anaerobic bacteria. Common aerobic or facultative pathogens are *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Streptococci*. Anaerobic bacteria (*Bacteroides*, *Prevotella*, *Porphyromonas*, and *Peptostreptococcus*) constitute on average 38% of the total number of microorganisms found in chronic wounds.[20,21] Their proliferation is encouraged by the low tissue oxygen level often observed in chronic wounds. Due to their nature, anaerobes are hard to be recovered and isolated from contaminated wounds with the traditional clinical methods, thus further increasing the risk of infection.[20]

Wound infection develops through a process that results in the formation of a biofilm in the wound bed.[21] Bacterial biofilms consist of a complex microenvironment formed by single or mixed species of bacteria attached to each other and encased in an extracellular polymeric matrix that bacteria themselves produce. Through the biofilm, bacteria can develop high resistance against the immune system and antimicrobial agents, thus leading to a quick proliferation.[22,23] The biofilm protects microorganisms from outer perturbations, allowing microbial communication, enhanced virulence, and breakdown of nutrients. Studies have shown that the majority of chronic wounds (60%) have a biofilm presence, compared with only 6% of acute wounds.[21]

3. Wound Dressings

The ideal wound dressing accelerates the healing process, prevents infection, and restores the structure and function of the skin. Historically, the first documentation of wound care can be found in the ancient Sumerians who used to apply poultices of mud, milk, and plants to wounds. The Egyptians prepared plasters of honey, plant fibers, and animal fats as bandages for the wounds. The

most important advances in the field came with the development of microbiology and cellular pathology during the 19th century.[24,25] One of the main contributions was the discovery in the 1960s that keeping a wound moist accelerates the healing process. This became a key parameter in the design and development of wound dressings.[24] However, wound dressings should satisfy other essential requirements for encouraging healing, including: i) absorbing excessive exudates from the wound bed, ii) providing thermal insulation, protecting the wound bed from mechanical trauma and bacterial infiltration, iii) allowing gaseous and fluid exchanges, iv) being removable without trauma, and v) being nontoxic and nonallergenic.[25]

Currently available wound dressings can be divided into four main categories according to the provided treatment: passive, interactive, advanced, and bioactive wound dressings (Table 1). Passive wound dressings provide protection of the wound bed from mechanical trauma and bacterial infiltration. They are dry and do not control moisture levels in the wound, thus they can adhere to wound bed causing pain and mechanical trauma when removed.[25,26] Interactive dressings are fabricated with polymeric films and/or foams, which are transparent and permeable to water vapor and oxygen; they provide an effective barrier against permeation of bacteria or other microorganisms from the external environment.[27,28] Advanced dressings such as hydrocolloids and alginates are capable of providing or maintaining a moist environment around the wound, thus facilitating the healing process.[28] The fourth category of bioactive dressings include those incorporating drug delivery systems, skin substitutes, and biological dressings, which play an active role in the healing process, by activating or driving cellular responses.[29,30] Bioactive dressings constitute an important step forward toward the development of effective systems capable of healing chronic wounds. However, research is still very intensive since these systems are only suitable for specific types of wounds, costs and fabrication techniques can be excessive, and a better control over drug release profiles and rates is an important parameter that to date has not been optimized. A detailed description of the wound dressings belonging to the described categories is provided in Table 1.

A multifunctional device, able to treat different types of chronic wounds while minimizing the risk of infection and wound recurrence is currently not available to patients. Research in this field currently focuses on the development of dressings able to combine three essential properties: i) controlling the physiological mechanisms on which the healing process is based; ii) monitoring markers of the healing and infection processes, including temperature, pH, and presence of bacteria; and iii) controlled release of drugs in response to wound infection. A wound dressing capable of delivering all three of these requirements would both stimulate the healing process while preventing infections.

4. Nanofibrous Meshes

One of the principal research drivers in the field of wound care development focuses on the manufacture of wound dressings in the form of nanofibrous meshes.[31] These structures are made of non-woven, ultra-fine polymeric fibers with diameters ranging from several micrometers down to a few nanometers. Nanofibrous meshes have several intrinsic properties, which make them particularly interesting for wound healing applications. First of all, the ideal wound dressing should be able to mimic the structure and the functional biology of the ECM in order to encourage the proliferation of epithelial cells and the formation of new tissue.[32,33] The ECM is the non-cellular component present within all tissues. It plays an important role during the wound healing process by acting as a scaffold for physically supporting cells and providing conditions for cell attachment, proliferation, migration, and differentiation.[34]

Nanofibrous meshes offer a good starting point toward the development of a synthetic scaffold able to reproduce the structure of the natural ECM. In fact, due to their nanometer diameter and random alignment within the mesh, fibers tend to imitate the fibrous architecture of the natural ECM. In addition, nanofibrous meshes have been shown to promote the hemostasis of injured tissues thanks to the presence of small interstices and the high-surface area of the fibers.[31] The high-surface area is also essential for fluid absorption, enhanced dermal drug and antimicrobial delivery and it provides the opportunity to modify the surface of the fibers with specific chemical functionalities.[31] Nanofibrous meshes show high interconnected porosity (60–90%),[32] allowing cell respiration and high-gas permeation and prevention of wound desiccation and dehydration.[31] The ideal nanofibrous mesh for wound healing should have pores with nanometer dimensions, thus preventing the infiltration of microorganisms from the external environment and discouraging cell/tissue ingrowth.[31,32] A list of the key properties that an effective wound dressing should possess is provided in Table 2.

Various techniques are available for the fabrication of nanofibrous meshes and they have been reviewed in detail by Zhang et al.[31] Currently, electrospinning is the preferred technique of the majority of researchers for the range of advantages outlined in the following sections.

4.1. The Electrospinning Techniques

Compared with other polymeric materials fabrication techniques (i.e., phase separation or self-assembly),

Table 1. Classification of commercially available wound dressing.

Dressing category	Product	Description	Wound type
Passive	Gauze	Made from woven and nonwoven fibers of cotton, rayon polyester or combination of both. Need to be changed regularly to prevent tissue maceration[29]	Minor clean and dry wounds[29,44]
	Tulle	Made of Tulle gauze and petroleum jelly. Adhesion to wound bed reduced. Secondary dressing often required[44,98]	Superficial, clean, flat and shallow wounds with light to moderate exudates[44]
	Bandages	Made from natural (cotton wool and cellulose) and synthetic (polyamide) materials[29]	Generally used as support for other dressings[29]
	Low adherent dressings	Manufactured in form of tulles, textiles, or multilayered or perforated plastic films. Adherence at the wound surface is minimized[26,98]	Minor wounds in patients with sensitive or fragile skin[26]
Interactive	Semi-permeable films	Made of polyurethane covered with hypoallergenic acrylic adhesive. Porous and permeable to water vapor and gases. Elastic, flexible and transparent for allowing wound check. They adhere to healthy skin but not to the wound bed[29,44]	Flat, shallow wounds with light to moderate exudates in difficult anatomical sites (over joints)[29,44]
	Semi-permeable foams	Made of polyurethane or silicone foam. Vapor and oxygen exchange and thermal insulation provided; highly absorbent, cushioning and protective. Generally nonadhesive, thus requiring secondary dressings[26,98]	Flat, shallow, moderate to heavily exuding wounds; not suitable for light exuding wounds[26,27]
	Amorphous hydrogels	Made from insoluble, swellable hydrophilic polymers (i.e., poly(methacrylates) and polyvinylpirrolydone). In form of amorphous gel or elastic, solid sheet or film. Moisture is maintained, vapor and oxygen exchange allowed; wound debridement promoted by rehydration of non-viable tissues. Fluid accumulation within the dressing can cause skin maceration and bacterial proliferation[25,44]	Dry, sloughing or necrotic wounds. Not suitable for moderate to heavily exuding wounds[25,44]
Advanced	Hydrocolloids	Made from colloidal materials, combined with elastomers, or adhesive materials. In form of thin films and sheets or as composite dressings. Gel forms on the surface of the wound maintaining or providing moisture and allowing gas and fluids exchange. pH of wound bed reduced for limiting bacterial growth[25,98]	Light to moderate exuding, sloughing or granulating wounds
			Not suitable for infected, necrotic, or heavily exuding wounds[25,98]

■ *Table 1.* Continued

Dressing category	Product	Description	Wound type
	Alginates	Made from the calcium and sodium salts of alginic acid. In form of freeze-dried porous sheets (foams) or flexible fibers. Highly absorbent. Optimal moisture level and temperature maintained. Clotting mechanisms encouraged[24,27]	Moderate to heavily exuding wounds Not suitable for dry or necrotic wounds[24,27]
	Hydrofibers	Made from sodium carboxymethyl cellulose fibers. Wound exudates absorbed and moisture provided. pH of wound bed reduced for limiting bacterial growth[27,28]	Infected, medium to heavily exuding wounds. Not suitable for dry or light exuding wounds[27,28]
	Dextranomers	Hydrophilic polysaccharide granules available in powder or paste form. Highly absorbent; optimal moisture level provided[28]	Medium to heavily exuding, infected wounds[28]
Bioactive	Drug delivery	Continuous release in the wound of antimicrobial agents (honey, iodine, silver, polyhexamethyl biguanide, and chlorhexidine gluconate) loaded into interactive or bioactive dressings. Agents released also if wound is not infected. Release profiles and rates to be optimized[29,99]	Infected or highly contaminated wounds[29,99]
	Biological dressings	Made from natural or biological systems (microorganisms, plants, and animals) or chemically synthesized from biological starting materials (starch, natural fats, oils, and sugars). Collagen, gelatin, chitosan, hyaluronic acid-based dressings encourage fibroblast activity, and endothelial cells migration. Immunogenic response can be induced[24,29]	Clean, non-infected and non-necrotic wounds[24,29]
	Skin substitutes	Made from tissue culture (allogenic or autologous section of skin harvested and cultured in laboratory to form sheets of cells to be implanted) or tissue engineering (natural or synthetic polymers are used as matrices to culture cells)[30,100,101]	Severe burns or chronic wounds with loss of important portion of the skin. Clean, non-infected and non-necrotic wounds[30,100]

electrospinning provides a simple and cost-effective way to produce fibrous meshes with an inter-connected pore structure and fiber diameters in the sub-micron range.[35] It allows the fabrication of fibers with high-surface area due to their diameters being scalable down to a few nanometers. Electrospun meshes can be surface functionalized to tune the physical and chemical properties of the fiber surface while the fiber structure, morphology, and spatial

Table 2. Ideal properties of nanofibrous meshes for wound healing applications.

Properties	Reasons	Refs.
Fiber diameter 50–500 nm	Mimic of the physical structure of the natural ECM	[32,33]
High surface area to volume ratio	Hemostasis promotion	[31]
	Surface functionalization	
High porosity (60–90%)	Cell respiration	[31,32]
	Gas permeation	
	Wound dehydration prevention	
Interconnected nano-porosity	Prevention from microbial infiltration and cell ingrowth	[38]
Mechanical strength	Similar to natural skin	[37,102]

distribution can be controlled to achieve specific mechanical properties. In addition, electrospinning allows the combination of different synthetic and natural polymers to be used to make nanofibers. The possibility of large-scale production combined with simplicity and versatility makes the electrospinning process very attractive for a broad variety of applications, which have been reviewed by Jian et al.[36] and by Huang et al.[37] (Figure 2). The use of electrospun 2- or 3-dimensional scaffolds for biomedical applications including drug delivery, vascular, bone, and heart tissue engineering has been reviewed by various authors.[32,35,38–40]

A typical electrospinning setup (Figure 3) consists of a syringe and capillary needle through which a polymer solution or melt is passed (the spinneret); a high-voltage power supply and a grounded collector.[41] Bhardwaj and Kundu[41] provided a detailed description of the electrospinning technique as well as the parameters affecting the process. Briefly, a high voltage up to 30 kV is applied at the tip of the capillary needle, where a pendent droplet of the polymer solution or melt gets electrified, inducing charge accumulation on the droplet surface. The charge causes the deformation of the droplet into a cone, called the Taylor cone, from which a fine charged polymer jet is ejected. The jet moves toward the collector while the solvent evaporates, thus obtaining ultrafine dry fibers that can be collected on the grounded electrode in form of a fibrous mesh.[41] The basic configuration shown in Figure 3 is used for the fabrication of non-woven meshes composed of randomly aligned fibers. More complex setups are available and have been reviewed by Sahay et al.[42] and by Migliaresi et al.[43] Various types of collector (i.e., rotating mandrel, rotating wheel, parallel electrodes or rings, and patterned electrodes) enable fiber alignment along a specific direction with uniform fiber distributions within the mesh (Figure 4). Two or more extruding capillaries can be used simultaneously for fabricating fibers in different polymers within the same mesh.[42,43] Multi-needle, needle-less, coaxial electrospinning are

advanced setups that create the opportunity to combine materials and compounds that normally do not tend to mix homogeneously, but when added together in a fiber structure add significant functionality to the final material.[43]

4.2. Electrospun Meshes as Wound Dressings

Electrospun polymer nanofibers for wound healing applications can be broadly classified as synthetically or naturally derived. The most frequently selected polymers have been reviewed by Zahedi et al.[44] and the key materials are summarized in Table 3. Traditionally, electrospun meshes for biomedical applications have been fabricated from single solutions of polymers. Considering the advantages and disadvantages of both synthetic and naturally derived materials (Table 3), mixtures of different polymers are becoming widespread. The so-called "poly-blended" nanofibers are obtained by electrospinning premixed or multiple polymer solutions. Synthetic polymers ensure easy processability and good mechanical properties of the resulting mesh, while natural polymers increase the capability of the fibers to actively interact with biomolecules involved in the healing process.[45] Electrospun meshes fabricated during the past decade for wound healing applications can be classified according to the same system previously adopted for existing commercial dressings: passive; interactive; advanced, and bioactive. This classification reflects the evolution of electrospun wound dressings in terms of selected materials and technologies for both fabrication and functionalization of the fibers.

4.2.1. Passive Electrospun Meshes

Meshes that provide the physical (i.e., water and gas permeability) and morphological (i.e., adequate porosity and nanometer scale) properties of wound dressings are classified as passive. These systems are able to
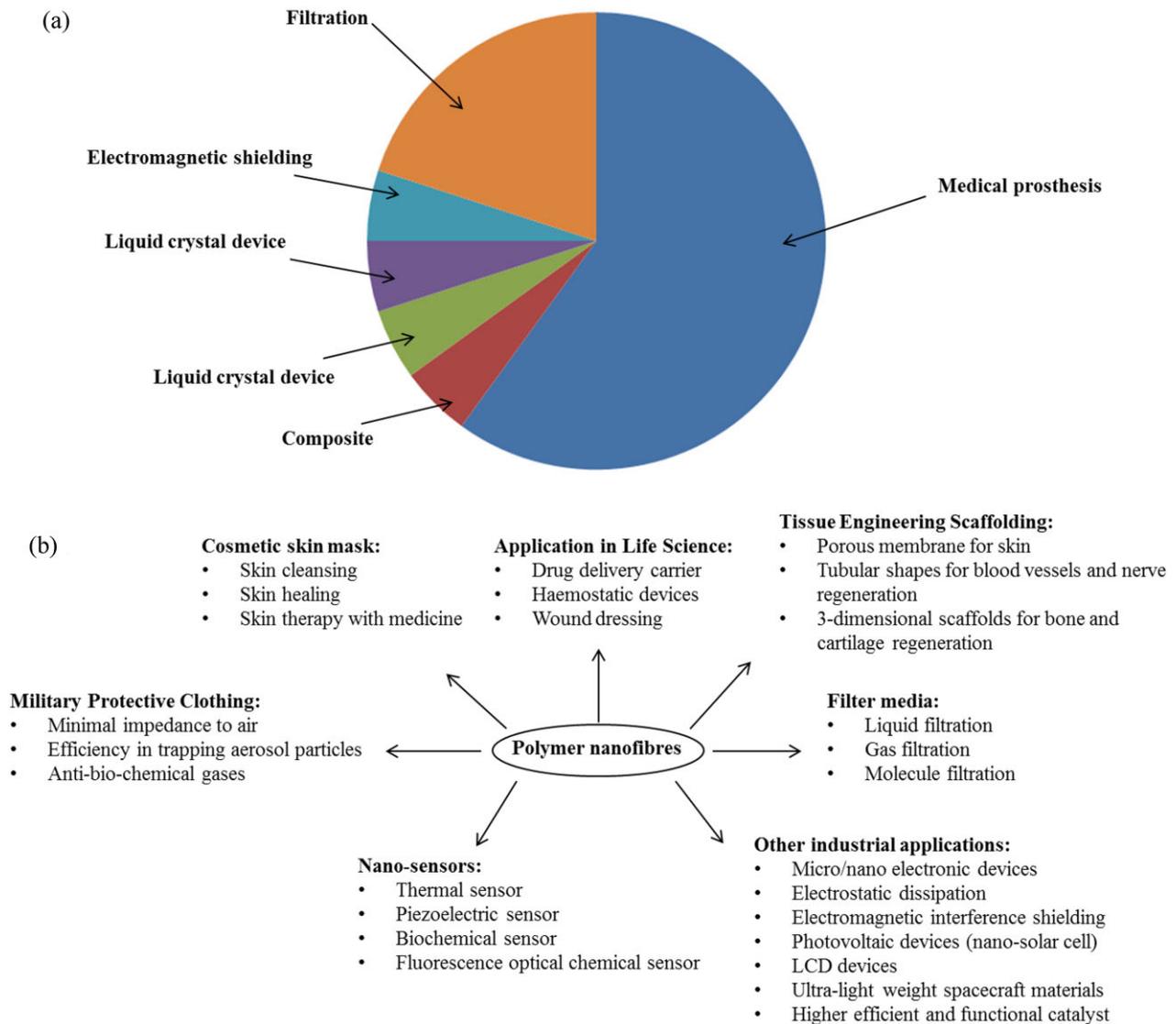
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Figure 2. a) Application fields of electrospun nanofibers targeted by US patents and b) potential application of electrospun polymeric nanofibers. Reproduced with permission.[37] Copyright 2003, Elsevier Ltd.

maintain suitable levels of moisture in the wound bed and protect tissues from mechanical trauma. Passive electrospun meshes are fabricated with both natural and synthetic polymers and are designed for those wounds that require ideal moisture levels and protection from external pathogens to achieve complete healing. Khil et al.[46] produced electrospun poly(urethane) membranes and both morphological characterization and in vivo experiments indicated that the membranes could be employed as wound dressings. Phachamud and Phiriyawirut[47] optimized the electrospinning parameters for the fabrication of poly(vinyl alcohol) (PVA) fibers. Due to the homogeneous fiber distribution, high swelling and weight loss of the meshes, the authors

suggested their potential use for wound healing applications.[47] Uppal et al.[48] fabricated nanofibrous meshes by the electrospinning of hyaluronic acid (HA). In vivo studies showed that meshes offered the best treatment of full-thickness wounds when compared with the other four commercial dressings (adhesive bandage, a sterilized HA film, gauze with Vaseline and an antibiotic dressing).[48]

This initial phase of research into fabrication of nanofibrous meshes as wound dressings focused on the optimization of the electrospinning process of various natural and synthetic polymers for achieving suitable morphological, physico-chemical, and mechanical properties. The more recent developments aim to create active
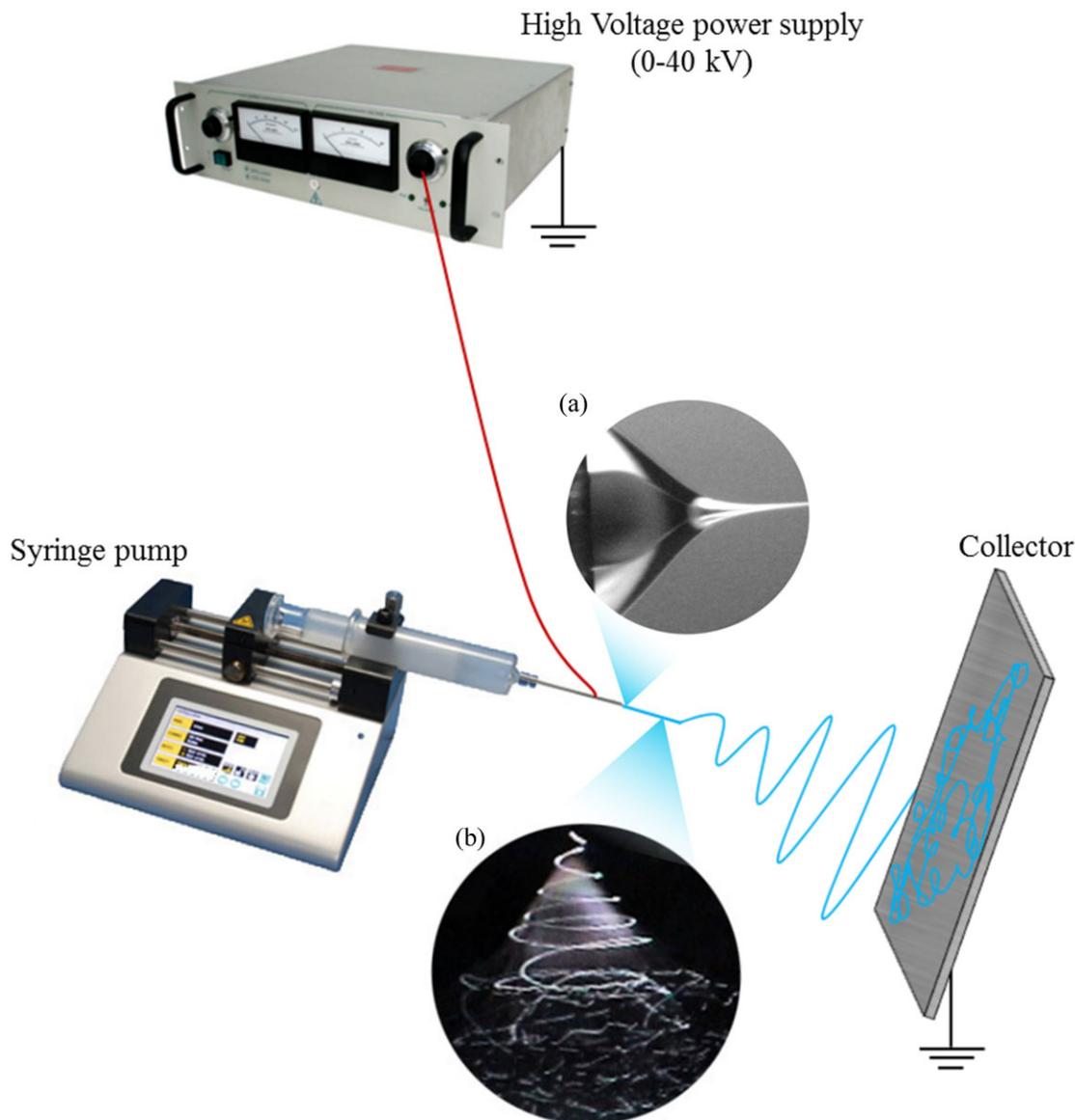
Figure 3. Schematic representation of electrospinning basic set up. a) Image of Taylor cone forming at the spinneret during the electrospinning process. Reproduced with permission;[94] Copyright 2002, American Association for the Advancement of Science. b) Image of polymeric filament forming from Taylor cone and moving toward the collector, reproduced with permission.[95] Copyright 2008, Elsevier Ltd.

devices able to drive the healing process and prevent or treat infection.

4.2.2. Interactive Electrospun Meshes

Electrospun meshes that combine the necessary morphological and physical requirements for wound healing with the value-added capability to address optimal cell responses and limit bacterial proliferation in the wound bed are classified as interactive. The main strategy, which has been used to develop interactive systems consists of the combination of synthetic polymers and biopolymers,

which exhibit antibacterial properties and affinity toward ECM components. Multicomponent systems more closely mimic the ECM. In fact, the ECM is composed of an interconnected structure of proteins (i.e., collagens, laminin, fibronectin, elastin), proteoglycans (i.e., heparan sulfate, chondroitin sulfate, and keratan sulfate), and glycoaminoglycans (i.e., HA) that can be included in the polymer formulation to be electrospun.

Two main strategies for combining natural and synthetic polymers within the same electrospun mesh can be identified: different polymers can be blended, thus forming a single solution to be electrospun; synthetic polymers are
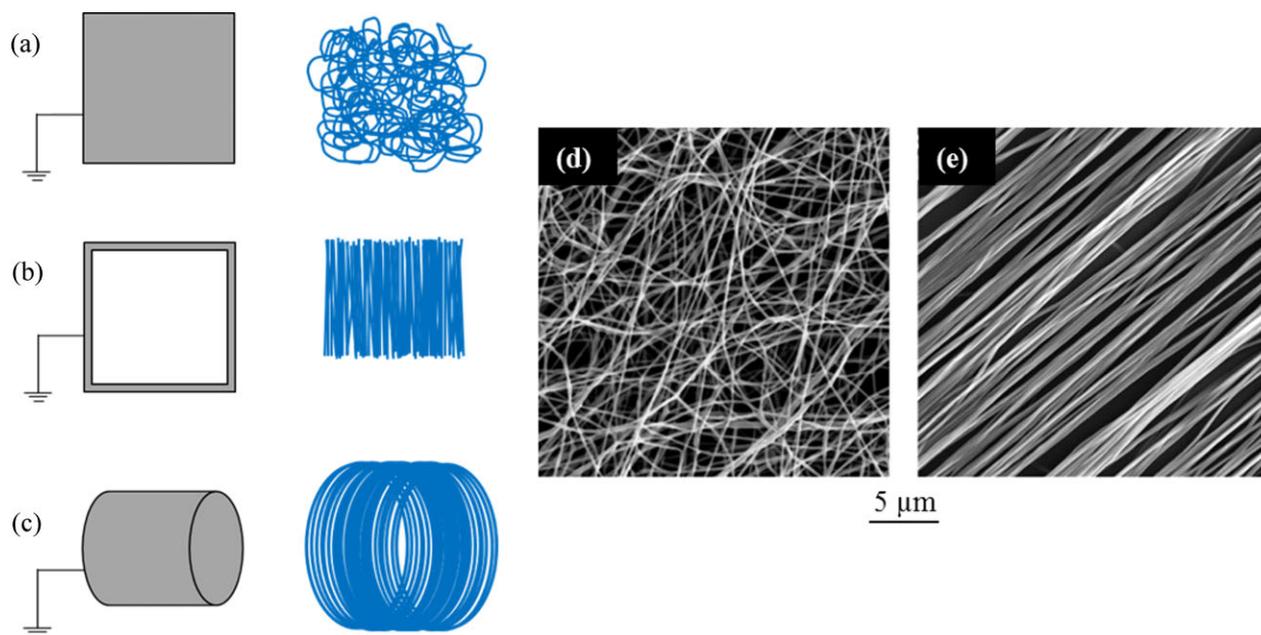
Figure 4. Schematic representation of electrospinning collectors: a) planar collector for non-woven meshes; b) square frame for unidirectional oriented fibers; c) cylindrical collector for tubular oriented fibers. d) Non-woven fibers fabricated using collector (a); e) aligned fibers that can be fabricated using collectors (b) or (c). Reproduced with permission.[93] Copyright 2012, Elsevier Ltd.

electrospun and subsequently the mesh is coated with the selected natural polymer. The second strategy aims to exploit the higher mechanical properties and easier spinnability of synthetic polymers for the fabrication of the mesh. A broad variety of reports based on the combination of natural and synthetic polymers is available in literature. Yuan et al.[49] fabricated meshes for wound healing by electrospinning a blend of modified keratin and poly(hydroxybutylate-*co*-hydroxyvalerate) (PHBV). Keratin is a family of fibrous proteins that are present in a wide range of biological tissues, performing a structural role in skin and hair. From wound healing and histological tests, the authors showed that the composite meshes accelerated wound recovery.[49] Kim et al.[50] fabricated electrospun meshes by blending polyurethane (PU) and gelatin and showed the potential application in wound healing. Gelatin is a natural polymer derived from collagen often chosen for biomedical applications since it is biodegradable, non-toxic, and easily available at low cost. Cheng et al.[51] fabricated composite nanofibrous meshes by blending type I collagen, chitosan, and poly(ethylene oxide) (PEO), that showed better performance in wound healing rates in rat models than traditional dressings. Chitosan is frequently chosen for fabricating composite electrospun meshes because it can function as a proliferation promoter, antibacterial agent, and wound healing accelerator.[51–55] Spasova et al.[56] coated electrospun poly(L-lactide) (PLLA) and bicomponent PLLA/poly(ethylene glycol) meshes with chitosan. Hemostatic and antibacterial activity against *S. aureus* of the

coating was demonstrated, thus presenting the meshes as possible candidates for wound dressings. Ignatova et al.[57] overviewed the most recent studies on electrospun chitosan-based meshes for biomedical applications.

There is also significant focus on alternative plant-derived compounds,[58] including essential oils and honey (Table 4). Natural substances cannot generally be electrospun into fibers unless they are blended with synthetic polymers as they lack mechanical and structural stability upon hydration. Normally, pure solutions of natural materials are not electrospun because the process would result in electrospray at low concentrations or complete occlusion of the spinneret at higher viscosities.[59] Among natural compounds, honey is a very attractive material due to its anti-inflammatory and antimicrobial properties.[60,61] Due to its low pH (3.5–4), honey is theorized to modify the alkaline environment characteristic of chronic wounds toward more acidic conditions favorable for wound healing.[62] Although reducing the pH in the wound bed has been shown as a possible strategy for controlling the bacterial load, very few reports exist trying to fabricate nanofiber meshes capable of providing this capability. Opportunities to develop interactive dressings able to provide healing conditions to the wound by reducing the pH to acidic values exist and should be further explored.

Although interactive electrospun meshes have been shown to encourage wound healing, they are not yet available on the market. This is due to the difficulties

Table 3. Selection of the most frequently used synthetic and natural polymers for fabrication of nanofibrous wound dressing by the electrospinning technique and their advantages and disadvantages.

	Advantages	Disadvantages	Polymers
Synthetics	Easily tailored to provide a wide range of functional properties Strong, cheap, and reliable, easily processable, surface modifiable, and sterilisable[38,39,45,77,103]	Some materials can release toxic degradation products Small particles can be released during degradation causing inflammatory response Systemic or local reactions can be induced. Loss of mechanical properties can occur very early during degradation[104]	Polylactic acid (PLA)[105] Polyglycolic acid (PGA)[106–109] Polyethylene oxide (PEO)[110,111] Polycaprolactone (PCL)[112,113] Polyvinyl alcohol (PVA)[112,114,115] Polyurethane (PU)[116,117] Polystyrene (PS)[118]
Naturals	Many materials present native biomolecular signals associated with cell binding/proliferation/migration and immune responses[77,103]	Processing can induce denaturation[77] Harvesting and processing can be complex[45] Sources of biopolymers, purity, and molecular weight distribution can influence process properties and resulting architecture of meshes. Risk of disease transmission and possible antigenicity[45]	Collagen[107,119] Gelatin[120–122] Chitosan[110,113,115] Fibrinogen[123] Hyaluronic acid[48,124] Cellulose[125–127]

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Table 4. Some naturally derived substances used in interactive electrospun wound dressings.

Alternative naturally derived materials	Properties	Scaffold material solvent	Electrospinning parameters	Fiber characterization
Aloe Vera	Improves wound healing; anti-inflammatory and antibacterial activity[128,129]	PVA/PVP-I/PEG Distilled water[130]	V = 20 kV; FR = 0.5 ml h^{-1}; N-D = 15 cm[130]	• Average diameters = 200–600 nm • Fibers with 6% aloe vera content are finer, more homogeneous and highly porous[130]
Emu-oil	Facilitates wound healing and alleviates pain; analgesic, and anti-inflammatory properties[131]	PU DMF/THF[131]	V = 16 kV; FR = NA; N-D = 15 cm[131]	• Average diameters = 400–600 nm • Antibacterial activity of emu oil is verified against *E. coli* and *B. subtilis* • Acceleration of fibroblasts proliferation is confirmed[131]
Honey	Antimicrobial activity due to different aspects, such as low water activity, low pH, generation of hydrogen peroxide, and presence of flavonoids[60,61]	PVA Distilled water[132]	V = 19 kV; FR = 1 ml h^{-1}; N-D = 20 cm[132]	Average diameters = 220–446 nm. Uniform and smooth fibers are obtained at PVA/honey ratios up to almost 40 wt% of honey[132]
		PVA Distilled water[133]	V = 20 kV; FR = 0.7 ml h^{-1}; N-D = 15 cm[133]	• Average diameter = 200 nm • No inhibitory effects are found against ten microbes[133]
		PEO Distilled water[134]	V = 9kV, 13 kV, 21 kV, 25 kV; FR = 0.15, 1.5, 5, 10 ml h^{-1}; N-D = 10 cm, 20 cm, 30 cm, 40 cm[134]	• Increases in honey content result in thicker and merged fibers[134]

Table 4. Continued

Alternative naturally derived materials	Properties	Scaffold material solvent	Electrospinning parameters	Fiber characterization
Zein	Enhances cell viability and proliferation[59,135,136]	Collagen Distilled water/acetic acid[135] Chitosan/PVP Distilled water/ethanol[136]	$V = 20$ kV; FR $= 0.75$ ml h^{-1}; N-D $= 15$ cm[135] $V = 12$–20 kV; FR $= 6$ ml h^{-1}; N-D $= 10$ cm[136]	• Addition of zein improves electrospinnability and fiber tensile strength. • Increases in zein content result in bigger diameters and higher rigidity of fibers[135] Fiber diameter increases with zein content. • Crosslinking of the fibers with HDI (hexamethylene diisocyanate) is necessary to improve stability and mechanical strength[136]
Soy protein	Promotes tissue regrowth, by integrating into blood clots and stimulating collagen deposition[59,137]	PEO HFP[59]	$V = 12$ kV; FR $= 0.8$ ml h^{-1}; N-D $= 15$ cm[59]	• Average diameters $= 200$–1000 nm • Fibers with flattened, ribbon-like morphology • Fibroblasts adhesion and proliferation within the fibers is shown[59]
Silk fibroin	Exhibits good oxygen and vapor permeability and minimal inflammatory reaction[138–140]	PEO Distilled water mixed with human EGF[141]	$V = 10$–11 kV; FR $= 1.2$ ml h^{-1}; N-D $= 15$–21 cm[141]	• Average fiber diameter $= 1000$ nm • Electrospun meshes are tested on wound model, resulting in fiber swelling and EGF release[141]
Thymol	Natural biocidal agent[142]	PCL; PLA; PCL/PLA Chloroform/DMF[142]	$V = 15$ kV; FR $= 0.7$ ml h^{-1}; N-D $= 12$ cm[142]	• Average diameter $= 300$ nm • Fibers showed satisfactory effects against *S. aureus* • In vivo studies showed wound closure after 14 d

Table 5. Compounds, which have been loaded into electrospun fibers for wound healing applications.

Compound class	Examples	Scaffold material (solvent)	Electrospinning set-up			
			Standard	Coaxial	Dual spinneret	Chemical modification
Antibiotics	Gentamycin sulfate[143]	PCL (chloroform:ethanol 3:1)[143]		x		
	Mupirocin[144]	PLLA (HFIP)[144]			x	
	Ciprofloxacin HCl[145]	PVA/PVAc (acetic acid/distilled water 1:1)[145]	x			
	Tetracycline HCl[146,147]	PLLA (chloroform:acetone 2:1)[146,147]	x[147]	x[146]		
		PCL/PLA (chloroform/DMF 9:1)				
	Cefazolin[109]	PLGA (DMF:THF 1:3)[109]	x			
	Fusidic acid[81]	PLGA (DCM)[81]	x			
Antiseptics/ antibacterials	Iodine[148,149]	PVA/PVP-I/PEG (deionized water)[148]	x			
		PVP-I, PEO/PVP-I (deionized water)[149]				
	Barberine chloride[150]	PVP/PLCL (n.a.)[150]		x		
	Silver nanoparticles[139,151,152]	Silk fibroin (formic acid)[139,152]	x[151]			x[139,152]
		Gelatin (acetic acid/distilled water 7:3)[151]				
	Titanium dioxide nanoparticles (light stimulation)[153]	Silk fibroin (formic acid)[153]	x			
Anesthetics	Lidocaine HCl[144,154]	PLA, PLA/PEG (DCM/DMSO 3:1)[154]	x[154]			
		PLLA (HFIP)[144]			x[144]	
Vitamins	Vitamin C[155]	Silk fibroin (n.a.)[155]	x[155–157]			
	Vitamins A, E[156,157]	Silk fibroin (deionized water)[156]				
		Cellulose acetate (acetone: DMAc 2:1)[157]				
Growth factors	bFGF, EGF[67]	PCL/PEG (methanol/chloroform 1:3)[67]	x[141]	x[67,158]		x[67,68]
	PDGF-bb[158]	PCL (DMF:ethanol 6:4)[158]				
	EGF[68,141]	PCL/PEG (methanol/chloroform 1:3)[68]				
		Silk fibroin (deionized water)[141]				

PCL, polycaprolactone; PLLA, poly-L-lactic acid; PLA, polylactic acid; PVA, polyvinyl alcohol; PVAc, polyvinyl acetate; PLGA, polylactide-*co*-glycolic acid; PVP-I, polyvinylpyrrolidone bound iodine; PVP, polyvinylpyrrolidone; PEO, polyethylene oxide; PEG, polyethylene glycol; PLCL, polycaprolactone-co-lactic acid; bFGF, basic fibroblast growth factors; PDGF-bb, human platelet-derived growth factor-bb; EGF, epidermal growth factors; DCM, dichloromethane; DMF, dimethylformamide; THF, tetrahydrofuran; HFIP, hexafluoroisopropanol; DMSO, dimethyl sulfoxide; DMAc, dimethylacetamide.

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associated in electrospinning naturally derived polymers in a reproducible manner and in large scale. The complexity associated with processing natural polymers due to issues with impurities and the possibility of inducing immunogenic reactions upon implantation are currently limiting the transference of these meshes into devices that can be used in reality.

4.2.3. Advanced Interactive Electrospun Meshes

In order to manufacture interactive dressings capable of treating bacterial infection, many researchers are currently developing drug loaded nanofibrous meshes. Meinel et al.[63] overviewed drug loaded electrospun nanofibers, providing the most frequently selected drugs for wound healing applications, which are summarized in Table 5. The most common chosen technique for loading compounds into the nanofibers is known as "coaxial electrospinning," which allows the compound to be retained in the fluid environment after being loaded into the fiber. The resultant nanofibers present a core/shell structure where the shell is normally made of a synthetic polymer for structural integrity while the bioactive compounds in their original liquid state or encapsulated in a second polymer remain in the core of the fiber. A slightly different setup than the traditional electrospinning is used at this purpose (Figure 5). Two syringes are used to transfer the polymer solution and the compound to the spinneret, which is constructed

of a single capillary with an inner and an outer channel. The polymer solution normally feeds the outer channel while the compound, which can be a liquid or a polymer composite, is extruded through the inner one.[64] This process is used to load a variety of compounds into nanofibers that could potentially lose their functionality unless they are in fluid or non-denaturing environment and include drugs, growth factors, and vitamins. Table 5 summarizes the compounds that have been loaded into electrospun nanofibers for wound healing applications.

The possibility of loading antibiotics or antimicrobials into electrospun fibers represents a great advantage in the development of systems able to treat infections in the wound bed. However, these systems have not been translated into an effective therapy for various reasons.[63,65] Leung et al.[66] highlighted that, depending on the type of wound optimal drug release profiles and rates of release are required. Furthermore, drug release is always associated with an initial burst effect, which can cause the local drug concentration to be toxic toward tissue cells.[38,39] The ideal wound dressing should be a smart device adaptable to treat every different kind of wound. It should be able to monitor the conditions of the tissues in the wound and subsequently trigger the release of drugs with the optimal delivery profile only when needed. As shown in Table 5, some papers report on nanofibers functionalized with growth factors in order to stimulate cell growth, thus encouraging and accelerating wound healing. Although the
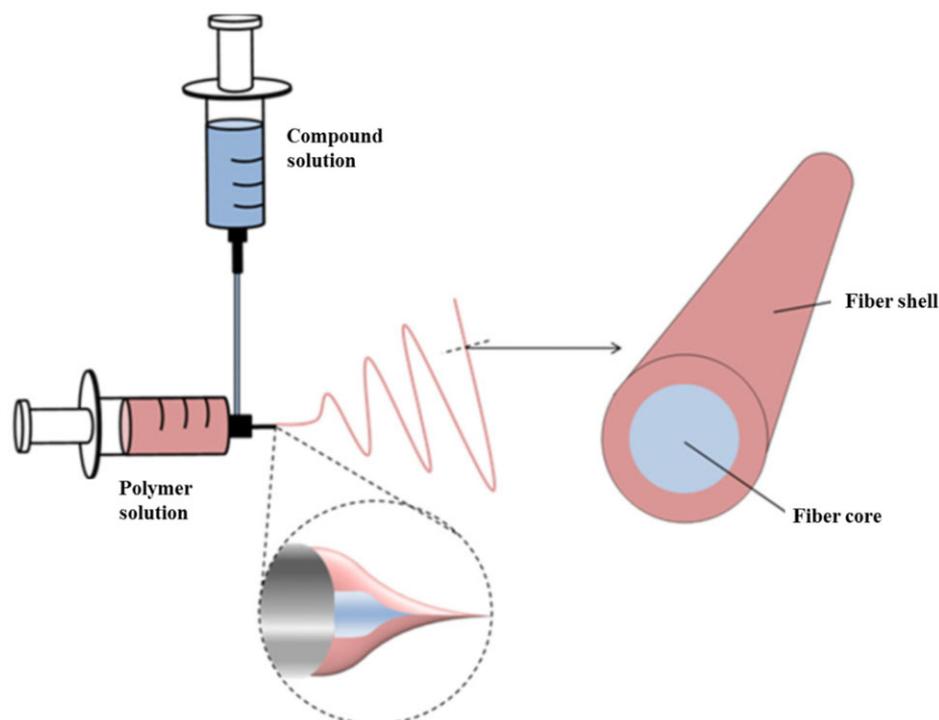

Figure 5. Schematic representation of coaxial electrospinning set up. Reproduced with permission.[96] Copyright 2013, Institute of Physics Publishing.

efficacy of these meshes in terms of encouraging proliferation and differentiation of fibroblasts and keratinocytes have been demonstrated,[67,68] the high cost of fabrication as well as the difficulties associated with processing are limiting the popularity of these systems. Moreover, as previously stated, the ideal wound dressing should be able to promote skin cell migration and proliferation within the wound bed, while preventing tissue ingrowth within the fibrous structure, in order to avoid tissue damage after dressing removal. The capability of electrospun meshes to prevent fibroblast and keratinocyte ingrowth has not been demonstrated yet.

4.2.4. Bioactive Electrospun Meshes

Bioactive electrospun meshes aim to be multifunctional systems, combining a range of properties capable of treating all aspects of the wound. Adequate mechanical and physico-chemical properties provide wound protection, the healing process is stimulated and the bacterial load in the wound bed controlled. In many studies, work is moving to include wound status monitoring as an indicator of the progression of healing and/or the bacterial load. This can be achieved by integrating a sensor within the electrospun mesh thus allowing the real-time detection of specific parameters from the wound bed. The sensor generates a visible output for the patient or the doctor providing continuous monitoring of the wound status. Dargaville et al.[69] reviewed the state-of-the art in the fabrication of sensors for monitoring the healing process of wounds. There are a range of potential markers and parameters associated with wound healing and infections that can be detected, including pH and temperature. A number of groups have developed pH sensitive dyes and immobilized them onto films and into fibers.[70–72] A few reports exploit the capability of hydrogels to swell in response to pH, temperature, or analyte concentration for sensing the status of the wound.[73,74] Van der Werff et al.[75] developed a bandage that changes color according to the temperature of underling tissues in order to monitor the healing processes of wounds. Although the literature suggests that pH and temperature sensors for wound monitoring are possible, few studies have actually integrated these systems into wound dressings or electrospun meshes for testing.

Biofouling represents a significant obstacle to the inclusion of sensors within wound dressings. As with any sensor, the uncontrolled adsorption of biomolecules (peptides, proteins, and subsequent attachment of cells) will impede analyte detection and can cause the failure of the device.[69,76] Moreover, when designing a sensor to be integrated into a wound dressing, an essential criterion needs to be addressed: the sensor outputs should never be used in isolation. Multiple signals and parameters should be simultaneously detected in the wound environment and combined for determining the final output in terms of current status of the wound.[69] Finally, cost-effectiveness of the fabrication and engineered processes cannot be ignored and given the low per-item cost of many wound dressings, this is a critical parameter.

4.3. How Do Bacteria Respond to Nanofibrous Meshes?

There is significant data available from the tissue engineering literature on how skin cells, in particular fibroblasts and keratinocytes interact with electrospun meshes with detailed in vitro studies used to assess cell viability and growth (Figure 6).[77–79] Sun et al.[79] studied the influence of fiber diameter, inter-fiber distance, and fiber alignment on the behavior of human dermal fibroblasts. They identified minimum values of fiber diameter and inter-fiber space necessary for cell adhesion and migration and for cell aggregate formation. Fiber alignment was shown to induce cell guidance.[34,79] Nisbet et al.[80] provided a detailed review of how different cells types respond to electrospun nanofibers. Although this knowledge is very useful for developing effective scaffolds capable of actively drive cell behavior, the study of cell responses is not the only aspect that must be considered in designing a dressing able to control and address the healing process. In fact, during the healing process, nanofibrous meshes are inevitably involved in dynamic interactions with the wound environment, which includes coexistence with bacteria.[81] Since all wounds are contaminated by bacteria, an understanding of how bacteria interact with the electrospun meshes is essential to develop devices able to not only communicate with cells but also minimize the microbial load in the wound bed, thus reducing the risk of infection. Currently, few studies focus on microbial adhesion and growth and biofilm formation on the surface of electrospun fibers and those that exist tend to focus on membrane fouling in water environments[82] or on bactericidal effects of drug loaded meshes. The mechanisms that bacteria use to adhere to flat surfaces with different chemistries and subsequently develop into biofilms has been reviewed in detail by Mitik-Dineva et al.[83] In other work, Mitik-Dineva et al.[84] and Anselme et al.[85] studied cellular and bacterial interactions with nano-structured flat surfaces and showed that the nanoscale topography of surfaces could be exploited to limit bacterial proliferation. A systematic study describing the mechanisms of adhesion and growth of bacteria onto fibers with different properties is not yet available. Knowledge of the mechanisms through which bacteria interact with fibers could allow the development of devices able to control and block microbial growth without drug release. In particular,
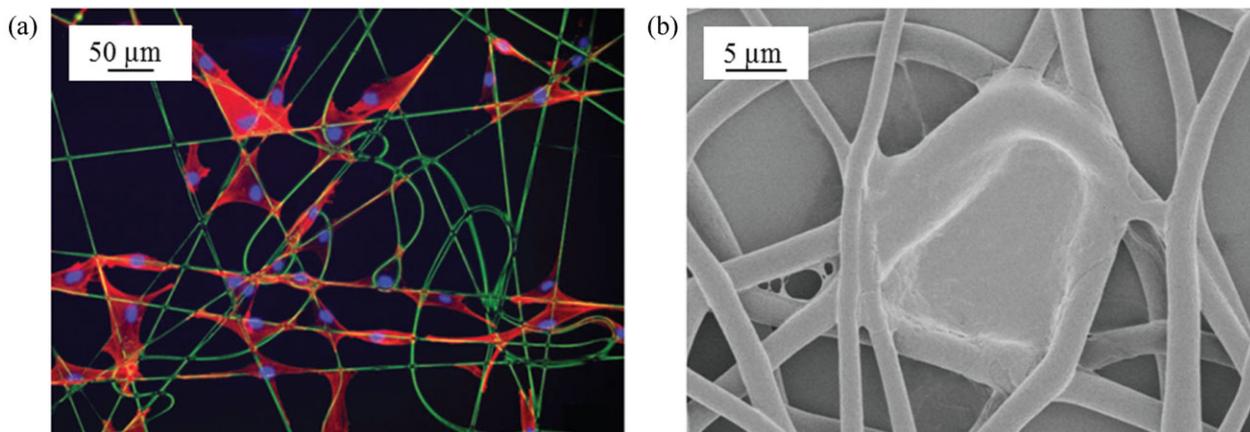
Figure 6. a) Fluorescence microscope image (nuclei blue, actin filaments red) of human dermal fibroblasts after 24 h in cell culture on protein-functionalized PLGA/sP(EO-*stat*-PO) fibers. b) SEM image of a single cell on protein-functionalized PLGA/sP(EO-*stat*-PO) fibers. Reproduced with permission.[97] Copyright 2011, Nature Publishing Group.

two main questions remain unanswered: i) How does fiber diameter, diameter distribution, fiber alignment, and mesh porosity influence the tendency of bacteria to adhere, proliferate, and form a biofilm? ii) Can this behavior be tailored either physically or chemically by changing the overall mesh properties to specifically address microbial attachment and proliferation behavior? A variety of surface modification and functionalization strategies for electrospun nanofibers were reviewed by Yoo et al.,[86] but few studies of how bacteria respond to these surfaces exist.[56,87]

Another important aspect, which has not been deeply explored yet is the effects induced by electrospun meshes on skin cells and bacteria in co-cultures. The most complete studies on electrospun wound dressings involve separate in vitro experiments on skin cells (fibroblasts or keratinocytes) and bacteria (*Escherichia coli*, *S. aureus*, and *P. aeruginosa*). These tests constitute valuable tools for studying the cytotoxicity as well as antimicrobial activity of electrospun meshes. However, they are performed in highly defined and controlled culture conditions, which do not reproduce the real environment of chronic wounds.[88] Strategies for establishing an in vitro chronic wound model by co-culturing various types of skin cells and bacteria can be found in the literature, but those models have not yet been used for testing electrospun dressings. Duell et al.[89] has provided an overview on epithelial cells co-culture models for studying infectious diseases in vitro. Wiegand et al.[88] established an in vitro infected chronic wound model by co-culturing human keratinocytes and S. aureus. Hill et al.[23] developed an in vitro model of a chronic wound biofilm by co-culturing various species of bacteria. Shepherd et al. cultured a three-dimensional normal human skin model by co-culturing fibroblasts and keratinocytes[90] and infected it with *S. aureus* and *P. aeruginosa* to simulate

wound infection.[91] Studies of the responses of nanofibrous meshes in co-cultured experiments between skin cells and bacteria could bring new insights that cannot be determined through traditional single-culture methods. This could allow further improvements to the design of a new generation wound care dressings considering the fact that cells and bacteria have different dimensions and most likely will respond differently to fibers of nanoscale dimensions.

5. Current Challenges and Future Prospects

The wound dressing of the future is a multifunctional device able to enhance the healing process, ideally prevent infection or effectively treat an infection when it occurs, while simultaneously monitoring the status of the wound. Dargaville et al.[69] suggest that the dressing of the future might incorporate a color map of the wound, pH readout, infection feedback, and an indicator displaying if a dressing change is necessary. To develop such a complex wound management device many fundamental steps still need to be achieved.

A possible strategy to prevent biofilm formation in the wound bed could be developing a mesh able to attract bacteria and trap them within its fibrous structure. By combining such a system with sensors for triggered drug release, a smart dressing would be achieved, able to reduce the bacterial load in the wound bed, treat infection only if it occurs, and stimulate growth of healthy tissue.

The combination of sensors and fibers with active properties that electrospun meshes can provide is a strong starting point toward the dressing of the future, although numerous challenges still need to be overcome. The biosensor integrated within the dressing should be able

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to detect low levels of bacterial contamination and consequently emit a recognizable output indicative of infection risk. This smart sensor will trigger a material response that releases a pre-loaded drug with a suitable release profile according to the conditions of the wound. The triggered release could be achieved by integrating switchable surfaces or stimuli-responsive materials[92] into the dressing. At the same time the sensor should provide the doctor/patient with a readout about different parameters indicative of the status of the wound, in particular pH, temperature, moisture, and exudates production.

Electrospun meshes provide all the essential requirements for effective wound care but some of the elementary aspects of the fabrication process are still poorly understood. For fabricating meshes with all the required properties, many parameters need to be optimized depending on the selected polymers and compounds to be loaded, making the process empirical and difficult to predict.[93] Advanced electrospinning sets-ups as well as innovative research involving combination of various materials are helping to overcome these obstacles. Eventually, it will be possible to predict polymer behavior during electrospinning and have control over the final fiber properties, particularly with new synthetic analogs whose solution behavior (viscosity, concentration, and conductivity) will need to be predicted and determined experimentally.[93]

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