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Electrospinning Technology: Designing Nanofibers toward Wound Healing Application

Daniela Sousa Coelho, Beatriz Veleirinho, Thaís Alberti, Amanda Maestri, Rosendo Yunes, Paulo Fernando Dias and Marcelo Maraschin

Abstract

Electrospinning is a widely used technology to obtain nanofibers. Electrospun systems have been especially investigated for wound dressings in skin regeneration given the similarity of structures with the extracellular matrix. Several efforts have been made to combine distinct design strategies, such as utilizing synthetic and/or natural materials, modifying fiber orientation, and incorporating substances, e.g., drugs, peptides, growth factors or other biomolecules, to develop an optimized electrospun wound dressing. This chapter reviews the current advances in electrospinning strategies for skin regeneration.

Keywords: electrospinning, nanofiber, wound healing, drug delivery system

1. Introduction

Skin is the essential interface between the body and its environment [1]. Besides providing a physical barrier that prevents pathologic infection, the skin also performs a range of vital functions that maintain hydration, thermoregulation, and body metabolism. Several injuries, such as burns and chronic wounds, result in lifelong functional impairment, and they represent a substantial burden on healthcare by the necessity of chronic medical care [2]. One promising approach to promote skin regeneration involves engineering of the local environment to promote coordinated cellular infiltration and organized deposition of extracellular matrix (ECM), and to provide a microenvironment prone to neodermis regeneration and appendage formation when combined with competent dermal cells. An ideal nanofibrous cell scaffold should resemble the native extracellular matrix and be capable of supporting cell adhesion, proliferation, and maturation [3, 4]. Nanofibrous scaffolds obtained by electrospinning have been attracting the attention of researchers owing to the morphological and structural similarities between the electrospun structures and the natural ECM, making these materials potential substrata for cell growth. Several electrospun scaffolds have been proposed for skin regeneration based on different polymers and their blends [5]. In this chapter, we present some recent advances in electrospun

nanofibers for wound healing. We further highlight recent studies that have used electrospun nanofibers for wound healing applications and devices, including burns and nonhealing wounds.

2. Electrospinning nanofibers

Electrospinning (ES) is a technology to obtain nanomaterials formed by the deposition of polymer nanofibers, which results in an interconnected three-dimensional network [6]. Despite their extremely small diameter, these nanofibers show large surface area to volume ratio and high porosity. In addition, it is possible to obtain scaffolds from hundreds of different polymers capable of carrying bioactive substances [1]. Versatility is one of the most important advantages of the electrospinning technique. Different morphologies can be achieved by varying configuration and parameters of the electrospinning process [7]. Taken together, these characteristics show applicability in many different areas, such as high performance, intelligent textiles, biosensors, scaffolds for tissue engineering, and drug delivery systems [5]. A typical electrospinning apparatus includes a high voltage power supply, a spinneret system, and a collecting system (**Figure 1**). Tension, distance of the collector, and polymer solution flow rate are examples of parameters that could be changed. Creative electrospinning setups have been developed in order to obtain mats with distinctive characteristics, such as aligned, porous, hollow, and core-shell nanofibers [8]. Furthermore, many systematic studies have led to advances in knowledge about governing parameters of the electrospinning process. Nonetheless, optimizing the electrospinning system is still a laborious task as a result of the high number of parameters that affect the process and the interdependence among them. Even more, both the electrospinning setup and parameter optimization are tightly related to the polymer and solvent system [1]. In this section, some general principles about the parameters that affect the electrospinning process will be discussed, focusing on polymer characteristics that affect skin repair applications.

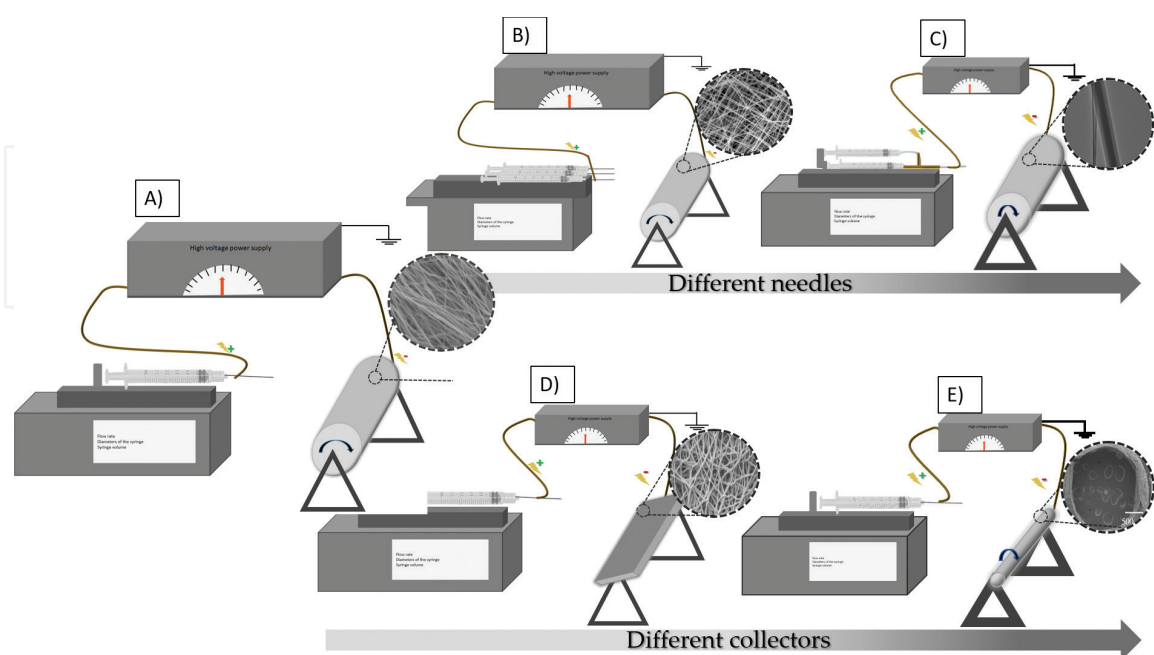


Figure 1.

Typical electrospinning apparatus equipped with different collectors and syringe systems. (A) Conventional electrospinning apparatus configured to produce aligned nanofibers (high-speed rotating drum). (B) Multijets for random nanofiber arrangement (low-speed rotating drum). (C) Co-axial electrospinning for obtaining core-shell nanofibers. (D) Static collector for random nanofibers arrangement. (E) Mandrel collector designed to produce nanofibrous tubes. The micrographs were adapted from De Prá and coworkers (2016).

2.1 Biomaterial characteristics

Materials considered as substitutes for skin repair should offer porosity to facilitate the clearing of exudates from the wound site, control water loss, and promote oxygen diffusion; hydrophilic surface to keep skin moist and moisturized; and controllable biodegradability to allow the controlled release of bioactive compounds that act on healing and suitable biocompatibility [9]. The chemical composition of the electrospinning solution determines the physicochemical, mechanical, and biological properties of the electrospun mat [10]. The intrinsic properties of the selected polymers are reflected in the final characteristics of the electrospun mat, while the nanofibrous arrangement brings unique features to the material.

A polymer consists of a long chain of molecules with repeating units called monomers that are mostly covalently bonded to one another [11]. Varying concentration and molecular weight (MW) of the polymer are the most effective ways to control the morphology of the electrospun mats, especially the diameter of the fibers [12]. Molecular weight (MW) is a key determinant of electrospinning processability of any polymer solution by strongly affecting its rheological and electrical properties, including viscosity, surface tension, conductivity, and dielectric strength [2]. Generally, low MW polymer solutions are more suitable for electro-spray purposes, i.e., formation of beads, while high MW polymer solutions possess the desired viscosity, i.e., sufficient polymer chain entanglements to generate fibers [13]. Katti et al. demonstrated the effect of poly(lactide-co-glycolide) (PLGA) solution concentration on the diameter and morphology of fibers. Nanofibers were formed for intermediate polymer concentrations, while for low polymer concentration (0.10 g/mL), no fibers were formed, only beads. The highest concentration (0.30 g/mL) produced fibers with thickness in the microns [14]. Similar results were found with poly(ethylene terephthalate) (PET) for concentrations lower than 10% (w/v). In this case, droplet spray occurred, and a continuous jet of polymer was not formed. For concentrations higher than 30% (w/v), the high viscosity of the solution limited Taylor cone formation, the cone observed in electrospinning, electrospraying and hydrodynamic spray processes from which a jet of charged particles emanates above a threshold voltage [12].

Recently, many researchers have been using electrospinning technology to develop new scaffolds made of natural polymers, such as collagen, gelatin, chitosan, and silk fibroin, as well as synthetic biodegradable polymers [15]. Natural polymers have been found to promote cell attachment and proliferation, whereas synthetic polymers provide mechanical stability to the scaffold [16].

2.2 Collagen

Collagen is the major fibrous protein of the ECM. It constitutes 20–30% of total body protein, plays an important role in the regulation of cell function, and provides structural support for tissues and organs [17]. Biocompatibility is the most favorable aspect of using collagen as biomaterial for nanofiber mats. As a result of its abundance in the body, it is easily available. Furthermore, while it is nontoxic and not antimitogenic, it is biodegradable by enzymes, which naturally occur in ECM substitution during the remodeling phase of the healing process. It is also possible to combine collagen with other copolymers since it is highly compatible and has good mechanical properties, such as malleability and bioresorbability [18]. However, the main reason against using collagen is the onerous work involved and high cost of its purification, as well as the risk of disease transmission.

Gelatin is the denatured form of collagen and has different physicochemical and biological characteristics compared to natural collagen [19]. A comparative study

between electrospun collagen and gelatin revealed that collagen induces a better cellular response [20].

2.3 Chitosan

Chitosan is a cationic polysaccharide and has been one of the most studied biopolymers in the biomedical field owing to its notable properties, i.e., biocompatibility and wound healing effect, as well as anti-inflammatory and antimicrobial activity [21, 22]. However, the poor mechanical properties of chitosan pristine fibers have restricted biomedical applications, even though some studies have reported good results for chitosan composite fibers, especially when combined with synthetic polymers [5, 22–25]. Nanofibrous mats electrospun with chitosan-graft-polycaprolactone have shown excellent properties in cell attachment and proliferation, and they are promising substitutes for skin tissue engineering [5, 24].

2.4 Silk fibroin

Silk is a typical fibrous protein produced by a variety of insects, including silkworm. Silk consists of two types of proteins: fibroin and sericin. Fibroin is the protein that forms the filaments of silkworm silk, and it can be regenerated in various forms, such as gels, powders, fibers, or membranes, depending on the application [26]. Among silk proteins, silk fibroin (SF) has recently been investigated as one of the candidate materials for biomedical applications based on its several distinctive biological properties, including good biocompatibility, biodegradability, minimal inflammatory reaction, and suitable oxygen and water vapor permeability [27].

2.5 Poly(ϵ -caprolactone)

Polycaprolactone (PCL) is a biodegradable and biocompatible poly(alfa-ester) and one of the polymers that has been extensively studied in tissue regeneration and wound healing applications because it promotes faster healing and reduced inflammatory infiltrate [28, 29]. PCL has some important physicochemical properties, including hydrophobicity, excellent spin ability, favorable mechanical properties, and slow degradation, all of which support its use as a good matrix for loading natural substances.

2.6 Polyvinyl alcohol (PVA)

PVA is a semicrystalline polymer that shows excellent electrospinnability in aqueous solution [30]. Furthermore, PVA has been used as a copolymer to enhance electrospinnability and mechanical properties of biopolymers like chitosan [31, 32]. The biocompatibility of PVA allows its application in biomaterials for dermal and orthopedic tissue engineering [7, 31]. PVA was associated with chitosan blends in which the increase of chitosan derivative ratio resulted in smaller fiber diameters and higher antibacterial effect, both advantageous properties against skin infection [23].

In this section, we describe polymer solution parameters and their resultant application in the electrospinning process. However, it should be noted that other parameters related to the process also affect fiber morphology obtained as a result of electrospinning. Some process parameters include the applied electric field, tip-to-collector distance, and flow rate [33].

Some parameters and their effects on fiber morphology are summarized in **Table 1**.

Parameters	Effects on fiber morphology	References
Applied voltage	Decrease in fiber diameter with increase in voltage	[37, 47, 48]
Type of collector	Decrease of fiber diameter and increase in fiber alignment with rotating drum (compared to static collector)	[34, 38]
Distance of collector	Generation of beads with too long or too short distance; minimum distance required for uniform fibers	[39, 40, 42, 49]
Flow rate	Decrease in fiber diameter with decrease in flow rate; generation of beads with too high flow rate	[41, 43]
Air humidity	High air humidity results in circular pores on the fiber surface	[44]
Temperature	Increase in temperature causes decrease in fiber diameter	[46]
<i>Adapted from Bhardwaj and Kundu [34].</i>		

Table 1.
Electrospinning process parameters and their effects on fiber morphology.

2.7 Effect of applied voltage

A crucial element in electrospinning is the application of high voltage to the solution. According to Ramakrishna et al., voltage of more than 6 kV can cause the solution drop at the tip of the needle to distort into the shape of a Taylor Cone during Jet initiation [35]. If the applied voltage is higher, the greater amount of charges will cause the jet to accelerate faster, and more volume of solution will be drawn from the tip of the needle. Thus, the formation of beads or beaded nanofiber can be attributed to an increase in the applied voltage [35]. Matabola and Moutloali evaluated the influence of applied voltage on the morphology and diameter of poly(vinylidene fluoride) (PVDF) nanofiber and showed that the diameter increased gradually with decreasing bead density at lower voltages, whereas at higher voltage, the reverse situation was observed whereby diameters decreased and beads reappeared [36]. In another study, it was observed that increasing voltage favors the formation of multiple jets. The different fibers repel each other owing to the flowing charge on their surface, and as a result, the fibers distribute themselves at a larger area on the collector [37].

2.8 Effect of collector

For electrospinning to initiate, an electric field must be present between the source and the collector. Thus, the collector plate is made out of conductive material. If a nonconducting material is used as a collector, charges on the electrospinning jet will quickly accumulate on the collector. Fibers collected on the non-conducting material usually have lower packing density compared to those collected on a conducting surface [34].

The electrospinning process is also affected by the use of a static or moving collector. While rotating collectors have been used to collect aligned fibers, static models randomly arrange nanofibers in the collector. Our group discovered that three distinct metallic collectors, including a rotating drum, 6 mm grounded parallel copper wires, and 1 mm rotating mandrel, had an effect on PCL nanofiber morphology. For the static drum, randomly oriented fibers with an average diameter were obtained (**Figure 1(D)**). Increasing the rotation speed to 2000 rpm caused a significant decrease in the mean fiber diameter (**Figure 1(A)**). A similar fiber alignment pattern was obtained using parallel copper. For the rotating mandrel, tubular scaffold formation was fundamental for engineering of nerves and blood vessels (**Figure 1(E)**) [38].

2.9 Distance between tip and collector

Varying the distance between the tip and the collector will have a direct influence on flight time and electric field strength [39–41]. If the distance is so short that the solvent is inadequately vaporized, then fused fiber may be formed. Depending on the solution property, the effect of varying the distance may or may not have a significant effect on fiber morphology. Ki et al. showed four series of spinning distance under a fixed electrical field. The results were not significant; however, many droplets on the electrospun gelatin web were observed at farther distance [42].

2.10 Flow rate

The flow will determine the amount of solution available for electrospinning. A lower flow rate is more favorable as the solvent will have more time for evaporation. In contrast, if a greater volume of solution is drawn from the needle tip, the jet will take a longer time to dry. As a result, the solvents in the deposited fiber may not have enough time to evaporate. In this case, residual solvent remaining in the collector may cause fusion between the fibers, forming unwanted webs [41, 43].

2.11 Air humidity

The humidity of the electrospinning environment may influence the polymer solution during electrospinning. Under high humidity, it is likely that water will condense on the surface of the fiber, which could have an effect on fiber morphology, especially polymer dissolved in volatile solvents [44]. However, it is possible to use humidity to develop porous electrospinning. Bae et al. explain how porous electrospun polymethyl methacrylate (PMMA) can be used as water filters to optimize humidification. Increased humidity will increase the amount of porosity. In this work, the PMMA fiber membrane obtained at 70% humidity was highly porous, compared to that at 25% humidity, but with no differences in the mean pore diameter [45].

2.12 Temperature

Increasing the temperature has two effects on the polymeric solution: increasing the evaporation rate of the solvent and reducing the viscosity of the polymer solution. As a result, the nanofibers show a decrease in diameter of the fiber and more homogeneous distribution. This will improve the solubility of the polymer in the solution and, hence, the attraction of polymeric particles to the collector. On the other hand, when the matrix is developed for biomedical application, biological molecules are added, and these substances can be degraded by high temperature, causing loss in functionality [33, 46].

3. Innovative electrospinning techniques

Despite the numerous advantages offered by nanofiber, the development of new composite nanofibers holds even greater potential, and investigation of new design and synthesis of composite materials further expands their applicability [50–52]. Consequently, nanofiber composite fabrication using electrospinning techniques has gained attention in recent years. Fiber composites obtained by blending multicomponent polymer mixtures or by dispersing nanofillers within fibrous matrix are promising as these systems can have excellent optical, electrical, or magnetic properties, making it easier to produce functional fibers [10]. For example,

next-generation wound dressing materials should not only prevent pathogens from entering the wound, but should also be capable of monitoring the status of the wound, aiding the healing process and delivering drugs directly to the wound area [53]. A diverse series of methodologies have been used to fabricate composite nanofibers. The biocompounds can be loaded to the mat by different methods, including coelectrospinning, side-by-side, multijet, coaxial, emulsion, and surface immobilization [9]. By coelectrospinning, the drug could be homogenized with the polymer solution. This tactic is valid when the compounds are stable and soluble in the same solvent as the polymer; however, the bioactivity of drug molecules may be affected as a result of interaction between solvents and the electric field [54]. Another problem commonly faced occurs when the biocompounds are insoluble in a common solvent. To solve the solubility issue, side-by-side electrospinning provides two solvent spinnerets at the same time [55]. Also, more than two spinnerets can be used to load different molecules by multijet electrospinning (**Figure 1B**). Coaxial electrospinning involves fabrication of nanofibers from two polymers from a coaxial capillary spinneret, and as a result, the core and the shell are formed by different polymers (**Figure 1C**) [33]. With this technology, some polymers which are difficult to process are coelectrospun and form a core inside the shell of another polymer. Electrospun nanofibers are also used as drug delivery vehicles, but because of their large surface area and high porosity, a significant burst release is frequently observed. The coaxial method is used to control the burst release of drugs as the shell of the polymer acts as a diffusion barrier for drugs [56]. Emulsion electrospinning can produce a drug/polymer nanofiber core-shell structure, which possesses an excellent ability to control the release rate of the drug and avoid the initial burst. In the surface immobilization method, the drug molecules can be covalently bonded to the surface of nanofibers by physical and chemical immobilization. This method can also protect the bioactivity of loaded molecules from the effects of high voltage [10].

4. Nanofibers and biomedical application

Nanofibers have been widely used in various biomedical applications, including drug delivery [57], tissue engineering [53], stem cell therapy [34], cancer therapy [13, 57], and wound healing [58–60]. This is because they offer numerous attractive features, such as large surface area, material design flexibility, and tunable functional properties, which facilitate and widen the use of nanofibers in a variety of biomedical applications [50, 61]. The following section describes the recent advances in the use of nanofibers for drug delivery and wound healing applications.

4.1 Applications of nanofiber in skin wound healing

As mentioned above, nanofibrous scaffolds seem to be a good candidate as a skin substitute for wound healing, especially by their similarity to ECM. The ECM is a complex structure that surrounds cells in all tissues of the body [62]. Its biochemical composition varies somewhat from tissue to tissue. In healthy skin, the ECM consists of fibrous structural proteins, including collagens, elastins, laminins, and a variety of polysaccharides and proteoglycans, e.g., dermatan sulfate and hyaluronan [1]. Furthermore, it helps to support cells and comprises key components of the basement membrane that anchor and help replenish epidermal cells [54]. An excellent work published by Felgueiras and Amorim cited a previous review about acute and chronic wounds. Acute wound healing is a well-organized process, following four phases known as hemostasis, inflammation, proliferation, and remodeling (**Figure 2**). Immediately after microvascular injury and extravasation of blood and

its components into the wound, a complex process involving coordinated interaction between diverse immunological and biological systems begins [7, 10]. Along with hemostatic events, the coagulation cascade is activated through extrinsic and intrinsic pathways, leading to platelet aggregation and clot formation in order to limit blood loss (**Figure 2B**) [29]. The fibrin clot also has an important function in signaling further events of the healing process since it elicits numerous cytokines and growth factors. The degranulation of platelets triggers the recruitment of inflammatory cells to clean the wound. This is the beginning of the inflammatory phase, which can be macroscopically identified by redness, heat swelling, and pain. Vasodilation and increased permeability of blood vessels occur, facilitating the penetration of plasma proteins and leucocytes into the wound area (**Figure 2C**). Macrophages and neutrophils are the first cells to arrive at the wound site. The main role of these cells is to eliminate bacteria, debris, and foreign bodies. Despite the rapid action of neutrophils, the activity of these cells is strictly associated with damage in the surrounding tissues. During the proliferative phase, fibroblasts are activated, proliferate, and start to produce and secrete collagen, which replaces the provisional ECM. The granulation tissue is characterized by a high density of new blood vessels as a result of intense angiogenesis (**Figure 2D**). Re-epithelialization occurs as a result of keratinocyte proliferation and migration from the wound edges and skin appendages toward the center of the wound. Remodeling of tissue initiates during the proliferative phase and persists for weeks, months, or years. During remodeling, the cellularity of the granulation tissue gradually decreases. Additionally, a series of rearrangements of ECM take place (**Figure 2E**) [7]. Unlike acute wounds, chronic wounds are a result of gradual tissue degradation by chemical and biological agents like proteolytic enzymes derived from neutrophils. In chronic wounds, the level of some proteases increased ten- to fortyfold over that in acute wounds. This proteolytic activity may lead to a continued degradation of the tissue and stop the healing process [63]. The main factors that contribute to the nonhealing condition of a wound include infection, advanced age, diabetes, and other chronic diseases [64], as well as high levels of metalloproteinases and lack of the integrin receptor for fibronectin binding and keratinocyte migration [65]. In the past, traditional dressings were used to simply manage wounds, including

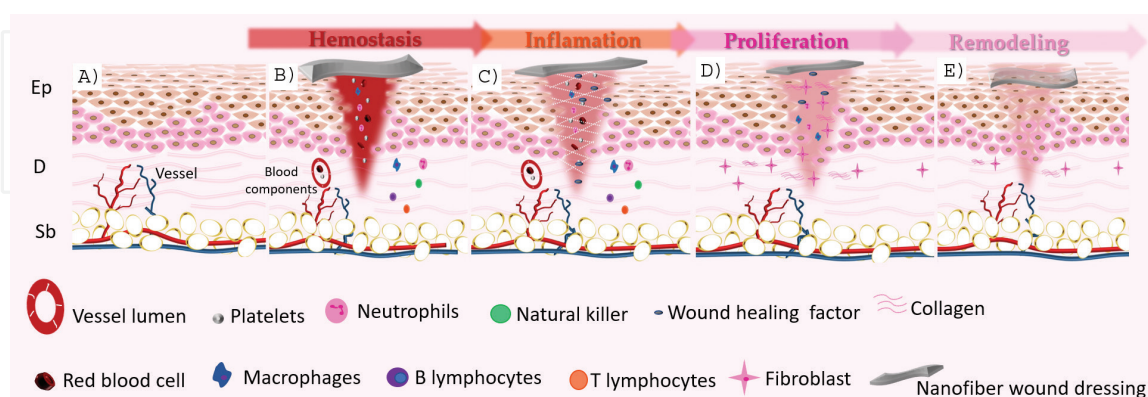


Figure 2.

Wound dressing nanofiber. Layers of epidermis (Ep), dermis (D), and subcutaneous tissue (Sc). Immediately following cutaneous injury, blood components (neutrophils, macrophages, platelets, and system immune cell) extravasate from the dermis and infiltrate the wound. The coagulation occurs as platelets aggregate with fibrin, which is deposited in the wound following its conversion in fibrinogen. Platelets release several factors, which attract neutrophils for the local injury, signaling the beginning of inflammation phase. Neutrophils and macrophages remove debris from the wound, release growth factor, which recruit fibroblast to the wound and start to synthesize collagen in the proliferation phase. As the rate of collagen synthesis slows down, the reorganization occurs in the remodeling phase. Throughout all stages, the nanofiber composite interacts with the tissue, releasing drugs that will facilitate the healing process. This figure is an adaptation from Alberti and coworkers [7].

gauze, lint, plaster, bandages, and cotton wool. Care included the use of antibiotics, medicated ointments and creams, steroids, vitamin injection, and laser therapy. Modern dressing technology has evolved considerably in the last 50 years. It is now based on the principle of creating and maintaining a moist wound environment that stimulates proliferation and migration of fibroblast and keratinocytes and enhances collagen synthesis [7, 63]. As a result, creating strategies to replace the missing or dysfunctional ECM may be a major goal of skin engineering, aiming to help the body to complete regeneration when a given clinical condition hampers the normal healing process. A common approach has been the use of biodegradable scaffolds to sustain and guide cellular growth throughout the regeneration process [66]. The scaffold's role is to provide an artificial environment for cell adhesion, migration, and spread, thus allowing cell proliferation. Furthermore, an ideal dressing scaffold should have certain characteristics, such as hemostatic ability; efficiency as a bacterial barrier; ability to absorb excess exudates (wound fluid/pus); exhibit appropriate water vapor transmission rate; exhibit adequate gaseous exchange ability; ability to conform to the contour of the wound area; exhibit functional adhesion, i.e., be adherent to healthy tissue, but nonadherent to wound tissue; be painless to the patient with ease of removal and, finally, be available at low cost [67]. Over the next few years, it is predicted that many materials with temporary therapeutic application will be substituted for biodegradable biomaterials with an active role in regeneration and repair of damaged tissues [7]. The marketplace offers a range of materials for wound dressing. For example, collagen-based Integra® sponges have been used as temporary coverage to promote granulation tissue formation prior to autografting for extensive skin defects [1]. Integra™ (Integra Life Sciences) is composed of an outer silicone epidermis and a dermis composed of bovine tendon collagen and chondroitin-6-sulfate [68]. A few other substitutes are Laserskin™, Biomembrane™, Bioseed™, and Hyalograft3-DTM [69]. These commercial mats were used in a clinical case report, and the results showed complete healing and an acceptable functional and cosmetic outcome with minimal morbidity to the patients [70]. Electrospinning scaffolds also serve as promising substrates for tissue repair owing to their nanofibrous architecture and amenability to tailoring of chemical composition. After modification with gelatin, the scaffolds improved human dermal fibroblast infiltration and proliferation throughout the scaffolds and the secretion of ECM proteins from the cells, showing potential for dermal tissue engineering [71].

4.2 Electrospun scaffolds for skin engineering

Engineering mats for wound healing requires not only the appropriate processing, solution, and environmental conditions, but also selection of the most suitable polymer matrix or rational combination of polymers [72]. Several electrospun materials have been proposed as wound dressing materials, including natural polymer, such as polysaccharides [73], polymeric carbohydrate molecules [74], chitin [75], chitosan [23], alginates [46], cellulose [4], and hyaluronic acid [76]. These natural polymers can be used alone or in combination with synthetic polymer, such as polyurethane [37], PVA/Ag [77], PCL [78], such as collagen/chitosan [79], chitosan/polyethylene glycol (PEG) [80], and water-soluble carboxyethyl chitosan/PVA [69, 81]. Additionally, electrospun mats can be seeded with dermal and epidermal cell lines. Bonville and coworker reported that collagen and PCL electrospun scaffold with dermal fibroblast promoted greater wound healing than acellular scaffolds [82]. Electrospinning scaffolds have also been used for controlled release of drugs [14], herbal extracts [83–85], growth factors, such as FGF [86], EGF [87], and angiogenesis factors [88], has shown successful improvement in the wound healing process, including *in vivo* experiments. Also, the incorporation of growth factors,

such as FGF [86] and EGF [87], or angiogenesis factors [88], has also been achieved and has shown successful improvement in the wound healing process, including *in vivo* experiments.

4.3 Drug delivery systems

Nanofiber composite-incorporated drugs play an important role in the healing process. This has been achieved by cleaning or debriding agents for necrotic tissue and antimicrobials, which prevent infection and promote tissue regeneration [51]. Some commonly incorporated compounds include antimicrobial agents, growth factors, and enzymes [69]. The main goal of drug delivery systems (DDS) is to efficiently deliver drug molecules within the recommended therapeutic level to the target cell, tissue, or organ for a defined period time [34]. A number of researchers have successfully encapsulated drugs within electrospun fibers by mixing the drugs in the polymer solution to be electrospun [7, 89, 90]. In most cases, polymer nanofibers are being used as candidate vehicles to carry the drug molecules. Depending on the polymer used, the release of a given pharmaceutical compound can be designed to have immediate, rapid, or delayed delivery [2]. This different profile of drug release is made possible by nanofiber biodegradability and can be adjusted according to the affinity of drug and mats to the target tissue. Commercially available antimicrobial dressings include Cutis orb™. Available silver impregnated dressings include fibrous hydrocolloid, polyurethane foam film, and silicone gels. Antiseptic iodine dressing acts on bacterial cells via oxidative degradation of cell components by interrupting the function of protein, which is widely effective against pathogens. Prolonged usage of iodine leads to skin irritation and staining [91]. Electrospun nanofibrous scaffolds constitute an excellent platform for local delivery of therapeutic agents, e.g., antimicrobial agents, antioxidants, anti-inflammatory drugs, anesthetics, enzymes, and growth factors, which have been incorporated into electrospun nanofibers for wound healing purposes [1]. Structural control of electrospun nanofibrous mats and loading suitable drugs are both important considerations in producing an active wound dressing material [92]. Therapeutic agents may be hydrophilic, hydrophobic, or both. Compounds such as vitamins, antibiotics, growth factors, anti-inflammatory agents, and other materials have been used. One of the most widely used additives is the nanoAg particle, which is incorporated into biopolymeric electrospun membranes by different methods. For example, Rujitanaroj and coworkers developed mats made of gelatin fibers containing silver nanoparticles lastly; the antibacterial activity of these materials was greatest against *Pseudomonas aeruginosa*, followed by *Staphylococcus aureus*, *Escherichia coli*, and methicillin-resistant *S. aureus* [93]. In another study, a mixture of PVA and chitosan oligosaccharides (COS) was electrospun with silver nanoparticles to produce fibrous mats for use in wound healing. *In vivo* wound healing experiments suggest that PVA/COS-AgNPs nanofibers can have clinical applications as a bioactive wound dressing [94]. Zhang et al. recently reported electrospun silver (Ag) nanoparticle-embedded polyvinyl alcohol (PVA) nanofibers as an antimicrobial scaffold. Silver nanoparticles (NPs) were first prepared and dispersed in PVA solution, these nanofiber mats showed good antibacterial activity against both gram-positive *S. aureus* and gram-negative *Escherichia coli* microorganisms [95]. Barani also reported the fabrication of an antibacterial nanofibrous mesh from PVA and poly-L-lactide acid (PLLA) with AgNPs [96]. For wound healing purposes, two specific requirements for a wound scaffold include rapid hemostasis and good antibacterial properties. Thus, antibacterial nanofibers have been fabricated by incorporating antibacterial materials into the polymers [67]. Beyond silver nanoparticles, other natural compounds have been associated with nanofibers for

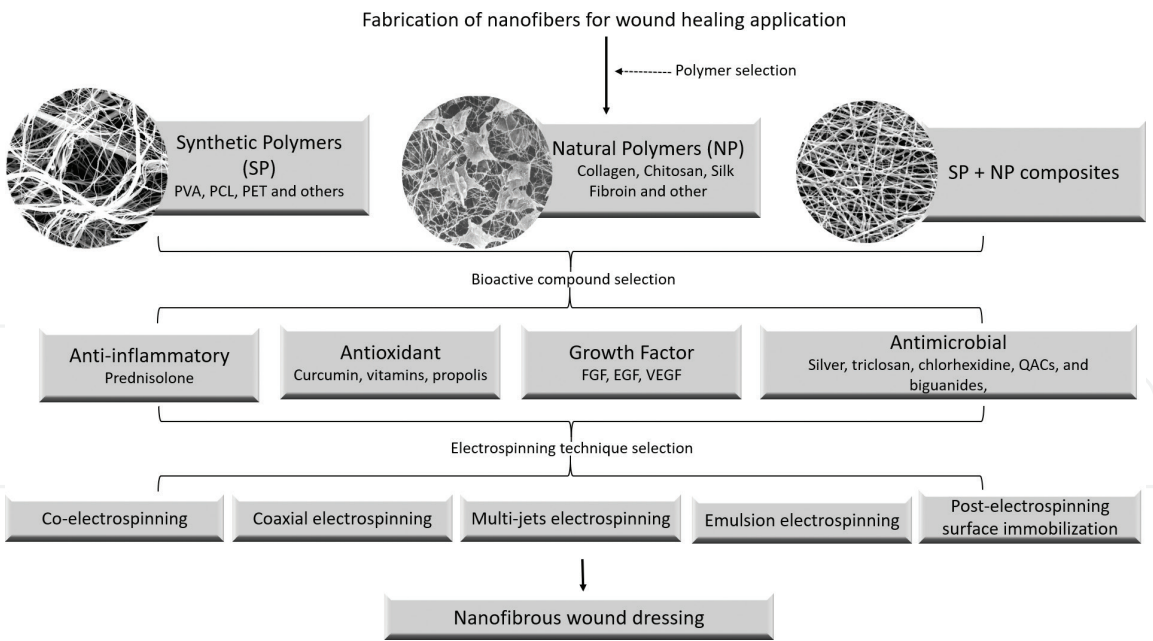


Figure 3.
Schematic illustration of the development of a nanofibrous wound dressing material.

antimicrobial activity, such as *Aloe Vera* [83], propolis [84], curcumin [97], and chitosan [66, 79]. Common antibacterial materials, such as antibiotics, triclosan, chlorhexidine, quaternary ammonium compounds (QACs), and biguanides, have also been reported for use in the fabrication of antibacterial nanofibers [3]. Silk/fibroin nanofibers were also functionalized with a sulfate group in order to test whether they exhibited antibacterial activity [60, 84, 90]. A schematic illustration of the main steps for the development of a nanofibrous wound dressing material is displayed in **Figure 3**.

5. Conclusion and outlook

Electrospinning has attracted the interest of researchers from different fields as a simple and versatile technique to produce nanofibers with a range of clinical applications. Moreover, because of enormous research progress over past decades, the development of electrospun scaffolds for skin engineering seems to be in the laboratory phase. Many studies have improved the knowledge of the electrospinning process, and different approaches have confirmed the potential of using electrospinning in wound healing applications, as demonstrated in this chapter. However, preclinical studies with promising results are needed before these products reach the marketplace. Furthermore, the transition of nanofiber technology remains confined owing to difficulties associated with upscaling the electrospinning process itself, such as control of pore size and elimination of artifacts like beads, as well as consistency in physical characteristics like porosity and distribution of nanofibers with homogeneous diameters. In conclusion, this chapter reports the main considerations for developing scaffolds that aid in the wound healing process. By developing nanofibers for wound dressing application, the selection of some parameters are crucial, including, for example, the selection of polymers, type of collector, and better systems for drug delivery in the local wound in order to provide low cytotoxicity, good biodegradation rate, permeability, avoidance of bacterial proliferation, provision of re-epithelization of the injured site, and promotion of keratinocyte and fibroblast growth since these cells act as an adjuvant in the wound healing process. Electrospun mats for skin tissue

engineering should serve as a barrier for the wound site and possess a structure with high porosity, oxygen permeability, wettability, suitable mechanical properties, antimicrobial activity, surgical handleability, biodegradability, cell adhesive properties, and wound healing properties.

Electrospun nanofiber scaffolds incorporated with cells and/or bioactive compounds are a promising approach for skin tissue engineering, facilitating treatment and promoting wound healing of many skin disorders. However, the risks of working in this field have still not been assessed, including, for example, the inhalation of nanosized fibers and solvent vapor, which could very well pose health hazards. Thus, the risk-benefit ratio of this technology toward realizing its therapeutic potential warrants an interdisciplinary approach.

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Abbreviations

Ag	silver
AgNO ₃	silver nitrate
AgNPs	silver nanoparticles
COS	chitosan oligosaccharides
DDS	drug delivery systems
ECM	extracellular matrix
EGF	epidermal growth factor
ES	electrospinning
FGF	fibroblast growth factor
MW	molecular weight
NPs	nanoparticles
PCL	poly(ε-caprolactone)
PEG	polyethylene glycol
PET	poly(ethylene terephthalate)
PLGA	poly(lactide-co-glycolide)
PLLA	poly-L-lactide acid
PMMA	polymethyl methacrylate
PVA	polyvinyl alcohol
PVDF	poly(vinylidene fluoride)
QACs	quaternary ammonium compounds
SF	silk fibroin

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Author details

Daniela Sousa Coelho^{1*}, Beatriz Veleirinho², Thaís Alberti¹, Amanda Maestri¹, Rosendo Yunes³, Paulo Fernando Dias¹ and Marcelo Maraschin¹

1 Federal University of Santa Catarina, Florianopolis, Brazil

2 NanoScoping—Soluções em Nanotecnologia, Florianopolis, Brazil

3 University of Itajaí Valley, Itajaí, Brazil

*Address all correspondence to: daniela.sousacoelho@gmail.com

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References

- [1] Chen R. Recent advances in electrospun nanofibers for wound healing. *Nanomedicine* (London, England). 2017;**12**:1335-1352
- [2] Dias JR, Granja PL, Bártolo PJ. Progress in materials science advances in electrospun skin substitutes. *Progress in Materials Science*. 2016;**84**:314-334
- [3] Anjum F, Agabalyan NA, Sparks HD, Rosin NL, Kallos MS. Biocomposite nanofiber matrices to support ECM remodeling by human dermal progenitors and enhanced wound closure. *Scientific Reports*. 2017;**7**:1-17
- [4] Liu R, Dai L, Si C, Zeng Z. Antibacterial and hemostatic hydrogel via nanocomposite from cellulose nano fi bers. *Carbohydrate Polymers*. 2018;**195**:63-70
- [5] Veleirinho B et al. Manipulation of chemical composition and architecture of non-biodegradable poly(ethylene terephthalate)/chitosan fibrous scaffolds and their effects on L929 cell behavior. *Materials Science and Engineering: C*. 2013;**33**:37-46
- [6] Alfaro De-Prá, matrizes nanoestruturadas bioativas para a aplicação na regeneração de nervos periféricos. 2017;**1**:1-138
- [7] Alberti T et al. Nanotechnology: A promising tool towards wound healing. *Current Pharmaceutical Design*. 2017;**23**:1-14
- [8] Passalacqua TG et al. Synthesis and evaluation of novel prenylated chalcone derivatives as anti-leishmanial and anti-trypanosomal compounds. *Bioorganic & Medicinal Chemistry Letters*. 2015;**25**:3564-3568
- [9] Alfaro De Prá MA, Ribeiro-do-Valle RM, Maraschin M, Veleirinho B. Effect of collector design on the morphological properties of polycaprolactone electrospun fibers. *Materials Letters*. 2017;**193**:154-157
- [10] Liu M, Duan X, Li Y, Yang D, Long Y. Electrospun nano fibers for wound healing. 2017;**76**:1413-1423
- [11] Baji A, Mai Y-W. Polymer nanofiber composites. 2017;**3**:55-78
- [12] Ramakrishna S. An Introduction to Electrospinning and Nanofibers. *World Scientific*; 2005;**1**:1-382
- [13] Veleirinho B, Rei MF, Lopes-Da-Silva JA. Solvent and concentration effects on the properties of electrospun polyethylene terephthalate nanofiber mats. *Journal of Polymer Science Part B: Polymer Physics*. 2008;**5**:460-471
- [14] Thakkar S, Misra M. Electrospun polymeric nanofibers: New horizons in drug delivery. *European Journal of Pharmaceutical Sciences*. 2017;**10**:1393-1399
- [15] Katti DS, Robinson KW, Ko FK, Laurencin CT. Bioresorbable nanofiber-based systems for wound healing and drug delivery: Optimization of fabrication parameters. *Journal of Biomedical Materials Research*. 2004. DOI: 10.1002/jbm.b.30041
- [16] Huang S, Fu X. Naturally derived materials-based cell and drug delivery systems in skin regeneration. *Journal of Controlled Release*. 2010;**142**:149-159
- [17] Ghasemi-Mobarakeh L, Prabhakaran MP, Morshed M, Nasr-Esfahani MH, Ramakrishna S. Electrospun poly(ϵ -caprolactone)/gelatin nanofibrous scaffolds for nerve tissue engineering. *Biomaterials*. 2008;**29**:4532-4539
- [18] Zeugolis DI, Li B, Lareu RR, Chan CK, Raghunath M. Collagen solubility

testing, a quality assurance step for reproducible electro-spun nano-fibre fabrication. A technical note. *Journal of Biomaterials Science. Polymer Edition*. 2008;**19**:1307-1317

[19] Law JX, Liao LL, Saim A, Yang Y, Idrus R. Electrospun collagen nanofibers and their applications in skin tissue engineering. *Tissue Engineering & Regenerative Medicine*. 2017;**14**:699-718

[20] Maleknia L, Rezazadeh Majidi Z. Electrospinning of gelatin nanofiber for biomedical application. *Oriental Journal of Chemistry*. 2014;**30**:2043-2048

[21] Simpson DG et al. Electrospun collagen: A tissue engineering scaffold with unique functional properties in a wide variety of applications. *Journal of Nanomaterials*. 2011

[22] Lopes da Silva J, Veleirinho B, Delgadillo I. Preparation and characterization of electrospun mats made of PET/chitosan hybrid nanofibers. *Journal of Nanoscience and Nanotechnology*. 2009;**9**:3798-3804

[23] Wang M, Roy AK, Webster TJ, Webster T. Development of chitosan/poly (vinyl alcohol) electrospun nanofibers for infection related wound healing. *Npg Asia Materials*. 2017;**7**:2016-2018

[24] Alavarse AC et al. Tetracycline hydrochloride-loaded electrospun nanofibers mats based on PVA and chitosan for wound dressing. *Materials Science and Engineering: C*. 2017;**77**:271-281

[25] Chen H, Huang J, Yu J, Liu S, Gu P. Electrospun chitosan-graft-poly(ϵ -caprolactone)/poly(ϵ -caprolactone) cationic nanofibrous mats as potential scaffolds for skin tissue engineering. *International Journal of Biological Macromolecules*. 2011;**48**:13-19

[26] Ribeiro TG et al. An optimized nanoparticle delivery system based on chitosan and chondroitin sulfate molecules reduces the toxicity of amphotericin B and is effective in treating tegumentary leishmaniasis. *International Journal of Nanomedicine*. 2014;**9**:5341-5353

[27] Kaplan D, Adams WW, Farmer B, Viney C. Chapter 1. Silk: Biology, structure, properties, and genetics. 1994;**1**:2-16

[28] Rajkhowa R et al. Synthesis, characterization and efficacy of chemically crosslinked PVA hydrogel for dermal wound healing in experiment et al animals. *Journal of Applied Polymer Science*. 2008;**111**:1400-1408

[29] Moura LIF, Dias AMA, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment—A review. *Acta Biomaterialia*. 2013;**9**:7093-7114

[30] Dash TK, Konkimalla VB. Poly- ϵ -caprolactone based formulations for drug delivery and tissue engineering: A review. *Journal of Controlled Release*. 2012;**158**:15-33

[31] Koski A, Yim K, Shivkumar S. Effect of molecular weight on fibrous PVA produced by electrospinning. *Materials Letters*. 2004;**58**:493-497

[32] Lin T, Fang J, Wang H, Cheng T, Wang X. Using chitosan as a thickener for electrospinning dilute PVA solutions to improve fibre uniformity. *Nanotechnology*. 2006;**17**:3718-3723

[33] Gupta A, Kumar R, Upadhyay N, Sureka P, Roy P. Synthesis, characterization and efficacy of chemically crosslinked PVA hydrogels for dermal wound healing in experimental animals. *Journal of Applied Polymer Science*. 2008;**111**:1400-1408

[34] Bhardwaj N, Kundu SC. Electrospinning: A fascinating fiber

fabrication technique. *Biotechnology Advances*. 2010;**28**:325-347

[35] Reddy J, Venugopal et al. Nanofibrous structured biomimetic strategies for skin tissue regeneration. *Wound Repair and regeneration*. 2013;**21**:1-16

[36] Hairder A, Sajjad Haider I-KK. A comprehensive review summarizing the effect of electrospinning parameters and potential applications of nanofibers in biomedical and biotechnology. *Arabian Journal of Chemistry*. 2015

[37] Matabola KP, Moutloali RM. The influence of electrospinning parameters on the morphology and diameter of poly(vinylidene fluoride) nanofibers- effect of sodium chloride. *Journal of Materials Science*. 2013;**48**:5475-5482

[38] Demir MM, Yilgor I, Yilgor E, Erman B. Electrospinning of polyurethane fibers. *Polymer (Guildf)*. 2002;**43**:3303-3309

[39] Buchko CJ, Chen LC, Shen Y, Martin DC. Processing and microstructural characterization of porous biocompatible protein polymer thin films. *Polymer (Guildf)*. 1999;**40**:7397-7407

[40] Zhang N et al. Pharmacokinetics, tissue distribution and anti-tumor effect of low density lipoprotein peptide conjugated submicron emulsions. *Biomedicine & Pharmacotherapy*. 2016;**82**:614-619

[41] Sill TJ, von Recum HA. Electrospinning: Applications in drug delivery and tissue engineering. *Biomaterials*. 2008;**29**:1989-2006

[42] Ki CS et al. Characterization of gelatin nanofiber prepared from gelatin-formic acid solution. *Polymer (Guildf)*. 2005;**46**:5094-5102

[43] Han J, Chen TX, Branford-White CJ, Zhu LM. Electrospun shikonin-loaded PCL/PTMC composite fiber mats with potential biomedical applications. *International Journal of Pharmaceutics*. 2009;**667**:1-6

[44] Casper CL, Stephens JS, Tassi NG, Chase DB, Rabolt JF. Controlling surface morphology of electrospun polystyrene fibers: Effect of humidity and molecular weight in the electrospinning process. *Macromolecules*. 2004;**37**:573-578

[45] Bae H-S et al. Fabrication of highly porous PMMA electrospun fibers and their application in the removal of phenol and iodine. *Journal of Polymer Research*. 2013;**20**(158)

[46] Zeeb B, Saberi AH, Weiss J, McClements DJ. Formation and characterization of filled hydrogel beads based on calcium alginate: Factors influencing nanoemulsion retention and release. *Food Hydrocolloids*. 2015;**50**:27-36

[47] Jun Z, Hou H, Schaper A, Wendorff JH, Greiner A. Poly-L-lactide nanofibers by electrospinning— Influence of solution viscosity and electrical conductivity on fiber diameter and fiber morphology. *E-Polymers*. 2003;**3**:1-9

[48] Kim B, Park H, Lee S-H, Sigmund WM. Poly(acrylic acid) nanofibers by electrospinning. *Materials Letters*. 2005;**59**:829-832

[49] Geng X, Kwon O-H, Jang J. Electrospinning of chitosan dissolved in concentrated acetic acid solution. *Biomaterials*. 2005;**26**:5427-5432

[50] Geetha M, Asokamani R, Amit Kumar J, Ramalingam M. Nanofiber Composites for Biomedical Applications. 2017;**1**:117-175

[51] Pasricha R, Sachdev D. Nanofiber Composites for Biomedical Applications. 2017;**1**:157-196

- [52] Polini A, Yang F. Nanofiber Composites for Biomedical Applications. 2017;**21**:622-629
- [53] Naves LB, Almeida L, Rajamani L. Nanofiber Composites for Biomedical Applications. 2017. DOI: 10.1016/B978-0-08-100173-8.00011-9
- [54] Chen H, Peng Y, Wu S, Tan LP. Electrospun 3D fibrous scaffolds for chronic wound repair. *Materials (Basel)*. 2016;**9**:1-12
- [55] Xu F, Li Luming CX. Fabrication of aligned side-by-side TiO₂/SnO₂ nanofibers via dual-opposite-spinneret electrospinning. *Journal of Nanomaterials*. 2012;**5**:1-5
- [56] Nguyen TTT, Ghosh C, Hwang SG, Chanunpanich N, Park JS. Porous core/sheath composite nanofibers fabricated by coaxial electrospinning as a potential mat for drug release system. *International Journal of Pharmaceutics*. 2012;**439**:296-306
- [57] Dhand C et al. Nanofiber Composites for Biomedical Applications. 2017;**1**:199-223
- [58] Dai XY et al. Electrospun emodin polyvinylpyrrolidone blended nanofibrous membrane: A novel medicated biomaterial for drug delivery and accelerated wound healing. *Journal of Materials Science. Materials in Medicine*. 2012;**23**:2709-2716
- [59] Goins A et al. Fabrication of core-shell nanofibers for controlled delivery of bromelain and salvianolic acid B for skin regeneration in wound therapeutics. *Biomedical Materials*. 2017;**12**:1-17
- [60] Shan YH et al. Silk fibroin/gelatin electrospun nanofibrous dressing functionalized with astragaloside IV induces healing and anti-scar effects on burn wound. *International Journal of Pharmaceutics*. 2015;**479**:291-301
- [61] Caserta S, Sabetta L, Simeone M, Guido S. Shear-induced coalescence in aqueous biopolymer mixtures. *Chemical Engineering Science*. 2005;**60**:1019-1027
- [62] Haraway GD. The extracellular matrix in wound healing. *Healthpoint*. 2006;**800**:1-4
- [63] Felgueiras HP, Amorim MTP. Functionalization of electrospun polymeric wound dressings with antimicrobial peptides. *Colloids and Surfaces B: Biointerfaces*. 2017;**156**:133-148
- [64] Byung-Chul K et al. Fibroblasts from chronic wounds show altered TGF- β -signaling and decreased TGF- β Type II Receptor expression. *Journal of Cellular Physiology*. 2003;**195**:331-336
- [65] Wysocki AB, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9. *The Journal of Investigative Dermatology*. 1993;**101**:64-68
- [66] Veleirinho B et al. Nanofibrous poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/chitosan scaffolds for skin regeneration. *International Journal of Biological Macromolecules*. 2012;**51**:343-350
- [67] Rieger KA, Birch NP, Schiffman JD. Designing electrospun nanofiber mats to promote wound healing—A review. 2013;**1**:4531-4541
- [68] Çinar Medeni Ö, Baltaci G, Doğan Vayvay G. Acute effect of kinesiotape muscle technique on hamstring flexibility and pain during stretching. *Fiz Rehabilitation*. 2015;**26**:73-77
- [69] Dhivya S, Padma V, Santhini E. Wound dressings-a review. *Biomedicine*. 2015;**5**:24-28
- [70] Gonyon DLJ, Zenn MR. Simple approach to the radiated scalp wound

- using INTEGRA skin substitute. *Annals of Plastic Surgery*. 2003;**50**:315-320
- [71] Jingwei X, Bing M, Lorwattanapongsa MP. Fabrication of novel 3D nanofiber scaffolds with anisotropic property and regular pores and their potential applications. *Advanced Healthcare Materials*. 2012;**1**:674-678
- [72] Zhong SP, Zhang YZ, Lim CT. Tissue scaffolds for skin wound healing and dermal reconstruction. *Wiley Interdisciplinary Reviews: Nanomedicine Nanobiotechnology*. 2:510-525
- [73] Franz G. Polysaccharides in pharmacy: Current applications and future concepts. *Planta Medica*. 1989;**55**:493-497
- [74] Medusheva EO et al. New medical materials with an integral lasting effect based on fibre-forming polymers. *Fibre Chemistry*. 2007;**39**:268-271
- [75] Lim CT et al. Nanofiber technology: Current status and emerging developments. *Progress in Polymer Science*. 2017;**70**:1-17
- [76] Liu Y et al. Effects of solution properties and electric field on the electrospinning of hyaluronic acid. *Carbohydrate Polymers*. 2011;**83**:1011-1015
- [77] Hwa HK. Preparation and properties of electrospun poly(vinyl alcohol)/silver fiber web as wound dressings. *Polymer Engineering and Science*. 2006;**47**:43-49
- [78] Gumusderelioglu M, Dalkiranoglu S, Aydin RST, Cakmak S. A novel dermal substitute based on biofunctionalized electrospun PCL nanofibrous matrix. *Journal of Biomedical Materials Research. Part A*. 2011;**98**:461-472
- [79] Chen J-P, Chang G-Y, Chen J-K. Electrospun collagen/chitosan nanofibrous membrane as wound dressing. *Colloids Surfaces A: Physicochemical and Engineering Aspects*. 2008;**313-314**:183-188
- [80] Tchemtchoua VT et al. Development of a chitosan nanofibrillar scaffold for skin repair and regeneration. *Biomacromolecules*. 2011;**12**:3194-3204
- [81] Zhou Y et al. Electrospun water-soluble carboxyethyl chitosan/poly(vinyl alcohol) nanofibrous membrane as potential wound dressing for skin regeneration. *Biomacromolecules*. 2008;**9**:349-354
- [82] Bonvallet PP et al. Microporous dermal-mimetic electrospun scaffolds pre-seeded with fibroblasts promote tissue regeneration in full-thickness skin wounds. *PLoS One*. 2015;**10**:1-17
- [83] Suganya S et al. Aloe vera incorporated biomimetic nanofibrous scaffold: A regenerative approach for skin tissue engineering. *Iranian Polymer Journal*. 2014;**23**:237-248
- [84] Gomes T et al. Polymeric nanoparticles of Brazilian red propolis extract: Preparation, characterization, antioxidant and leishmanicidal activity. *Nanoscale Research Letters*. 2016
- [85] Sikareepaisan P, Suksamrarn A, Supaphol P. Electrospun gelatin fiber mats containing a herbal-Centella asiatica-extract and release characteristic of asiaticoside. *Nanotechnology*. 2008;**19**(15102)
- [86] Yang Y et al. Electrospun fibers with plasmid bFGF polyplex loadings promote skin wound healing in diabetic rats. *Molecular Pharmaceutics*. 2011;**9**
- [87] Rana D, Ratheesh G, Ramakrishna S, Ramalingam M. Nanofiber Composites for Biomedical Applications. 2017;**1**:325-344

- [88] Kuppan P, Vasanthan KS, Sundaramurthi D, Krishnan UM, Sethuraman S. Development of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) fibers for skin tissue engineering: Effects of topography, mechanical, and chemical stimuli. *Biomacromolecules*. 2011;**12**:3156-3165
- [89] Kenawy ER et al. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend. *Journal of Controlled Release*. 2002;**81**:57-64
- [90] Kheradvar SA, Nourmohammadi J, Tabesh H, Bagheri B. Starch nanoparticle as a vitamin E-TPGS carrier loaded in silk fibroin-poly(vinyl alcohol)-Aloe vera nanofibrous dressing. *Colloids Surfaces Biointerfaces*. 2018;**166**:9-16
- [91] Simões D et al. Recent advances on antimicrobial wound dressing: A review. *European Journal of Pharmaceutics and Biopharmaceutics*. 2018;**127**:130-141
- [92] Zahedi P, Rezaeian I, Ranaei-Siadat SO, Jafari SH, Supaphol P. A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. *Polymers for Advanced Technologies*. 2010;**21**:77-95
- [93] Rujitanaroj P, Pimpha N, Supaphol P. Wound-dressing materials with antibacterial activity from electrospun gelatin fiber mats containing silver nanoparticles. *Polymer (Guildf)*. 2008;**49**:4723-4732
- [94] Li C et al. Silver nanoparticle/chitosan oligosaccharide/poly(vinyl alcohol) nanofibers as wound dressings: A preclinical study. *International Journal of Nanomedicine*. 2013;**8**:4131
- [95] Zhou JY, Zhang Z, Qian GS. Mesenchymal stem cells to treat diabetic neuropathy: A long and strenuous way from bench to the clinic. *Cell Death Discovery*. 2016;**2**:1-7
- [96] Barani H. Antibacterial continuous nanofibrous hybrid yarn through in situ synthesis of silver nanoparticles: Preparation and characterization. *Materials Science and Engineering: C*. 2014;**43**:50-57
- [97] Alberti TB. Desenvolvimento de nanomatrizes de álcool polivinílico e própolis com aplicação em cicatrização de pele. *UFSC*; 2016;**1**:1-63