Chapter 11
Multifunctional Wound Dressings Based on Electrospun Nanofibers

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Abstract The skin, the largest and most external organ of the human body, acts as the first line of protection against traumata. Therefore, skin wounds and injuries can expose the organism to many severe diseases. Some wounds show chronic aspects, usually taking a long time to heal and, therefore, being more susceptible to infections. Thus, for the sake of health, effective strategies to protect and coat the affected skin are highly demanded nowadays. In this context, applying wound dressings based on electrospun nanofibers at the local injury site can speed up the healing process by protecting the wound from external harm and enhancing tissue recovery, fluid draining, and moisture regulation. Besides, wound dressings can also present antibacterial activity and promote drug delivery, being easily integrated with regenerative therapies. In this context, we present recent developments in the design of multifunctional nanofiber-based systems produced by electrospinning for wound dressing applications. Besides basic fundamental aspects of skin wounds and the types of multifunctional nanofibers features suitable for wound dressing, we also discuss future trends and challenges related to the smart wound dressing.

Keywords Skin injuries · Wound healing · Wound dressing · Nonwovens · Polymer nanofibers

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The skin is the largest and most external organ in the human body, being the first barrier against mechanical, chemical and biological shocks. Besides, it performs fundamental functions as thermoregulation, prevention of water and fluid loss, immune surveillance, hormone synthesis, and sensory detection [1]. Damages in skin's structure can make the organism susceptible to several diseases. The traditional technique to overcome this issue consists in cover the injured skin area with wound dressings, protecting it against external agents and waiting for the natural restoration of the tissue. Advanced interdisciplinary researches combining wound healing approaches and nanotechnology have resulted in novel strategies to assist the rapid wound healing, treatment of chronic wounds, and monitoring and combination of modern therapies. In this sense, wound dressings based on electrospun nanofibers structured as nonwoven layers can enable the protection of the injured area, absorption of exudates, and improve gas flow and exchange. Besides, their fibrous network offer a biomimetic environment that stimulates skin's cells proliferation, and can encapsulate active compounds for their controlled release. In the next sections we discuss the types of wound dressings fabricated by electro spinning, using both synthetic and natural polymers, as well as we discuss how their distinct properties can be used for designing distinct multifunctional wound dressings.

11.1 Introduction to Electrospun Nanofibers for Wound Dressing

11.1.1 Skin Wound and Wound Healing: Basic Aspects

The skin is the organ in the first line of defense of the body against environmental exposure, and also provides essential functions in thermoregulation, hydration, excretion and synthesis of vitamin D. Therefore, skin lesions could lead to the loss of essential functions of the human body [2–4]. When a skin injury occurs, it generates open and closed wounds, which are healed through four interconnecting phases to recover its functions, namely: hemostasis, inflammation, proliferation, and remodeling [5], as depicted in Fig. 11.1. The hemostasis and inflammation phases occur concurrently after injury and last from 1 to 5 days. In the hemostasis phase, neutrophils and later macrophages produce inflammatory mediators [interleukin (IL-4)], transforming growth factors β (TGF-β), which induce platelets to release coagulation factors, such as clots of fibrin that allow the migration of cells to the wound, and decrease the inflammation phase with the release of lipoxins and TGF-β [6, 7]. The proliferation phase lasts approximately 1 week, when the epidermal barrier is rebuilt from a matrix containing fibrin, fibronectin and keratinocytes, released from stem cells that proliferate and differentiate. Growth factors modulate this epithelialization process and promote tissue reconstruction through the action of biomolecules, such as fibroblasts, macrophages, blood vessels, and collagen [6, 7]. The tissue remodeling phase coincides with the proliferation phase, although this restoration process

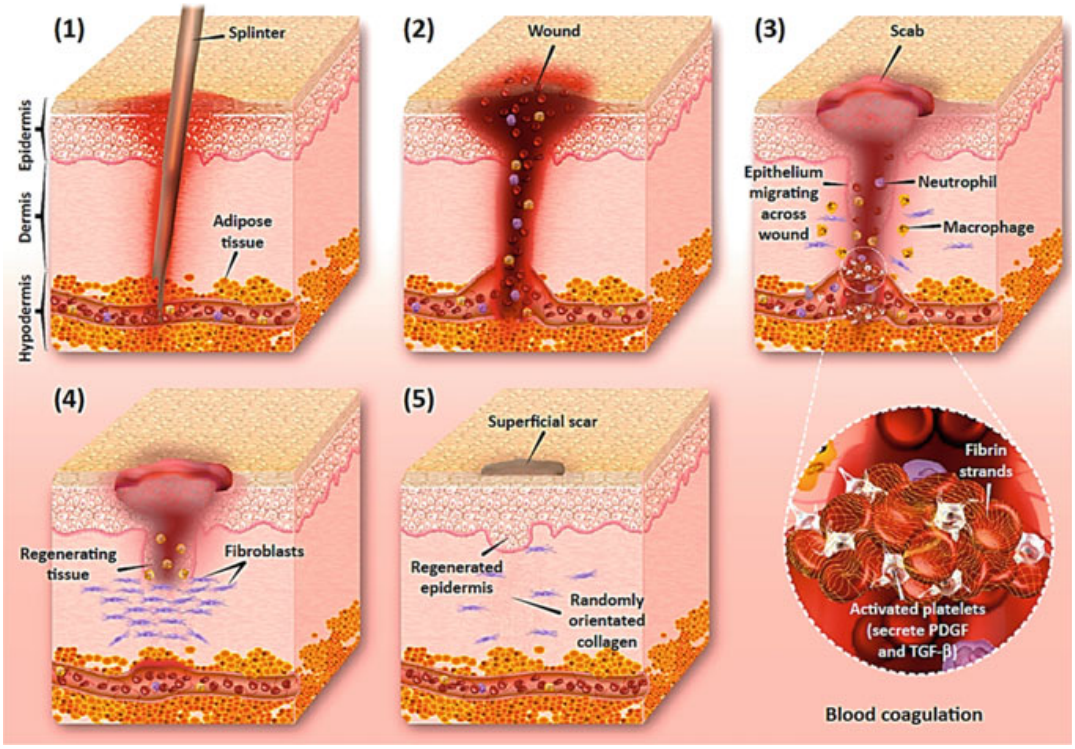

Fig. 11.1 The wound healing process involves four phases: hemostasis, inflammation, proliferation, and remodeling, in which a great diversity of biomolecules acts to reduce bacterial infection, and improving tissue remodeling. Adapted with permission from [5]. Copyright 2018 Elsevier

can take from 3 weeks to 2 years. It is the most clinically important phase where the assistance of growth factors such as TGF-β and platelet-derived growth factor (PDGF) contribute to the collagen deposition in the matrix to form an organized and healthy tissue [4, 8].

Skin wounds are classified into two types: acute and chronic. Acute wounds are wounds that heal in less than 3 months [4, 6]. Chronic wounds are the result of complications in tissue recovery, disease, pressure, and diabetic ulcers. Chronic wounds are the first focus of research for conventional and advanced treatment, since these wounds can stop healing in the inflammatory phase due to infections, hypoxia, biofilms, and poor delivery of biomolecules for tissue recovery [4, 9].

11.1.2 Types of Wound Dressing: Conventional and Novel Multifunctional Ones

Conventional treatments for wound healing usually employ dressings to protect the wound, creating a physical barrier against contamination and dangerous agents [10]. In addition, these dressings are designed to absorb exudate without causing dryness, allowing the production of a microclimate that promotes wound healing [11]. The

most suitable treatment is for chronic wounds, because of the economic costs and the impact on the life quality of patients. Conventional treatment methods are divided into two, namely: (i) passive dressings that coat the wound for protection after the healthcare specialist treatment, and (ii) multifunctional dressings that provide a humid environment that alters the wound atmosphere and interacts with the surface to promote healing [10, 12]. These types of wound dressing are designed with an optimal level of adhesion, thickness, contact area with the wound, absorption capacity, friction, and antibacterial properties. Such dressings are usually fabricated using three layers, in which the internal level prevents adherence to the wound dressing, the intermediate layer absorbs and retains the exudate excess, maintaining a humid environment, while the outer layer prevents bacterial invasion [10–12].

Nanostructured materials can be applied in wound dressings design, providing matrices for an organized cell growth and healthy regeneration of the skin, promoting scar formation, tissue integration, and avoiding bacterial infections [13, 14], as illustrated in Fig. 11.2. Among the most efficient nanomaterials for skin wound treatment are the electrospun nanofibers (here named as ESNF), which can yield a high surface/volume ratio platform displaying appealing properties such as biodegradability, high porosity, and the possibility of surface functionalization [15, 16]. Polymer nanofibers can mimic the biological extracellular matrix (ECM), contributing to the wound healing process, since the interaction of their large surface area improves drainage, nutrient exchange, antibacterial protection, and air permeability. In addition, nanofibers can be loaded with drugs [14, 17], antimicrobials, [18] and active biomolecules [19] to be released by diffusional process or triggered by external physicochemical stimuli, and thus promote cell regeneration, which makes this multifunctional treatment superior to conventional treatments [11, 12, 14, 15]. Multifunctional nanofibers for wound healing with externals agents activation and portable deposition in situ are called smart nanomaterials [20]. Besides the possibility to trigger the mechanism of interest, they can also be designed with advantageous properties such as biocompatibility and biodegradability, gas-permeability, surface hydrophilicity, antimicrobial properties, capability to absorb exudates and regulate nutrients and gases, and also to maintain local humid environment [12].

11.1.3 Electrospinning as a Suitable Alternative for Wound Dressing

11.1.3.1 Electrospun Nanofibers

Nonwovens based on ESNF have been employed in the last years for biomedical application, including as wound dressing, due to their advantageous features, including their unique physical and chemical properties, a morphology similar to the fibrous ECM, ability to encapsulate and release different bioactive compounds that improve the healing process (antimicrobial, micro and macromolecules, and

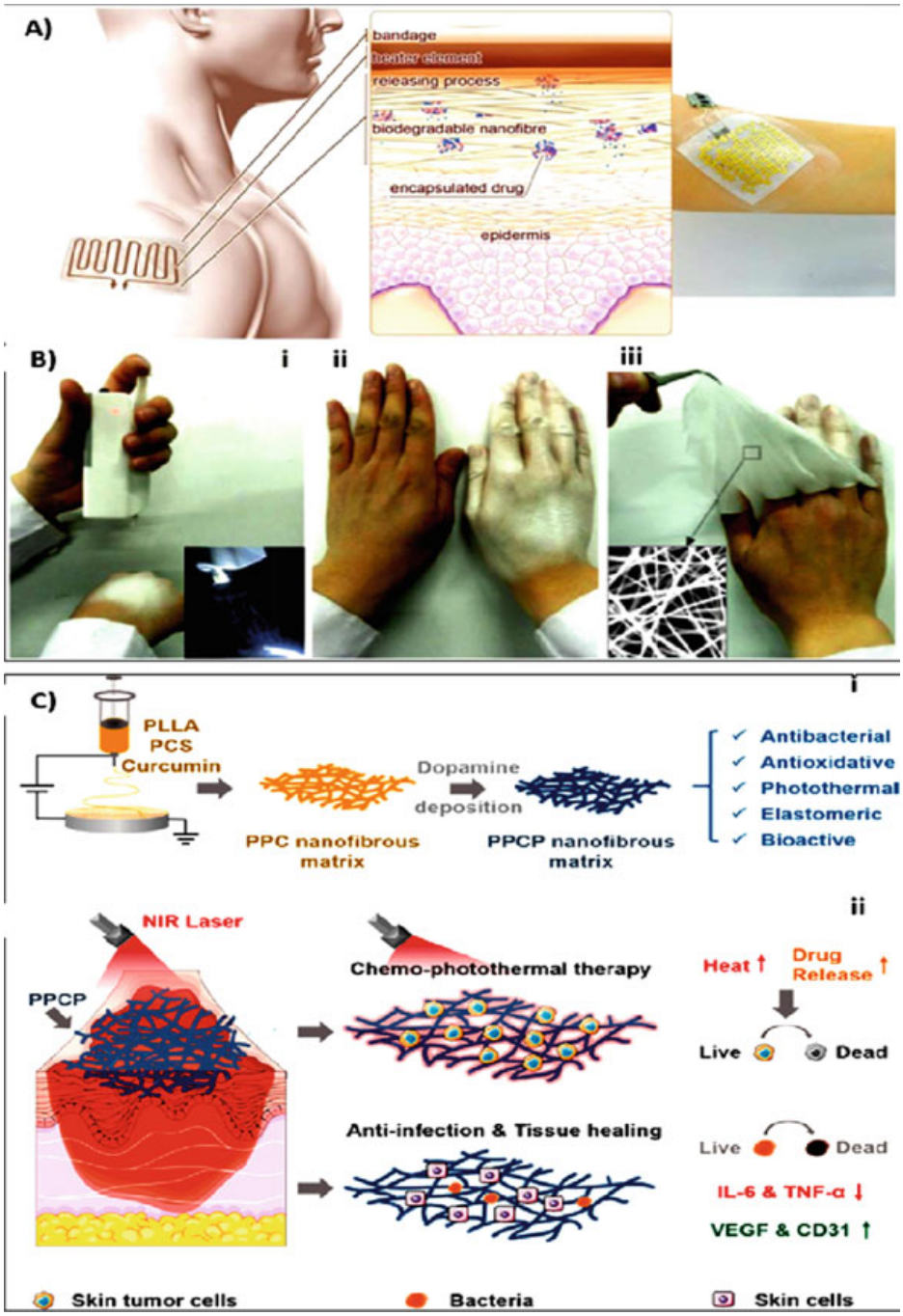

Fig. 11.2 **a** Thermosensitive drug nanocarriers are embedded within ESNF in a flexible system, in which the drugs are released as the temperature increases to enhance wound healing. Adapted with permission from Ref. [17]. Copyright 2017 Springer. **b** A battery-operated portable handheld electrospinning apparatus (BOEA) produce poly(lactic acid) (PLA) nanofibers to rapid hemostatic treatments. Adapted with permission from [21]. Copyright 2015 Willey. **c** (i) Multifunctional wound dressing composed of poly(l-lactic acid)–poly(citrate siloxane) nanofibers loaded with curcumin and polydopamine (PPCP), (ii) after NIR laser irradiation, the heat produced stimulates the release of curcumin, which exerts antibacterial and anti-inflammatory effects, improving skin healing. Adapted with permission from [22]. Copyright 2020 American Chemical Society

growth factors). Other properties of interest include release control modulated by different morphologies and compositions, exudate absorption capacity, and capability to prevent the penetration of bacteria and external microorganisms into the wound bed [23–26].

The electrospinning technique (ES) employs electrostatic forces to promote the elongation and stretching of a viscoelastic solution to form fibers at the nanometer scale [27]. Conventional components for ES setup are a high voltage source, a polymer solution with suitable viscosity, a syringe with a needle, and a grounded collector [28]. In the typical ES process, the polymer solution placed in the syringe flows through the needle at a constant rate, initially forming a polymer drop, as the electrical tension between the tip of the needle and the collector increases, leading to Taylor's cone formation. When the repulsive electrostatic forces on the surface of a droplet overcome surface tension forces, under a threshold value of high voltage, the Taylor's cone is stretched, starting the ES process, followed by evaporation of the solvent used in the solution and the formation of solid nanofibers, which are then collected in the grounded collector. Modifications in the ES process and apparatus have been reported including needleless ES [29], bubble ES [30], centrifugal ES [31], bubble melt ES [32], melt ES, [33] and portable ES [34].

The variables that influence the morphology, size, and homogeneity of the nanofibers are dependent on the properties of the chosen materials (e.g. types of synthetic and natural polymers, solvents, viscosity, conductivity, etc.), as well as processing parameters, such as the distance between the collector, and the ejection site of the polymeric solution, applied voltage, type of collector and diameter of the needle. Environmental parameters, such as temperature and humidity also play an essential role [35, 36].

The versatility of the ES process allows the use of more than 200 polymers, including synthetic and natural polymers [37, 38]. For applications in wound dressings, the most common materials include collagen [24], gelatin [39], chitosan [40], PLA [41], proteins [42], cellulose, [43] and poly(ε-caprolactone) (PCL) [44]. Composite materials have also been used to produce nanofibers applied to wound dressing [45].

11.1.3.2 Morphologies of Nanofibers

The ES process allows the incorporation of bioactive compounds and the modification of the nanofibers' morphology and properties by using (i) pre-modification or (ii) post-modification approaches. In (i), the modification is carried out before the ES step, that is, the bioactive agents are incorporated into the polymer solution [46]. For instance, Homaeigohar and coworkers [44] first developed a wound dressing using green ES to produce PCL nanofibers with bovine serum albumin (BSA). The protein was added to the polymeric solution before the ES process [44].

On the other hand, in ii) the modification is carried out after the ES process, where the compounds are added after the formation of nanofibers through different surface modification processes [47]. For example [48], quercetin-copper (Qu-Cu) chelates

and cuprorivaite (Cup), a highly bioactive bio-ceramic, have been incorporated into a PCL/gelatin solution for ESNF production. The nonwoven showed that the release of Qu, Cup and Cu acted in the regeneration of burned skin, hair follicle related cells, and antibacterial action against *S aureus* [48]. The layer-by-layer self-assembly technique coated the PCL/SF nanofibers with positively charged quaternized chitin and negatively charged SF. In another example, Hu and collaborators [49] used PCL and silk fibroin (SF) to design a multifunctional wound dressing and a hierarchical structure of electrospun nanofibers with antimicrobial activity against *E. coli* and *S. aureus*. The PLC/SF nanofibers were coated with positively charged quaternized chitin and negatively charged SF by layer-by-layer self-assembly technique. In vivo animal evaluation showed vascular reconstruction with hair follicle growth of 22 $\pm$ 4 mm^{-2}, comparable to normal tissue (27 $\pm$ 2 mm^{-2}) [49]. It is important to mention that in some cases, both pre-modification and post-modification approaches can be employed to render ESNF with optimized properties. In this direction, Ballesteros et al. [50] developed ESNF based on PCL ESNF containing silver nanoparticles (AgNP) in their bulk (by pre-modification approach) while their surface was further decorated (by post-modification approach) with photo-responsive nanogels containing AgNP.

The distinct morphologies presented by ESNF include core–shell [51], hollow [52], Janus [53], asymmetric dressings [1, 54], porous structure [55] and sponge [56] enable different performances as a wound dressing. For example, asymmetric dressings [1, 57] are composed of two or more layers and have great potential for wound healing by mimicking the dermis and epidermis layers and avoid the invasion of external microorganisms to the wound site. In another example, Khan and coworkers [58] reported core–shell multifunctional composite nanofibers with oregano essential oil and hyaluronic acid (HA) in the core and zinc oxide nanoparticles (ZnO) were blended with poly (*l*-lactide-co-caprolactone) in the shell layer. The ESNF produced showed strong antibacterial action, angiogenic potential, anti-inflammatory action, and complete healing of wounds with good vascularization and organized collagen fibers [58].

11.2 Characterization of ESNF for Wound Dressings

The performance of ESNF for wound dressings are highly dependent on diverse aspects including (i) morphological characteristics, (ii) porosity and surface area, (iii) fluid handling capacity, (iv) oxygen permeation, (v) mechanical properties, (vi) antimicrobial activity, as well as (vii) in vitro and in vivo cytotoxicity studies [59–61]. In the following subsections we present the main characteristics of ESNF for wound dressing applications.

11.2.1 Morphology, Porosity and Surface Area

ESNF morphology may influence the adhesion, spreading, and proliferation of cells related to the healing process [62, 63]. The surface morphology of these materials is usually characterized using scanning electron microscopy (SEM) and atomic force microscopy (AFM). At the same time, the internal structure of fibers can be assessed through transmission electron microscopy (TEM) and, in some cases, by fluorescence microscopy [51, 64, 65]. The inherent high porosity and surface area to volume ratio exhibited by ESNF matrices are beneficial for exuding fluid from the wound, transporting nutrients to cell and gas permeation [59]. Porosity measurements of electrospun nonwovens pose significant challenges and several methods such as water flux permeability [66] and liquid displacement [67] methods have been proposed to estimate the porosity. The surface area measurement and porosity of ESNF nonwovens can be performed by the Brunauer–Emmett–Teller (BET) gas adsorption method [68].

11.2.2 Fluid Handling Capacity and Oxygen Permeation

The fluid handling capacity allows estimating the ability of nonwoven on the control of moisture balance at the wound surface [60]. The fluid handling capacity is mainly assessed through three principal tests: (i) swelling capacity, (ii) surface hydrophilicity, and (ii) water vapor transmission rate. The swelling capacity is generally evaluated via gravimetric method and provides information about the ability of electrospun materials to absorb excessive exudates from the wound beds [67]. This property is highly related to other characteristics of the wound dressing material such as composition, pore size, and porosity [69]. The surface hydrophilicity character of ESNF is related to many interfacial processes such as absorption and wetting of aqueous fluids, and is intrinsically affected by nanofibers morphology, and composition, being evaluated through contact angle measurements [70, 71].

The ability of wound dressings to control the water loss from the wound to the atmosphere is evaluated by determining their water vapor transmission rate (WVTR) [72]. A wound dressing with a suitable WVTR is required to avoid excessive dehydration or exudate accumulation, where high WVTR values may result in dehydration and a low WVTR may lead to the accumulation of wound exudates [59]. The WVTR is mainly affected by the pore size, porosity, hydrophilicity, and thickness of ESNF, being commonly evaluated by the method E96/E96 M—16 proposed by the American Society for Testing and Materials (ASTM) [73].

The high porosity and surface area to volume ratio exhibited by ESNF nonwoven favor the oxygen permeation, which is beneficial for the wound healing process, since O_2 is an essential nutrient for cell metabolism [59]. To date, there is no standard test to measure the permeability of oxygen across the ESNF and a gas permeability analyzer is commonly used to evaluate this property [74].

11.2.3 Mechanical Properties

ESNF nonwoven should exhibit mechanical characteristics that facilitate handling during application at the wound site and also along the healing period [59]. Overall, the mechanical properties of ESNF are commonly assessed through uniaxial tensile tests, according to adaptations of the D882-18 standard test method proposed by ASTM (2002) [75]. The tensile properties of these materials are strongly influenced by the composition, diameter and degree of orientation of the fibers as well as by the wound dressing thickness [62, 76]. The mechanical properties are typically assessed in terms of Young modulus (or elasticity modulus), which expresses the tension applied to elastically deform a material by a set amount of elongation, relative to the original length. The calculation of the tension is based on the force applied by the measuring instrument, divided by the transversal section area of the material. Other important parameters are the tension at break or failure, the maximum amount of tension the material can receive before breaking or tearing apart, and the maximum elongation. Wound dressing materials typically present low Young modulus and tension at break, while the maximum elongation is high. These properties can be fine-tuned to better suit the needs with the usage of different polymers, different treatments, or the usage of additives or composite structures.

11.2.4 Chemical Composition

From the available techniques used to analyze the chemical composition of materials, the Fourier Transformed Infra-Red spectroscopy (FTIR) stands out. The technique allows a fast, cheap, and non-destructive analysis of the covalent chemical bonds the material, based on the different absorption of the infra-red spectrum wavelengths [77, 78]. Comparing the observed peaks in absorption with pre-established values, it is possible to infer what covalent bonds are present, and thus determine if the spinning process itself caused any alteration in the original material, or if the different molecules used are interacting with each other, creating or breaking bonds. Changes in the typical covalent bonds could mean a molecule of interest is strongly linked to the fiber material, or that a degradation process occurred, or even if there are impurities in the material [78].

11.2.5 Biological Characterizations

Micro- and nanofibrous materials are promising for wound dressing applications due to their physical similarity with ECM [79, 80]. In general, ESNF with a less compact structure [81], composed by fibers with rough surface, [82] and presenting moderate hydrophilicity (between 45 and 90° of water contact angle) [83] show better

cell adhesion. Hydrophobic materials would thus difficult the adhesion of microorganisms. Larger fiber diameters are also linked to fewer incidences of inflammatory responses [84]. Natural polymers or polymers derived from biomolecules are inherently biodegradable [79], which means that they are more readily degraded by biological entities, such as microorganisms present in the natural environment and more complex living beings. Natural polymers also present better biocompatibility [79]. They also less often trigger inflammatory responses and are also more prone to be bio-resorbed (or metabolized) by the host organism [85].

11.2.5.1 Biocompatibility Analyses

The biocompatibility of ESNF as wound dressings may be assessed through a great variety of experiments and analyses. ISO 10993-5 [86] lists in vitro tests to determine cytotoxic activity in mammalian cells, which must be chosen according to the desired application. All the tests must be conducted under aseptic conditions and with control of the material sterility.

Tests can be conducted using extract, direct contact, or indirect contact analyses [87]. For the usage of extracts, the conditions used, such as extracting vehicle composition, time of extraction, and temperature must match the desired application, avoiding significant alteration on the material, unless it is intended during the proper usage. The extract concentration may be varied through dilutions for better assessing the cytotoxic effects [87]. For the direct contact tests, it is advised that the solid test sample presents at least one flat surface, and samples that are adsorbent should be soaked with culture medium prior to testing [87]. Indirect contact tests are conducted with the usage of a diffusion medium, such as agar or other filtering medium, according to the leachate's ability to diffuse through the selected medium without altering itself or the chemical composition of the medium [87].

The determination of the impact on cell viability can be evaluated through the morphological analysis of cells with measurement of cell damage, measurement of cell growth, or measurements on specific aspects of the metabolism, in qualitative or quantitative terms. Cytotoxicity may be manifested as poor cellular adhesion (round shape), abnormal morphology, and metabolism and/or cellular lysis [87]. Cell lines of keratinocytes and fibroblasts are typically tested for wound dressings since they compose the cell population of skin layers [61]. Tests with immune system cells, such as leukocytes, could provide additional information on biocompatibility and inflammatory responses. ISO 10993-4 [88], which presents tests specifically for interaction with blood, could also be followed for assessing effects on blood cells lysis and blood clotting, which may be crucial for the usage of wound dressings.

It is relevant highlight that, although these in vitro tests provide preliminary data about the safety of the material, they do not provide definitive responses for the biological behavior. Simple cell cultures demonstrate whether the cells are affected or not by the exposure in an individual basis. The effect of fewer damages on cell function, although allowing it to thrive, might result in functional or structural losses when analyzed at tissue or organ levels of structural organization. It is fundamental

thus to assess the impact of the material on more complex structures. Organs-on-a-chip and bodies-on-a-chip templates may provide great models for toxicity analyses and bring less ethical concerns. However, the complexity and costs of producing these platforms render them unavailable for many research centers [89]. Then, the wound dressing must be tested in vivo for better assessment of therapeutic and toxic properties.

11.2.5.2 Antimicrobial Activity

The antimicrobial analysis is conducted similarly to the cytotoxicity tests, replacing the animal or human cells with microorganisms of interest, but with a small adjustment. Instead of analyzing the microbial cells growth and evaluating how the presence of the material stimulates or impairs the further development of the culture, the material is present since the beginning of the inoculation and the effects on growth inhibition, either by making the cells static, or effectively promoting their death, is investigated. For wound dressings, tested microorganisms are related to healthcare-associated infections (HAIs) [90]. Usually, *Staphylococcus aureus* and *Enterococcus* sp. are models for gram-positive bacteria; *Salmonella* sp., *Escherichia coli* and *Pseudomonas aeruginosa* are models for the gram-negative group; *Candida albicans* often represents fungal pathogens. Besides providing a physical barrier to microbial penetration [91], nanofibrous wound dressings do not possess intrinsic antimicrobial activity. Therefore, the usage of specific polymers or additives promotes the protective effect.

11.2.5.3 Degradation Analysis

Degradation can be defined as the loss of chemical or physical structure by any means, while biodegradation implies the participation of enzymes in a defined degradation route. There is proof of biological molecules being involved in the process [85]. Materials with adequate hydrophilicity not only enhance cell adhesion, but are also better suited for the action of enzymes [92]. Degradation rates could be determined by observing how the material loses weight or has its properties changed over time. Simulating the chemical environment of the wounded injuries is advised for a good estimation of the degradation behavior. However, the complexity of the whole metabolism is hardly represented by this simplified system. Therefore, in vivo tests are still crucial for the determination of the biological activity of the material. For the material itself, drugs loaded in it, or by the compounds resulted from the degradation of them, wound dressings desirably must not trigger inflammatory responses or in any other way negatively affect the healing process [93]. Significant losses on material integrity must be considered for determining removal and reapplication, although biopolymers could be used for absorbable wound dressings. For drug-loaded materials, the analysis of the release profile must be considered so the concentration is at the same time simultaneously antimicrobial and non-cytotoxic.

11.3 Applications of ESNF Wound Dressings

This section provides an organization of a wide range of ESNF formulations for application as wound dressings, essentially when combined with nanostructured materials in their polymer composition. They can be classified as natural polymers, synthetic polymers, polymer blends (synthetic/synthetic, synthetic/natural, natural/natural), or composite nanofibers, when combined with nanostructured materials. The following topics aim to help readers understand the types and properties of nanofibers formulations, exemplifying their uses and facilitating the search and reading.

11.3.1 Synthetic Polymers Applied to ESNF Wound Dressing Design

Synthetic polymers are fabricated through chemical reactions between monomers, yielding versatile macromolecules with outstanding properties for varied applications, including in modern medicine [94, 95]. The possibility of controlling physicochemical properties, including the absence or at least low level of impurities, good mechanical and chemical properties make them suitable to be processed by ES, and for wound dressing applications [95, 96], as depicted in the examples of Table 11.1. The current research strategies for wound dressings that employ synthetic polymers for wound dressings are developing with biocompatible synthetic polymers under the approval by government agencies, for example, Food and Drug Administration Agency (FDA).

Poly(lactic-co-glycolic acid) (PLGA) is a synthetic polymer that undergoes a thermal shrinkage near human body temperature (37 °C). This shrinkage behavior of PLGA allowed it to be explored as a tape to induce fibroblast growth in loose

Table 11.1 ESNF based on synthetic polymers and application as multifunctional wound dressing

Composition		Main finds	References
Pristine	PLA	Biodegradable, biocompatible and potential keratinocyte growth	[97]
	PS[a]	Non-biodegradableand potential keratinocyte growth	[97]
	PVP[b]	Non-biodegradable, water soluble and potential keratinocyte growth	[97]
	PLGA[c]	Biocompatible, poor hydrophilicity and potential fibroblast growth	[98]
	PVDF[d]	Poor hydrophilicity and comparison of aligned/random fibers for human-induced pluripotent stem cells growth	[99]
	PCL	Poor hydrophilicity, biocompatible, bioabsorbable and poor human skin foreskin fibroblast growth	[100]

[a] polystyrene, [b] poly(vinylpyrrolidone), [c] poly(lactic-co-glycolic acid), [d] poly vinilidene fluoride

soft tissue (LST) [101]. Firstly, the authors studied the contractability of a sample of PLGA fibrous tape—with a size of 4 cm × 4 cm—immersing in phosphate buffer and observed that PLGA tape shrank after five days to 2 cm × 2.1 cm approximately, changing their morphology from straight fibers to high crimped fiber. For comparison, poly(L-lactide)acid (PLLA) shrinkage was smaller than PLGA shrinkage and human vaginal fibroblasts (HVF) cultured over PLGA yielded a higher aspect ratio and propagation area than those cultured in PLLA, which was attributed to the dynamic shrinkage behavior of the PLGA polymer [101].

In another work, Castellano et al. reported the fabrication of two synthetic polymers nanofibers, PCL and PHB (Polyhydroxy butyrate-co-valerate). They compared them in terms of fibroblasts and keratinocytes growths. The PCL fibers presented lower fibroblast and keratinocyte proliferation than PHB fibers. The authors conclude that PHB nanofibers present promising vasculogenic behavior and cell adhesion [102]. In another work, the stratification of proteins from epidermal region growth over poly(ethylene terephthalate) (PET), poly(1,4-butylene terephthalate) (PBT) and poly(N,N′-hexametyleneadipinediamide) (N6/6) synthetic polymers ESNF was evaluated. The results from epidermal growth demonstrated that N6/6 ESNF prevented fibroblast growth, possible due to the small pore size of nonwovens associated with the fiber diameter (0.13 μm). On the other hand, the fiber diameters of PET (1.9 μm) and PBT (1.7 μm) nanofibers improved the fibroblast permeability, facilitating adhesion and proliferation. From this observation, the authors proposed that N6/6 ESNF with a small pore size mimicking human skin tissues can be used as a model for corrosion and irritation tests [103].

Antimicrobial synthetic polymers comprise another class of polymers suitable for wound dressings. They can be synthesized via functional group modifications during the polymer reaction synthesis, allowing the production of zwitterionic polymers. For example, the monomers of methyl methacrylate (MMA) (47 mmol) and carboxybetaine (4.7 mmol) reacted to produce a zwitterionic copolymer named poly(carboxybetaine-co-methyl methacrylate) (CBMA). After fabrication of CBMA ESNF, the authors demonstrated that cell proliferation assay was lower in CBMA than in pristine PMMA ESNF or the control sample. Moreover, this result indicates that zwitterionic nonwovens are less adherent to the wound than pristine neutral PMMA. The bacterial assays showed that the zwitterionic character confers to CBMA fiber antibacterial properties against *S. aureus*/*E. coli*, a property not observable in PMMA fibers [104].

Synthetic electrospun fibers can also improve wound healing performance by loading drugs or other medicinal compounds in their composition. Such strategy is suitable releasing medicinal compounds from wound dressings to accelerate wound injury recovery [105]. As the morphology of synthetic/natural nanofibers mimics ECM very well, novel functionalities and drugs to tailor their surface/bulk can be used to enhance the wound dressing final properties. As mentioned before, one pristine synthetic polymer that composes the ESNW can be modified by pre- or post-modifications to obtain a novel composite membranes, especially by encapsulating organic/inorganic substances, combining different polymers in blends, or combining membranes into unique devices.

Injuries in the wound of diabetic patients can result in sepsis, or in some extreme cases into foot ulcers. These are examples of the lack of appropriate therapies to treat this disease. In this context, Zehra and coworkers [106] synthesized PCL ESNF containing sodium percarbonate (SPC) salt at a loading capacity of 2% v/v^{-1} to be applied in chronic diabetic wounds induced in rats. The SPC-PCL ESNF improved local oxygen release accompanied by an increase in pH from 7.3 to ≈ 7.55, which can play a vital role in the recovery of chronic diabetic wounds. Additionally, SPC-PCL ESNF promoted the local angiogenic process and blood vessel formation better than PCL. The histological study and gene expression analysis confirmed that PCL-SPC ESNF enhanced the dermis and epidermis recovery, which were mainly associated with HIF-1α protein expression [106]. In the context of the dermatology viewpoint, the anti-scar property of wound dressings is another advantage presented by ESNF. For example, Guo and coworkers studied the wound recovery in a second-degree burn promoted by PCL/ALA (α-lactalbumin) nanofiber dressings, compared with commercial microfiber dressing Sorbalgon® and demonstrated that the anti-scar performance of PLA/ALA nanofibers is similar to commercial dressing [107].

Diverse nanofiber composites have been successfully prepared with the modification of sub-micrometer fibers with nanoparticles (NPs) including TiO_2 [108], CuNPs [109], AgNPs [110], ZnO [111], TeNPs [112], CQDs/SiNPs [113], sulfadiazine silver [114], CeO_2 [115], silver-MOF [116] conferring the ESNF antimicrobial activity properties. The adaptability of ES solution parameters allows the combination of NPs with antibacterial agents, enhancing electrospun antimicrobial performance [117–119]. In another strategy, Sun et al. proposed a novel approach to inorganic Upconvertion NPs (UCNPs), by preparing core–shell nanoparticles NaYF4:Er/Yb/Gd recovered by SiO_2 (S) and Methylene Blue (M) [120]. After the PVDF ESNF fabrication, they induced antibacterial properties in UCNPs/SM-PVDF upon excitation at 980 nm. Without NIR light, no S. aureus/E. coli mortality was perceived, while when NIR light was employed, remarkable antibacterial properties were observed [120].

Core–shell electrospun nano- and microfibers rely on spinning polymer solutions through coaxial configuration. The fiber morphology obtained by this approach opens a variety of opportunities to combine polymers into a single fiber and also prevent undesirable burst release in drug release systems [121–123]. Bi- and three-layered fibrous non-wovens compass another strategy for the developing of 3D wound dressing [124]. The design of these multilayered dressings allows the outer/top layer to protect the inner/bottom layer from environmental exposure, and contributes to enhancing mechanical performance [125–127].

Decellularized cells are cells in which the cellular and nuclear materials are removed from ECM without damage to the three-dimensional scaffold structure of ECM and to the vascular network, which provide a microenvironment for tissue regeneration, and minimize rejection risks [128]. Nanofibers from synthetic polymers loaded with these regenerative cells are another outstanding innovative possibility of ES for the fabrication of wound dressings [129, 130]. In this context, decellularized human amniotic membranes (HAM) were encapsulated in nanofibrous matrices [131]. The authors demonstrated that when HAM were embedded into

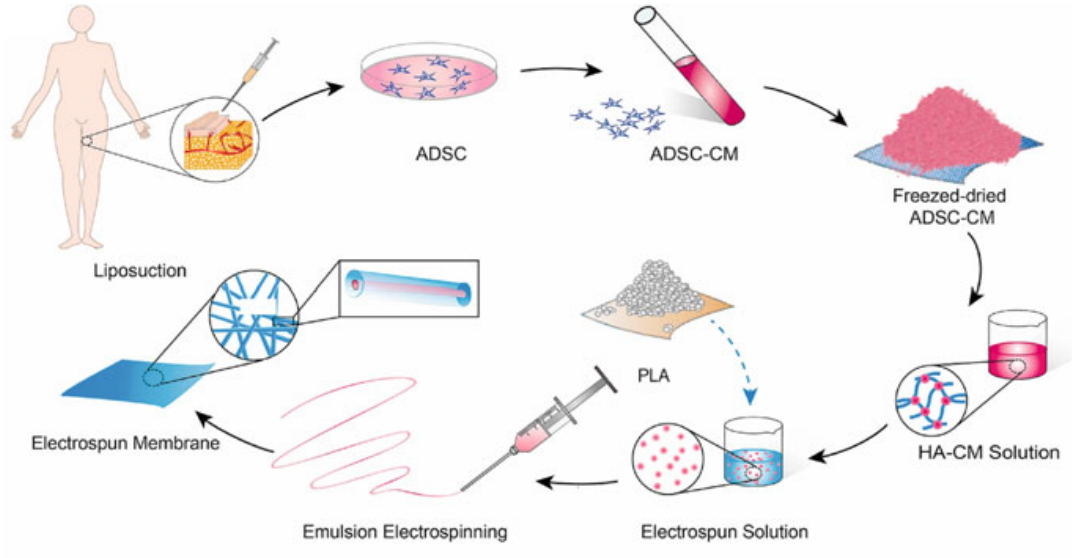

Fig. 11.3 Schematic representation of fabrication of micro-nano PLA fiber (MPF) with Adipose-derived stem cell (ADSC) Conditioned Medium (CM). Adapted with permission from [132]. Copyright 2020 Elsevier

PLGA aligned electrospun sub-micrometer fibers, skeletal muscle growth orientation was improved [131]. In another work, Adipose-derived stem cells conditioned medium (ADSC-CM) were successfully extracted from adipose tissue, freeze-dried and loaded into micro-nano PLA fibers (MPF) matrix to fabricate a regenerative wound therapy material, as outlined in Fig. 11.3 (B). In this case, electrospun emulsion fabrication leads to a core distribution of cells in the interior of the PLA fibers, which contributes to shielding the cell against external ambient conditions, affecting the kinetics release. In vitro studies indicated that MPF@CM decreased the expression of scar-related protein and the relative scar area after fifteen days [132].

11.3.2 Natural Polymers Applied to ESNF Wound Dressing Design

Natural polymers have been employed to design advanced wound dressings, offering a broad spectrum of groundbreaking solutions [133, 134]. The most advantageous properties is biocompatibility, since natural polymers' chemical structures are normally based on carbohydrates and proteins, which show great similarity to the native ECM [59]. Other advantageous properties include cell affinity, low antigenicity, and favorable bioactivity, which stimulate cell attachment, re-epithelialization, and healing effect, as well as antibacterial effect in some cases. Recent studies on the use of natural polymers for wound dressings are summarized in Table 11.2.

Table 11.2 ESNF based on natural polymers and application as multifunctional wound dressing

Composition		Main finds	References
Pristine	β-Chitin	The use of pristine β-chitin nanofibers allowed epithelial regenerating faster than control groups, higher percentage of collagen deposition at 3rd day	[135]
	Collagen	Electrospun of neat collagen extracted from tilapia skin allowed differentiation of human keratinocytes stimulated by collagen amino acids, and complete healing after 14 days, faster than the control group	[136]
	Zein	Bilayered dressing based on casting film layer and electrospun fiber layer. Synergistic effect of the different morphologies, in which the fiber layer ensured a high surface area for cell proliferation and the film layer protected the wound. Antibiotic effect given by sustained release of gentamicin	[137]
	Gelatin	Electrospun of neat gelatin enabled the release of vitamins A and E, proliferation of fibroblasts in presence of vitamin A, stimulated secretion of collagen in presence of both vitamins, and yield significant decrease of wound area after 14 days, with complete regeneration before control groups	[138]
	CA[a]	Controlled release of benzocaine at pH 9.0, which would correspond clinically to the pH of an infected wound. The loading of dye bromocresol green led to fast color changes according to the wound pH, as an easy-to-interpret indicator of the healing process	[139]
Multicomponent	Collagen/Elastin/PCL	Increased elasticity, while stiffness decreased due to presence of elastin. Keratinocyte and fibroblast proliferation, tissue integration and accelerated early-stage angiogenesis	[140]
	PU[b]/Keratin/AgNP	Significant level of fibroblasts differentiation, cell attachment and cytocompatibility in the presence of keratin. Antibacterial activity exerted by AgNP	[141]
	Chitosan/PVA[c]/ZnO	The presence of ZnO implied in antibacterial and antioxidant activity, which factors contributed to accelerate the healing of diabetic wounds	[142]

(continued)

Table 11.2 (continued)

Composition		Main finds	References
	SF/PCL e SF/HA	Mimetic asymmetric two-layered dressing, where the top one protects against bacteria and the bottom one releases antibacterial natural agent and enables fibroblasts growing and proliferation	[143]

[a] cellulose acetate; [b] polyurethane; [c] poly(vinyl alcohol)

Biomimetic ESNF constituted of collagen extracted from tilapia skin has enabled accelerated wound healing. Collagen comprises a protein of animal connective tissues found in bovine and porcine. Recently, fish collagen has been investigated for applications in skin wound healing, due to its immune-modulatory and anti-inflammatory activities. Besides, this material has also displayed antimicrobial effects, due the presence of collagencin, an antimicrobial peptide identified from fish collagen hydrolysate [144, 145]. For instance, Zhou and coworkers [136] employed collagen extracted from tilapia skin to produce ESNF and later crosslinked with glutaraldehyde vapor. Smooth surface nanofibers were obtained and due to the crosslinking, the ESNF presented good mechanical properties, hydrophilicity and swelling ratio of approximately fourfold than it dry weight owing to the presence of hydroxyl, carboxyl, and amino groups in collagen composition. The biomimicking of tilapia collagen nanofibers to the ECM was demonstrated by the firm attachment, and equal distribution of human keratinocytes along with the nanofiber network, as observable in Fig. 11.4 (A1), which was attributed to synergetic effects of collagen amino acids on stimulating the differentiation of human keratinocytes. The improved wound healing rate was verified comparing to the control groups, combined with a significantly lower inflammatory response. At the end of experiments, the epidermal cells were found fully differentiated, basal cells were closely arranged, the horny layer (the outermost layer of the epidermis) could be observed, and layers of keratinocytes were evident [Fig. 11.4 (A2)].

Polysaccharides represent a class of natural polymers that have received significant attention for the development of novel materials. Chitin and chitosan are structural carbohydrates obtained from the exoskeleton of various crustaceans and arthropods, such as crabs and shrimps [135, 146]. Jung et al. [135] developed a electrospun dressing constituted of β-chitin extracted from cuttlefish bone. Although the ES of the neat chitin only resulted in nanosized beads, as verified in Fig. 11.4 (B1), the blending with small concentrations of PEO allowed fiber formation (ratios of 2.0:0.1 to 2.0:1.0). PEO is commonly added to ES polymer solution to adjust its viscosity, and improve their electrospinnability. In this work, PEO was soaked in water and removed afterwards, which led to decreased nanofiber diameter and increased porosity, providing enhanced hydrophilicity and higher contact angle. The resultant β-chitin ESNF are shown in Fig. 11.4 (B2).The biocompatibility and wound

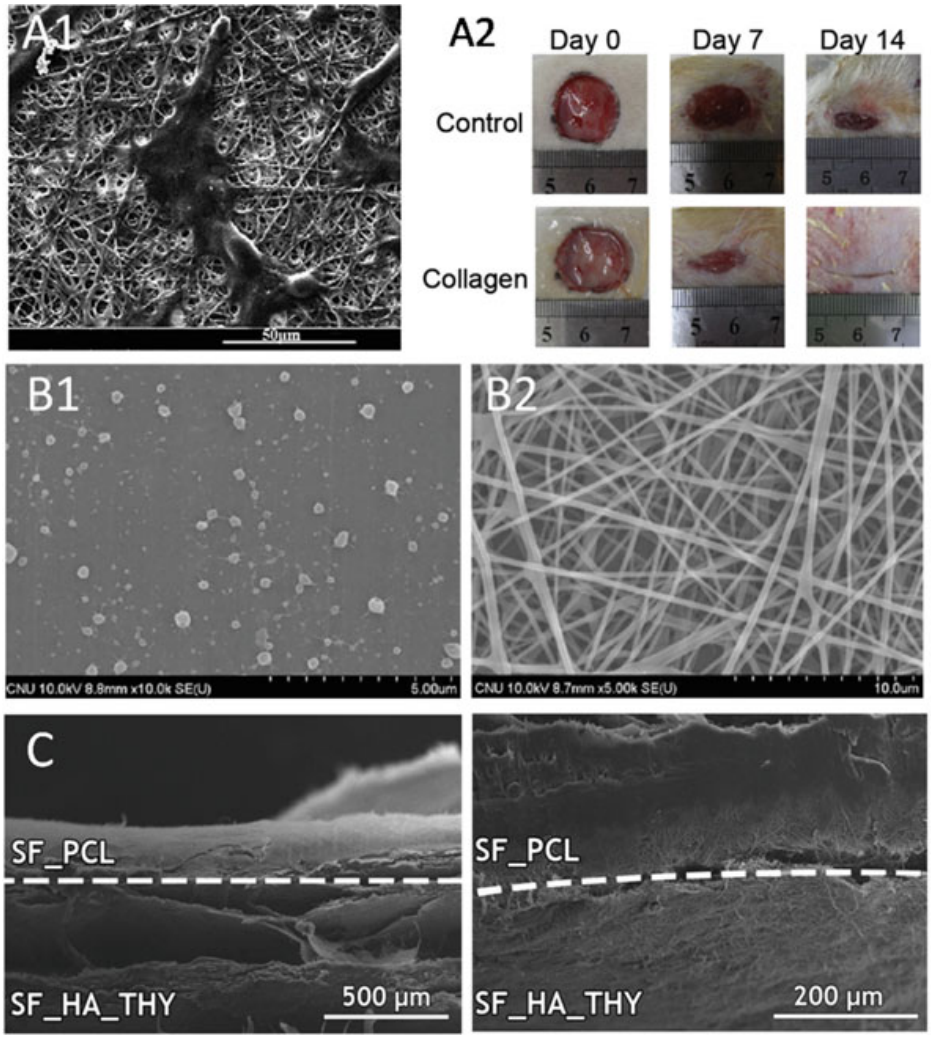

Fig. 11.4 (A1) human keratinocytes firmly attached and equally distributed along biomimetic ESNF constituted of collagen extracted from tilapia skin. (A2) Improved wound healing rate of biomimetic electrospun nanofibers in contrast to the control groups, combined with a significantly lower inflammatory response. Adapted with permission of [136. Copyright 2016 Elsevier. b ESNF constituted by β-chitin extracted from cuttlefish bone: (B1) neat chitin only resulted in nanosized beads, while in (B2) the blending with small concentrations of PEO followed by its removal, allowed the formation of porous and small diameter ESNF. Adapted with permission of [135]. Copyright 2018 Elsevier. **c** SEM image of zein asymmetric membrane designed as two layers aiming to mimic epidermis and dermis. Adapted with permission from [143]. Copyright 2018 Wiley

healing effects were evaluated by in vitro tests, showing enhanced collagen deposition and wound recovery when compared with control samples.

Cellulose acetate (CA), another polysaccharide widely applied in ES, was used as a dual nanocarrier system, namely (i) benzocaine, aiming the controlled delivery of anesthetic for local pain reduction, and (ii) dye bromocresol green, to detect different stages of wound healing by mean of wound pH variation [139]. The loading of dye bromocresol green led to fast color changes according to the wound pH, as an easy-to-interpret indicator of the healing process. The color change from green to yellow

indicates that the wound healing course follows as expected and the pH is decreases (since the pH of a healthy skin is slightly acidic). In contrast, while the color change to blue indicates the media alkalinization, suggesting bacterial infection and tissue inflammation, for example. Moreover, in vitro release test showed that the system behaved as pH-dependent benzocaine release and therefore controllable.

The number of recent research papers using ESNF based on neat natural polymers as a multifunctional wound dressing is lower when compared to ESNF based on blends and nanocomposites involving this class of polymers. An often challenge comprises the fabrication step, since in many cases, attaining flexible, smooth and uniform ESNF mat is limited by factors such as poor solubility in the solvents used in ES, degradation towards specific solvents, very high molecular weight, and therefore very high viscosity [59]. Innovative combinations of synthetic and biopolymers showed ability to overcome the issues related to both classes of polymers. For instance, the inclusion of collagen and elastin in PCL nanofiber formulation increases flexibility and elasticity [140], while the use of keratin extracted from human hair combined with PCL and AgNP enhances cell affinity and proliferation [141]. Some compounds can also add extra functions in dressings. The recent literature shows the practical application of antibacterial effect aside from of AgNP [141], ZnO [142], but also by incorporation of bacteriophages [147]. Controlled release of conventional therapeutical compounds can also be performed, such as tetracycline [148], erythromycin [149], nitrofurazone [150], gentamicin [137], *aloe vera* [151], grape seed extract [152], vitamins [138], among many others.

The combination of structures and materials has enabled the fabrication of asymmetric wound dressings, which are designed as two layers aiming to mimic both skin layers: epidermis and dermis. By exploring the silk fibroin (SF), Miguel and coworkers [143] produced an asymmetric wound dressing using ESNF of SF combined with other elements in both layers. As demonstrated by SEM image of Fig. 11.4c, a blend of PCL and SF was employed as top layer to reproduce the epidermis dense nature and waterproof ability. In contrast, the bottom layer was constituted of SF ESNF blended with hyaluronic acid. Moreover, the bottom layer was loaded with thymol (Thy), an herbal drug with antimicrobial effects.

The resultant ESNF presented excellent mechanical properties, whose data were similar to those displayed by the native skin [153], higher porosity in the bottom layer, superior swelling profile at alkaline pH, and cell adhesion, proliferation and spreading. SEM analysis demonstrated that bacteria were found only at upper side of the top layer, confirming that a denser structure protects the wound from bacteria colonization. Moreover, the thymol loaded in bottom layers increased inhibitory effect, demonstrating a 2–3 times larger inhibitory halo area and no biofim formation, unlike to ESNF without this compound.

Integrating (bio)sensor devices to wound dressings constitute an outstanding trend for smart wound dressings. As Kurecic et al. work [139], many recent investigations explores the possibility to monitor wounds and the healing process [154, 155]. Pakolpakçil et al. [155] described that ESNF based on sodium alginate and PVA containing anthocyanins extracted from black carrots undergo color changes under different pH environments. The selection of alginate and PVA nanofibers allowed

achieving a hydrophilic mat, which was fundamental for exudates absorption and for promoting the color change. Thereafter, they developed a similar halochromic system, just changing the anthocyanins extract, now from purple cabbage [154]. The color scheme for the ESNF containing cabbage anthocyanins ranged between purple and blue shades, clearly distinguishable by the naked eye and also measured by UV–Vis. The in vivo performance was tested, and in Fig. 11.4c is possible to observe the color changes of this system in contact with the wound in different stages.

11.4 Conclusions

Acute and chronic skin injuries affect many people worldwide and can be a serious source of diseases and infections. Therefore, novel treatments and innovative solutions concerning functional wound dressings are required to tackle this problem. This chapter presented some representative results related to advanced multifunctional electrospun nanofibers applied in wound dressings for skin healing. Such systems are highly suitable for this application because they can accelerate the healing process by protecting the wound, increasing fluid draining and tissue regeneration, besides helping in the moisture regulation. Additionally, appropriately modifying the bulk or the surface of wound dressings can render antibacterial properties and drug delivery capacity. It is important to say, though, that evaluating the safety and biocompatibility of such multifunctional dressings are also fundamental and considerable progress must be achieved in this direction to warrant biocompatibility and non-toxicity. Due to the similarity in composition with human tissue, natural polymers such as collagen, keratin, silk fibroin, chitosan and cellulose stand in performance regarding cell affinity, low antigenicity, cell attachment, and re-epithelialization. However, some synthetic polymer can also be tailored for this end. In summary, multifunctional advanced electrospun nanofibers applied in wound dressings have become a clear trend in the skin healing process, which products shall become more popularized and produced at a larger scale in following years.

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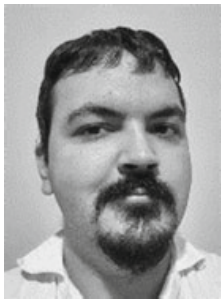

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