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Chapter

Frontier Electrospun Fibers for Nanomedical Applications

Emilija Zdraveva and Budimir Mijovic

Abstract

Nanofibers fabrication nowadays has become unimaginable without mentioning or research involving the technique of electrospinning. Due to the vast possibilities that this technique offers in regard to nanofibers morphology, nanofibrous architecture, and application perspective, it has become the main interest of many scientists with various expertise profiles. Electrospun nanofibers are advantageous over conventional fibers due to their lightweight, high surface-to-volume ratio, adjustable fiber diameter/morphology, and well-controlled functionality. This chapter will highlight the possibilities of nanofibers’ functionalization toward nanomedical applications including, drug delivery, wound healing systems, and tissue engineering scaffolds with a focus on bone and nerve tissue repair. The latest studies (from 2017 onwards) are discussed in terms of materials’ composition, fabrication technologies, and significant performance of cultured cells in vitro and most importantly regenerated tissue after implantation in vivo.

Keywords: electrospinning, nanofibers, drug delivery, wound healing, scaffolds

1. Introduction

The principle of the electrospinning process is based on the physical phenomenon that describes the cone stretching of a water droplet when charged amber is held above it. Similarly, an electrostatic force stretches a polymer solution or melt, to form the popular Taylor cone while generating nano-scaled fibers with the aid of a pump and a high voltage power supply. As produced nanofibers have advantageous properties over conventional ones including, small diameter (few nm to 1 μm), high surface-to-volume ratio, light weight structures with interconnected pores, high porosity, and ease of controlled functionality. Their uniqueness makes them perfect candidates for the application in nanomedicine. This review will focus on the most reported nanomedical application areas such as tissue engineering, thus the development of scaffolds for both hard (bones) and soft tissues (cartilage, skin, tendons and ligaments, blood vessels, muscles, and nerves), drug delivery, and wound healing. Special attention will be given to the latest frontiers in functional nanofibers, facing challenges and future aspects.

Apart from mimicking the extracellular matrix (ECM) in native tissues, electrospun nanofibrous materials can meet the requirements in scaffold development that is, biodegradability and biocompatibility, adjustable porosity and mechanical
integrity, as well as sufficient delivery of oxygen and nutrients through permeability. Functionalization of these structures by means of medical/biological species incorporation or surface modification provides them to act as delivery systems for fast, sustained, or tunable drug release. Further, in wound healing the electrospun dressing due to its porous structure allows both breathability and waterproofness. Finally, the promotion of rapid wound healing is achieved by specific cell type culture while supporting cell adhesion, migration, and proliferation.

2. Latest progress in nanofibrous drug delivery systems

A drug delivery system is an engineered formulation or device that can carry a therapeutic agent and deliver it at a specific time, with a controlled release rate and dosage, to a target site in the body. The advantages of a drug delivery system over conventional drug administration routes are improved efficiency or sustained drug concentration over time, reliability or reproducible release rates, low cytotoxicity, no side-effects or repetitive dosing, therapy optimization, elimination of the drug stability issue, and conserved agent activity [1, 2]. These systems are designed to treat cancer, and certain ailments and for tissue regeneration [3]. With emerge of nanotechnology, modern drug delivery systems like electrospun nanofibers have attracted much attention within the scope of smart therapies. Electrospun nanofibers offer suitable polymer utilization, controllable process conditions, and ease of drug release design in a protracted, stimulus-activated, and biphasic manner. In order to fabricate this specific on-demand drug delivery nanofibrous material many variables need to be optimized in terms of composition, process requirements, and possible post-processing treatment [4].

2.1 Drug incorporation technologies

Both medical and biological components (single or multiple) are incorporated into nanofibers by blend electrospinning [5], emulsion electrospinning [6], bi-component (co-axial, side by side) [7], tri-axial electrospinning [8] or post-treatment via surface immobilization [3]. Blend electrospinning combines the same solvent-dissolving components, while heterogeneous systems are spun through emulsion electrospinning. Core-shell fibers can be fabricated by both co-axial or emulsion electrospinning where usually the core contains the drug while the shell is a polymer. The first is made by co-axial nozzles while the latter is spontaneous due to the different polymeric solutions’ inherent surface energies [9]. A special nozzle is designed for side-by-side electrospinning where the resulting fiber contains the polymer matrix and the drug separately. This approach is used when the drug is not soluble in the polymer solvent [10]. Target drug molecules are loaded in the nanofibers through simple physical adsorption, nanoparticle encapsulation, or surface coating via layer-by-layer deposition. Bioactive molecules can also be immobilized on the fibers’ surface through chemical modification by covalent bonding (i.e., carboxyl, amine, and hydroxyl groups) [11].

Blend electrospun chitosan/polyvinyl alcohol (CS/PVA) nanofibers were loaded with ofloxacin to be used as an ocular drug delivery system for a sustained release of up to 96 h. The fabrication process involved multilayered electrospinning to result in a sandwich structure, thus the CS/PVA was covered with a hydrophobic polymer, Eudragit RL100, on top and bottom and further cross-linked by glutaraldehyde [12].
An anticancer agent doxorubicin was successfully incorporated into polyvinyl alcohol/polycaprolactone core-shell nanofibers by coaxial electrospinning. These pH-responsive drug-release fibers were efficient against cervical cancer cell attachment and proliferation [13]. Similarly, core-shell drug-loaded polyvinyl pyrrolidone (PVP)/polyactic acid (PLA) nanofibers were prepared by electrospinning an emulsion through a single nozzle set-up. The drugs loaded were procyanidins, a natural antioxidant, and Apocynum Venetum cellulose nanofibers. The core was the water phase and was prepared by adding the fourth-mentioned hydrophilic drugs into the PVP aqueous solution. These were added into the oil phase (the sheath) containing the PLA/emulsifier solution. The antioxidant efficiency of the drug delivery system was 88.62%, as confirmed by the 2,2-diphenyl-1-picrylhydrazyl assay [14]. A side-by-side setup was used to electrospin the so-called Janus beads-on-a-string fibers comprising polyvinylpyrrolidone K90 on one side and ethyl cellulose on the other side loaded with two model drugs, methylene blue and ketoprofen, respectively. In this complex double drug-loaded system, the bead sides were the insoluble ethyl cellulose and the ketoprofen drug. These nanofibers performed with double drugs controlled-release profiles [15]. Multiple functional molecules with different therapeutic activities can be produced by multiaxial electrospinning. For example, triaxial fibers consisted of a polyvinylpyrrolidone core, a polycaprolactone (PCL) intermediate layer, and an outermost PCL layer as well (the two were dissolved in different solvents). The model molecules used were keyacid blue dye, loaded in the core and keyacid uranine loaded in the sheath layer. In this type of drug delivery vehicles, the intermediate layer serves as the barrier as to prevent leaching from the core [16]. Generally, polymers mostly used in drug delivery systems include natural proteins or polysaccharides like gelatin, collagen, albumin or chitosan, dextran, alginic acid, respectively. Synthetic polymers used include both biodegradable and non-biodegradable ones, that is, polyesters, poly(ortho esters), poly(alkyl cyanoacrylates), acrylic polymers (poly(methyl methacrylate), and poly(hydroxyl ethyl methacrylate)), respectively. Cellulose derivatives including, ethyl cellulose and hydroxypropyl methylcellulose are used as well [17]. A range of natural and synthetic drugs have been reported to be incorporated into electrospun nanofibers such as: antibiotics, antioxidants, antibodies, anticancer drugs, proteins, etc., as well as compounds like growth factors, DNA, and RNA [17, 18].

2.2 Drug release pace mechanisms

Drugs can be released from the electrospun nanofibers immediately, through the so-called burst effect. When immediate action is required the drug is released shortly. Further, the release can be sustained or slow through a certain period of time. This means low drug concentration delivered within several hours, days, or years. Finally, the release can be triggered by external stimuli, which will result in the first two release rates. External stimuli may involve changes in pH, temperature, light, solvent, ionic strength, etc. [19]. In electrospun nanofibers drug release rate can be controlled by polymer type (i.e., hydrophilic, hydrophobic, biodegradable), drug properties (solubility, stability, loading locations), fabrication technology, fibers morphology, and micro-structure [19, 20]. The mechanisms involved in the drug release profiles include diffusion and swelling followed by diffusion, degradation, or erosion (surface or bulk erosion) [19, 21]. An additive is released from a polymer matrix through diffusion, relaxation, or degradation. When diffusion occurs the added component diffuses down due to concentration difference, while in the relaxation state, it moves out from the polymer as a result of the chain relaxation. The diffusion depends on the drug’s...
molecular weight, drug concentration, and solubility, also the diffusion coefficient and diffusion distance. A medium can cause the polymer to dissolve/degrade thus will release the added component. In surface erosion, the polymer surface erodes due to chain scission, while in bulk erosion the whole matrix erodes. In electrospun fibers, drugs are released from the fibers into the pores due to relaxation/degradation mechanisms or both, as well as from the pores via the diffusion mechanism [19, 22, 23]. As forth-mentioned, the fabrication technology will certainly affect the drug release profile thus the delivery system will be designed in compliance with the therapeutic requirements. The immediate burst release effect is achieved with the blend of electrospun fibers, while co-axial fibers will prolong the drug release as usually, the drug is within the fiber’s core. The burst release of the drug is usually in the initial stage and if necessary this can be delayed by the side-by-side electrospinning technique. Emulsion electrospun fibers will also reduce the initial burst release effect. To further slow down the drug release rate several polymer layers/barriers can be added in the co-axial fibers resulting from the multi-axial approach. These fibers can provide a combination of several drugs and both immediate and sustained release and thus will be used for short or long-term therapies.

Unlike covalent bonding in the fiber’s surface chemical modification approach, the physical adsorption results in fast drug release due to weak hydrogen bonds, and electrostatic or hydrophobic interactions [24]. Special vehicles encapsulating the drug can be added into electrospun fibers thus promoting drug-sustained release. Such vehicles include: liposomes, micelles, nanoparticles, nanotubes, nanospheres, microspheres, etc., which provide intracellular drug delivery [25–27]. These hybrid formulations can eliminate the burst release problem, improve drug loading efficiency, and kidney excretion and minimize drug fluctuations [28].

A study described in detail a three-stage long-term drug release profile of electrospun poly(D,L-lactide-co-glycolide) (PLGA) combined with one of the following polymers, poly(ethylene glycol) (PEG), poly(ethylene glycol)-b-poly(D,L-lactide) (PEG-b-PDLLA), polyglycolide (PGA), poly(dioxanone) (PDO), or poly(trimethylene carbonate) (PTMC), as well as ciprofloxacin hydrochloride (CiH) as an antimicrobial agent. Stage I is characterized by a burst release effect due to fiber swelling and the second polymer hydrophilicity. The second stage results in drug release through diffusion into the gel-continuous structure and in this stage the drug is released slowly. Stage III involves remaining drug release due to the polymer’s hydrolytic degradation [29]. Another release mechanism was described for core-sheath polyvinylpyrrolidone-curcumin/poly (3-hydroxybutyric acid-co-3-hydroxyvaleric acid) (PVP-Cur/PHBV) electrospun fibers with the aid to delay the release of poorly water-soluble drugs. In a water-based medium this composite system increased the drug diffusion path between the core and the dissolution medium. More precisely, the water penetrates the PHBV layer first, then reaches the PVP core and returns back through the same diffusion path with a small amount of the core molecules. When the shell is fully penetrated by the water a large amount of the PVP layer along with the drug molecules passes to the release medium [30]. These are examples of drug delivery systems designed for the release of drugs in a perfectly controlled manner.

2.3 Most significant therapeutic performances

This section gives a brief overview of recently reported studies that concern mostly discussed therapies in drug delivery applications of electrospun nanofibers.
As forth-mentioned three groups of therapy areas were recognized, including cancer treatment, tissue repair, and some minor ailments.

As reported by the WHO, cancer is the second leading death worldwide and is the cause of one in six deaths, in 2018. The most common cancer in men and women are lung, prostate, colorectal, stomach and liver, and breast, colorectal, lung, cervical, and thyroid, respectively [31]. Recently, drug delivery systems are found promising in local chemotherapy and thus can provide high therapeutic performance, but also can be used in diagnostics. Table 1 lists some examples of recent research on electrospun fibers for the treatment of hepatoma (liver), colon, breast, prostatic, and pancreatic cancer. Besides blend, emulsion, and co-axial electrospinning the drug delivery, nanofibers were fabricated by consecutive layering. Orthotopic hepatoma [32] and subcutaneous hepatoma [33] were successfully treated by emulsion and blend nanofibers composed of methoxy poly(ethylene glycol)-block-poly(lactide-co-glycolide) (mPEG-b-PLGA)/Dextran/10-Hydroxycamptothecin/Tea polyphenols and Poly(ethylene oxide) (PEO)/Poly(L-lactide) (PLA)/Doxorubicin hydrochloride, respectively. The sequential release and synergistic effect of the two drugs in the first study resulted in tumor inhibition as well as metastasis prevention [32]. In the second study, the authors highlighted the biphasic release profile of the PEO/PLA/Doxorubicin hydrochloride nanofibers which satisfied the demand for suppression of the initial excessive drug release, as to avoid its blood toxic level, as well as the demand to reach constant high drug level over a long period of time [33]. Tri-layered sandwich NFs composed of poly methyl methacrylate/polycaprolactone (PMMA/PCL), PCL/PMMA/6-Mercaptopurine, and PCL/PMMA layers showed high selective index for breast cancer and reduced cancer cells viability by 10% [34]. In another study, human prostatic cancer PC3 cells exhibited 38% alive cells, while breast cancer cells were death by 40–50%, when core-shell PCL or PCL/PVA NFs were used in combination with 5-fluorouracil or/and paclitaxel [35]. Pancreatic cancer treatment was also studied in terms of NFs compositions (PCL with 5-fluorouracil or methotrexate) and processing condition influences on the drugs release profiles [36].

Some of the diseases treated by drug-loaded electrospun NFs reported were malaria, allergies, corneal abrasion, prosthesis, and gastroenteritis infections (Table 1). In the treatment of malaria, electrospun PCL/collagen/Artemisinin (ART) NFs have overcome the limitations of a neat ART, that is, short half-life, poor solubility, limited bioavailability, re-crystallization, and performed with a sustained release in vivo [37]. Soft tissue and bone infections caused by methicillin-resistant Staphylococcus aureus were studied by the local administration of Linezolid blended within electrospun PLGA/PCL. In vivo results in infected (due to tibia fracture) rats showed healing acceleration (cell growth and proliferation) due to drug sustained release over a longer time, minimized side effects, and reduced drug dose by 37-fold [38]. Bletilla striata polysaccharide (BSP) porous wafer was coated by electrospun PCL and loaded with Levofloxacin hydrochloride for the healing of acute infectious gastroenteritis. The system showed minor cytotoxicity to human gastric epithelial cells and high effective clearance of Helicobacter pylori compared to the pure drug [39]. The main problem in the administration of eye drugs is their short lifespan, due to immediate clearance as the eye cannot accommodate additional liquids. Authors developed a new solid in situ gelling system composed of electrospun gellan gum/pullulan NFs that forms gel immediately after contact with the ocular tissue. When compared to commercial eye drops in in vivo porcine corneas study the results showed higher fluorescein (dye model) signal intensity (up to 40%), thus prolonged residence time due to fiber higher viscosity, as well as more homogenous surface distribution due to lens curvature simulation [40].
A similar purpose was demonstrated by core-shell PVP/PLGA NFs encapsulating two types of drugs pirfenidone and moxifloxacin in the inner and outer layers, respectively. The system proved sustained drug release over a period of hours due to the effective entrapment of the same in the two compartments [41]. Besides medications generally in the field of tissue repair drug delivery systems incorporate genetic materials as well as bioactive molecules. Here studies reported on the fabrication of electrospun NFs with the combination of co-axial and layer-by-layer techniques, NFs with incorporated micro and sub/micro vehicles as well as NFs fabricated into

<table>
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<tr>
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<td>mPEG-b-PLGA/Dextran</td>
<td>10-Hydroxycamptothecin / Tea polyphenols</td>
<td>Emulsion-core-shell NFs</td>
<td>Orthotopic hepatic cancer</td>
<td>[32]</td>
</tr>
<tr>
<td>PEO/PLA</td>
<td>Doxorubicin hydrochloride</td>
<td>Blend NFs</td>
<td>Subcutaneous hepatic cancer</td>
<td>[33]</td>
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<tr>
<td>PMMA/PCL</td>
<td>6-Mercaptopurine</td>
<td>3-layered NFs</td>
<td>Colon, liver and breast cancer</td>
<td>[34]</td>
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<tr>
<td>PCL/PVA</td>
<td>5-Fluorouracil / Paclitaxel</td>
<td>Core-shell NFs</td>
<td>Breast and prostatic cancer</td>
<td>[35]</td>
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<td>PCL</td>
<td>5-Fluorouracil / Methotrexate</td>
<td>Core-shell NFs</td>
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<td>PLGA/PCL</td>
<td>Linezolid</td>
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<td>PCL/BSP</td>
<td>Levofloxacin hydrochloride</td>
<td>Porous wafer coated with electrospun NFs</td>
<td>Acute infectious gastroenteritis</td>
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<td>Gellan gum/pullulan</td>
<td>Dye model</td>
<td>Blend NFs</td>
<td>Ocular diseases</td>
<td>[40]</td>
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<tr>
<td>PVP/PLGA</td>
<td>Moxifloxacin / Pirfenidone</td>
<td>Core-shell NFs</td>
<td>Corneal abrasion</td>
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<tr>
<td>(SF/PCL)/PVA</td>
<td>Bone morphogenetic protein 2/ connective tissue growth factor</td>
<td>Core-shell/LBL NFs</td>
<td>Bone regeneration</td>
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<tr>
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<td>Nerve growth factor/ Glial cell line-derived neurotrophic factor</td>
<td>Dual emulsion electrospun NFs</td>
<td>Nerve regeneration</td>
<td>[43]</td>
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<tr>
<td>PCL/gelatin</td>
<td>Vascular endothelial growth factor</td>
<td>NFs-encapsulated gelatin micro or sub-micro particles</td>
<td>Vascular tissue regeneration</td>
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<tr>
<td>PCL</td>
<td>Cilostazol</td>
<td>Blend NFs – tubular structure</td>
<td>Cardiovascular tissue regeneration</td>
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<td>Chitosan/poly-cyclodextrin</td>
<td>Simvastatin</td>
<td>Stent coated with NFs</td>
<td>Restenosis prevention</td>
<td>[46]</td>
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Table 1. Recent studies in drug delivery NFs for cancer treatment, tissue repair, and some minor ailments.
tubular structures. In bone tissue regeneration, co-axially electrospun NFs were electrospun with the incorporation of bone morphogenetic protein 2 (BMP 2) into silk fibroin (SF)/PCL as the core, while pure PVA was the shell. PVA was further coated with surface immobilization of connective tissue growth factor (CTGF) with LBL assembly. Time controlled dual bioactive compound delivery resulted in enhanced bone formation with a pro-angiogenic effect (promotion of vessel formation) on bone healing due to sustained release of BMP2 and transient release of CTGF, respectively, when implanted subcutaneously in the abdominal midline of a nude mice [42]. For peripheral nerve regeneration poly(D, L-lactic acid) (PDLLA)/PLGA NFs incorporating nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF), separately, were prepared by dual emulsion electrospinning. In the in vitro studies with rat pheochromocytoma cell line culture, both released incorporated components induced high neurite outgrowth and neural differentiation, Figure 1. The bioactivity of the growth factors was well preserved as indicated by the minor decrease (about 10%) of the degree of neural differentiation [43]. Each year 17.9 million deaths result due to cardiovascular diseases such as coronary heart disease, cerebrovascular disease, rheumatic heart disease, etc. [31]. Stent structures were prepared by tubular electrospinning of blend PCL/Cilostazol [45] and by coating self-expandable nitinol stent with blend electrospun Chitosan/β-cyclodextrin/Simvastatin [46]. In the first study, according to reported diffusion and polymer relaxation, the cilostazol release mechanism of the delivery system will facilitate the reendothelialization process [45]. In the second study, the cell viability tests showed that endothelial cells were less affected by the simvastatin than smooth muscle cells, thus confirming the system’s selective activity toward the two types of cells present in the vessel wall [46]. When gelatin micro- or sub-micro particles carrying vascular endothelial growth factor, were incorporated into electrospun PCL, the drug delivery system showed to induce mesenchymal stem cells differentiation to endothelial cells and maintain angiogenesis for long periods of time as the nodes and tubes remained around 54.7% and 50.3%, respectively, from the original number after 24 h [44].

Figure 1.
The release of GDNF (upper images), the release of NGF (lower images) from PDLLA/PLGA scaffold [43].
3. Advances in nanofibrous wound dressings

This section will partially overlap with the previous one due to medicated electrospun nanofibers used in the wound healing process, thus the focus will be on their performance with no detailed discussion on materials or fabrication technologies.

A wound is a cellular/tissue structure (i.e., skin) damage caused by traumatic injuries from external mechanical forces, surgeries, burns, chemical agents, or chronic disease ulcers, which results in normal tissue function loss [47, 48]. The process of wound healing involves complex interactions between cells and “mediators” and undergoes through the stages of hemostasis (days 1–3), and inflammation (days 4–6), chemotaxis and activation, proliferation (epithelization, angiogenesis, and provisional matrix formation, days 4–14) and maturation and remodeling (days 8–1 year) [49]. There are acute and chronic wounds, but also some chronic wounds are non-healable and result from acute ones [50]. Wound dressings are used in the process of wound healing and are categorized as passive, interactive, advanced, and bioactive wound dressings. An ideal wound dressing should provide: moisturized, clean and warm environment, hydration, protection to the peri-wound area, elimination of excess exudates, is permeable to gas exchange and impermeable to microorganisms, its nontoxic, nontraumatic, wound shape conforming, eliminates discomfort, easy to handle, and cheap [51, 52]. Electrospun nanofibrous dressings can be categorized as advanced or bioactive wound dressings due to the usual drugs/bioactive components incorporation and the fact that these modern materials offer advanced features. Primarily they can prevent wound desiccation by liquid exudation, provide controlled evaporation, excellent oxygen permeability, and promote fluid drainage capacity, as well as microorganism invasion inhibition [53]. Secondarily, encapsulated active components will enhance the healing process.

Recently reported studies are discussed in terms of in vitro and in vivo materials performances as well as to-date clinical trials.

**Table 2** summarizes some of the most significant studies reported recently concerning wound dressings categorized as antibacterial, diabetic wounds, skin burns, and general or non-categorized dressings. Chronic wounds in diabetic patients are due to uncontrolled blood sugar, thus delaying the healing process and developing foot ulcers due to intense inflammation [54, 55]. The study of electrospun cellulose acetate (CA)/gelatin (Gel)/berberine (Beri) concerns the fourth-mentioned issue. It reveals that the developed dressing has both microbial and antibacterial effects as the number of the bacterial colony after 7 days of incubation was less than two and the minimum inhibition concentration for the *S. aureus* and *Pseudomonas aeruginosa* was 44 ± 5.7, respectively. The MTT assay also confirms the highest cell proliferation, while the histopathology and histomorphometry on the animal wounds showed the highest re-epithelialization after 16 days, healthier-looking skin with a thin epidermis, normal rete ridges, and skin thickness [54]. The incorporation of the alkannin/shikonin mixture in electrospun CA/PCL [56] and beta-glucan in hydroxypropyl methylcellulose/PEO [57] confirmed great cytocompatibility to fibroblast and keratinocyte cells, respectively. In the first study, the Hs27 fibroblast cells were elongated, well distributed, and in the formation of clusters [56]. The latter proved that the excipients in the in situ gel-forming of the βG-nanofibers had a positive effect on wound healing, while the mats improved the repair physically as well [57]. A multi-layered, chitosan/PVA + chitosan/PVA + nanobioglass (nBG), sequentially electrospun dressing provided a multifunctional activity thus accelerating the repair of chronic diabetic wounds. The authors reported that the nBG reduced the effect
<table>
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<tr>
<td>CA/Gelatin/ Berberine</td>
<td>Diabetic foot ulcer (DFU)</td>
<td>Enhance proliferation of L929 murine fibroblastic cells</td>
<td>Diabetic Wistar rats, highest collagen density, 88.8 ± 6.7%, highest angiogenesis, 19.8 ± 3.8</td>
<td>[54]</td>
</tr>
<tr>
<td>CA/PCL/Alkannin/ Shikonin</td>
<td>Skin chronic wounds</td>
<td>Elicit Hs27 fibroblast cells migration of 77.3%, high wound closure of 117.9%</td>
<td></td>
<td>[55]</td>
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<tr>
<td>Chitosan/ PVA + Chitosan/ PVA + nBG</td>
<td>Skin chronic (diabetic) wounds</td>
<td>The bioactive ions promoted human dermal fibroblastic cells proliferation, and expression of bFGF and VEGF</td>
<td>Wound closure acceleration in Sprague-Dawley diabetic model rats, through upregulation of VEGF, TGF-β, and downregulation of the inflammatory cytokines</td>
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<td>PLGA/ Lipopoly saccharide (LPS)/IFN-γ activated mice RAW264.7 or human THP-1 cell membrane /load of BMSCs or hBMSCs</td>
<td>Skin chronic (diabetic) wounds</td>
<td>Augment BMSCs or hBMSCs proliferation, promotes resistance to oxidative stress, gene expressions, and keratinocyte (JB6 or HaCaT) migration</td>
<td>In situ immunostimulation capacity (rapid re-epithelialization, collagen remodeling, antioxidant stress, better angiogenesis)</td>
<td>[57]</td>
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<td>Hydroxypropyl methylcellulose/ PEO/beta-glucan</td>
<td>Hard-to-heal diabetic wounds</td>
<td>Cytocompatible to (HaCaT) keratinocyte cells</td>
<td>Faster wound closure in diabetic db/db mice of 76.8–82.3%, day 4</td>
<td>[58]</td>
</tr>
<tr>
<td>PVA/ Chitosan/ Starch</td>
<td>Antibacterial skin wound treatment</td>
<td>L929 mouse fibroblast cells viability of 68.98% after 48 h, PVA/chitosan/starch (90/10/10) wound healing effectiveness of 100%</td>
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<td>[59]</td>
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<tr>
<td>PCL/Surfactin + Gelatin/ Curcumin</td>
<td>Antibacterial skin wound treatment</td>
<td>Cytocompatible with L929 fibroblast cells, round-like cell morphology</td>
<td>Wistar rats' skin wounds model completely healed at day 14</td>
<td>[60]</td>
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<td>PVA/Lysine/ Ibuprofen + coated Lavender oil</td>
<td>Antibacterial skin wound treatment</td>
<td>Excellent biocompatibility with human dermal fibroblasts, remaining viable cells with a number increase along time; with normal phenotype and biological activity</td>
<td></td>
<td>[61]</td>
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<tr>
<td>Composition</td>
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<td>Cell performance</td>
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<td>L1 - PCL, L2 - PVA/ Collagen/ Momordica charantia</td>
<td>Antibacterial skin wound treatment</td>
<td>Highest bitter melon extract content significantly increased L929 murine fibroblastic cells proliferation</td>
<td>Highest wound closure in the Wistar rats with the value of 94.01 ± 8.12%</td>
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<td>PLA/PVA/ Sodium alginate</td>
<td>Anti-inflammatory and antibacterial skin wounds treatment</td>
<td>After 7 days the L929 mouse fibroblast cell number was higher</td>
<td>At day 16, the wound in Sprague Dawley male rats completely healed, with denser and ordered collagen fibers, and significant enhancement of angiogenesis</td>
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<td>CA/Gelatin/ Nanohydroxyapatite</td>
<td>Skin wounds</td>
<td>Highest proliferation of L929 murine fibroblastic cell line at 25 mg nHA</td>
<td>Highest wound closure in the Wistar rats with the value of 93.5 ± 1.6%</td>
<td>[64]</td>
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<tr>
<td>PCL/Gelatin/ Naringin</td>
<td>Skin wounds</td>
<td>Highest proliferation of L929 murine fibroblastic cell line at 6% of Naringin</td>
<td>Highest wound closure in the Wistar rats with the value of 89.82 ± 3.30% and 99.39 ± 0.58% 7 and 14 days post-wounding</td>
<td>[65]</td>
</tr>
<tr>
<td>Chitosan/ Bromelin</td>
<td>Skin burns</td>
<td>Low cytotoxicity of the non-crosslinked membrane on human dermal fibroblasts</td>
<td>Greater re-epithelialization, debridement, and reduction of necrosis in second-degree burn rat's skin</td>
<td>[66]</td>
</tr>
<tr>
<td>POCA/PPF</td>
<td>Mild skin burns</td>
<td>Marked reduction by about 99% of the epidermis thickness and by about 85% in derma cell density in male UVB-burned C57BL/6 J mice</td>
<td></td>
<td>[67]</td>
</tr>
<tr>
<td>PVA/Birch bark dry extract (TE)</td>
<td>Skin burns</td>
<td>Porcine ex-vivo greatest wound area reduction and complete re-epithelialization at the lowest TE</td>
<td></td>
<td>[68]</td>
</tr>
</tbody>
</table>

**Table 2.**  
In vitro/in vivo studies in wound healing.
of the inflammatory cytokines, the chitosan was infection protective, while the PVA maintained the microenvironment moisture [58]. An extensive study was conducted on cell membrane modified electrospun PLGA with an in situ immunostimulatory capacity for exaggerated bone marrow-derived mesenchymal stem cells (BMMSCs) biofunctions.

PLGA was modified by LPS/IFN-γ activated mice RAW264.7 or human THP-1 macrophages cytomembrane for an in vitro study, while the further load of BMMSCs or hBMMSCs ameliorate healing in diabetic wound mice, Figure 2. This novel living dressing supports the cells under oxidative stress and favors immunoregulation, collagen remodeling, and neovascularization in the wounded areas [59]. Concerning antibacterial properties in wound dressings two studies were conducted in vitro for the evaluation of mouse and human fibroblast viability and proliferation. The first study used electrospun PVA/chitosan/starch with an antibacterial effect against Gram-positive and Gram-negative bacteria and an absolute wound healing effectiveness in a scratch assay [60].

In the second study, the ibuprofen, which was directly loaded into the electrospun PVA/lysine, and the coated lavender oil showed high radical scavenging values of 17.68 ± 3.99% and 38.54 ± 5.58%, respectively. This activity is important in order to avoid the oxidative stress that promotes the inflammatory process in the wound [61].

Therapeutic and regenerative effects were evaluated in a hybrid PCL/Sur + Gel/Cur electrospun dressing. The material resulted in the rapid development of the dermis and collagen arrangement, thus a complete wound repair at day 14 [62]. Similar successful results were obtained in the studies that concern the production of two-layered electrospun PCL and PVA/Collagen/Momordica charantia [63], CA/gelatin/ nanohydroxyapatite [64], and PCL/gelatin/naringin [65]. The studies have shown that the concentration of the active components relates to the fibroblast cells proliferation rate. Also all of the dressings performed with a wound closure efficiency higher than 90%.

In the study of PLA/PVA/sodium alginate (SA) membranes, the wound area revealed denser and ordered collagen fibers, with a high number of thick blood vessels and reduced levels of the inflammatory cytokine factor [66].

In the treatment of skin burn injuries, electrospun chitosan was loaded with the pineapple enzyme, bromelain. Lower bromelain concentration has shown both lower cytotoxicity against human fibroblasts and accelerated wound healing in the rat model [67]. Electrospun poly(octyl cyanoacrylate) (POCA)/polypropylene fumarate (PPF) acted as a strong anti-inflammatory dressing with an 80% cytokines reduction, comparable skin thickness, and dermal cells density with the native ones [68]. Another interesting bioactive component used was birch bark dry extract, which accelerated wound repair of an ex vivo porcine skin, when compared to the same composition of oleogel [69].

Figure 2.
Wound closure in diabetic mice from day 0–15 [59].
A recent clinical trial in the wound healing application field reported on the usage of electrospun PCL/CS-Zein-Curcumin dressing in the treatment of emergency burn patients. The efficiency of the same was compared with traditional gauze wound dressing and a silver ion alginate dressing. Selected patients were evaluated in terms of wound healing and scar repair, bacteria rates, patients' pain assessment, and overall nursing satisfaction. The dressing has shown antibacterial superiority with a decreased infection of 78.2%, as well as a total healing rate of 97%. Patients have had a great relief of pain in all burn treatment stages with a lessened experience of anxiety and depression [70]. Phase I clinical trial of electrospun fibrin dressing (commercial name SurgiClot) has demonstrated its efficacy in cancellous bone bleeding. The same was superior to standard US army dressing and is suggested to be used in different surgical procedures such as orthopedic, spine, cardiovascular, or head/neck surgery [71]. Phoenix wound matrix is a 3D electrospun material out of various synthetic polymers for the treatment of acute, chronic, and burn wounds. This commercial product was reported to be successful in different clinical cases, including patients with pressure injuries, DFU, chronic lower extremity, complex chronic or acute, surgical, trauma, or burn wounds [72]. Clinical case studies are also available for the market product SpinCare concerning donor site wounds [73] and partial thickness (or mixed) burns [74, 75]. In the case of split-skin graft surgery, dyslipidemia and diabetes mellitus type 2 patient was treated with the spinicare layer, which served as a temporary skin and wound epithelization support [73].

4. Electrospun nanofibers in tissue repair

Probably the most investigated application field of functional electrospun materials would be the field of electrospun scaffolds for tissue engineering. A scaffold acts as a temporary structural support for cell attachment, growth, and proliferation and most importantly for subsequent tissue regeneration. In order to credibly mimic, the native extracellular matrix (ECM), the scaffold should possess functions that consider its architecture, mechanical property, cyto- and tissue compatibility, and bioactivity. Briefly, porous structure, certain void volume as well as mechanical integrity that will match the host tissue would facilitate tissue repair. The scaffold material should be biocompatible with both cells and tissues and when necessary should match the tissue degradability rate. Incorporated bioactive components should provide cell cues for their direction and differentiation [76]. The following section will discuss the latest studies on electrospun fibrous scaffolds that consider the application in hard tissues or bone and soft non-connective or nervous tissue regeneration.

4.1 Bone tissue engineering

The bones are natural composite materials with two types of bone tissues, that is, the compact and the spongy tissue. The structure of the compact tissue is regularly organized in lamellae and differs in thickness or form depending on the bone type it constitutes. About 80% of the total human bone mass belongs to this tissue. Collagen fibers have an irregular arrangement in the lamellae of the spongy bone tissue. This tissue has higher metabolic activity than the compact one [77]. There are also five types of bone cells, including osteoprogenitor cells, osteoblasts, bone lining cells, osteocytes, and osteoclasts. Osteoblasts, osteocytes, and bone lining cells originate from the osteoprogenitor or the mesenchymal stem cells, while the osteoclasts
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 originate from the hemopoietic stem cells [78]. In terms of chemical composition the bone organic ECM consists of collagen type I and non-collagenous proteins, while the bone inorganic ECM is represented by minerals with a hydroxyapatite structure, that is, calcium, phosphate, and carbonate. There are different types of bones pathological conditions categorized as: fracture injuries, orthopedic surgeries, ischemic, hereditary, and metabolic diseases as well as bone cancer [77]. Bone disorders such as arthritis, bone cancer, osteosarcoma, and osteoarthritis are addressed as one of the greatest causes of humans deaths [79].

This section will discuss the latest studies concerning electrospun scaffolds for bone repair with a focus on the type of cells used for the in vitro experiments and the development of 2D or 3D architectures.

4.1.1 In vitro studies of osteoblasts performance

Electrospun scaffolds were prepared from PCL and pomegranate peel extract as a natural food waste with high phenolic content. Such scaffold revealed enhanced antioxidant activity by 96% and the cultured osteoblasts showed complete embedment in the scaffolds, with an active osteogenic matrix secretion for bone ingrowth [80]. Nano-hydroxyapatite (nHA) was deposited onto electrospun poly-3-hydroxybutyrate-co-3-hydroxyvalerate/polyaspartic acid resulting in a porous, hydrophilic, and good-strength scaffold. The scaffold was promising in the new bone formation due to enhanced human fetal osteoblast adhesion and osteointegration as well as tissue mineralization with Ca and P deposition [81]. Silver-doped nHA incorporated into electrospun PCL showed initial high burst release for bacteria clearance, while further silver content reduction resulted in a booster effect of the rat mesenchymal stem cells’ (MSCs) metabolic activity on the 21st day of culture. This result is in accordance with the start of the healing process [82]. Bone marrow mesenchymal stem cell behavior was observed depending on electrospun PLLA nanofibrous scaffold surface topography, that is, random or aligned structure. The cells exhibited increased migration speed due to the contact guidance with the orientation of the aligned nanofibers. This alignment also improved osteogenic differentiation and significantly promoted osteogenic gene expressions [83]. PLGA scaffold with a bioactive interface was prepared by electrospinning and post-layer-by-layer deposition of hematite nanoparticles (αFeNPs). The performance of rat adipose-derived stem cells was enhanced in terms of cell spreading, cytoskeletal organization, osteogenic differentiation, and bone matrix mineral synthesis [84].

4.1.2 Bioactive scaffolds incorporating growth factors, genes and ECM vesicles

Electrospun PCL was loaded with nHA and chitosan-based nanoparticles carrying NELL-1 protein. The system had a double barrier which resulted in a sustained release of the growth factor. The highest osteogenic activity of MC3T3-E1 cells was observed on the 21st day of cell culture. The scaffold promoted cells’ adhesion, proliferation, osteogenic differentiation, and maturation [85]. Three-component simultaneously electrospun layers scaffold incorporated PLGA and PEG or both with recombinant human vein endothelial growth factor (rhVEGF), recombinant human BMP-2 (rhBMP-2) factor, and Ca nanoparticles. The scaffold resembled an ECM-like hybrid microstructure with a high initial rhVEGF release and high bioactivity to promote vascularity in the first and further bone formation stages. The scaffolds induced human umbilical vein endothelial cells proliferation as well as murine pluripotent
mesenchymal cells osteogenic differentiation with high alkaline phosphatase expression, calcium deposition, and gene expression [86]. ECM vesicles are proteolipid-packaged particles with bioactive cell contents that have a crucial role in the bone mineralization process, but also mediate the cell-cell signaling in the mechanical load bone formation process [87, 88]. Collagen-coated electrospun PCL scaffold was functionalized by osteocyte-derived mechanically activated-extracellular vesicles to enhance bone tissue regeneration. As fabricated scaffolds resulted in a significant increase in the alkaline phosphatase (ALP) activity and a continuous increase in matrix mineralization, thus promoting osteoblast differentiation [89]. Preosteoblast and endothelial cells exhibited improved osteogenic differentiation and angiogenic activity when cultured on mesenchymal stem cells-derived ECM vesicles loaded SF/PCL scaffolds. The same also promoted the regeneration of a calvarial rat bone defect [90]. Plasmid DNA (pDNA) polyplexes were loaded into electrospun gelatin/polyethylene glycol scaffolds to obtain a functional gene expression system. Further loading of the scaffolds with BMP-2 protein resulted in osteogenic ALP activity with an absorbance rate above 8 or 4 mAbs/min in human myoblast C2C12 and mouse osteoblast MC3T3-E1 cells, respectively [91].

4.1.3 3D electrospun structures for in vivo implants

Electrospun 3D cell/mesh complexes were fabricated via layer-by-layer deposition of PLLA/gelatin in a random and nestlike structure. Each layer (four in total) was prior cultured with bone mesenchymal stromal cells and afterward implanted into rat cranial defects. The in vitro study showed the promotion of the cells’ osteogenic differentiation, while the in vivo study showed new calcified bone formation with greater bone healing in case of the nestlike cell/mesh complexes [92]. Similarly, the cell/scaffold complex was fabricated by culturing human fetal osteoblasts onto PCL/nHA, which was electrospun onto stainless steel mesh via layer-by-layer assembly. This 3D system showed cell migration between the adjacent layers. The complex was further functionalized by alendronate to promote osteogenic differentiation [93]. Successful osteoblast adhesion and proliferation, as well as gene expression for their differentiation and mineralization, was accomplished by electrospun poly(butylene-adipate-co-terephthalate)/nHA. The scaffolds resulted in the highest bone volume formation in rat tibia defect model after six weeks of implantation [94]. Electrospun poly(D, L-lactic acid)-poly(ethylene glycol)-poly(D, L-lactic acid) (PELA) immobilized with BMP-2 was used for the treatment of secondary hip osteoarthritis. Cultured human bone marrow-derived mesenchymal stem cells (hMSCs) were well attached with minor cytotoxicity, Figure 3a. The study revealed a positive effect on the osteogenesis, the complete acetabular defects repair, Figure 3b, but also an incomplete bone formation which is influenced by the insufficient BMP-2 dose [95]. Several techniques were combined along with electrospinning to fabricate nHA/PLA/gelatin 3D scaffold. Firstly, short nanofibers were formed from the nHA/PLA/gelatin mat by homogenating, while the 3D nanofibrous scaffold was fabricated by freeze drying and thermo-crosslinking of the nanofibers. The final structure was obtained by immobilization of BMP-2 with a prior polydopamine coating and subsequent freeze drying. The as-prepared architectures enhanced BMSCs osteogenic differentiation and most importantly, the volume and rate of growth of the newly formed bone in the rat cranial bone defect model was significant, from the fourth to the eighth week of implantation [96]. Tibia bone defects in rabbit models were treated by a tubular 3D structure consisting of a shell and a core from electrospun collagen/PCL/HAl
and freeze-dried collagen/icariin-loaded chitosan microspheres, respectively. These scaffolds had excellent osteoinductivity and osteoconductivity due to the simultaneous effect of the HA and the icariin [97]. The scaffolds’ pore structure provided bone remodeling, while the matching degradation rate with the host defect [98] provided bone matrix mineralization [99].

4.2 Nervous tissue engineering

Trauma, neurological disorder, or tumor excisions are the known causes of nerve injuries. Peripheral nerve injuries (or neuropathy) are a major problem for millions of people yearly, resulting in a painful condition due to motor function and sensory perception mitigation. Nerve tissue engineering as the current alternative to autologous nerve transplantation, is the solution to provide a biomimetic material for both mechanical and chemical support of the native tissue repair [100, 101].

4.2.1 Peripheral nerve and spinal cord injury

3D hollow cylinder structure was electrospun combining uniaxially aligned PCL and PCL/PLGA nanofibers as the outer and the inner layer, respectively. The scaffolds were implanted into the sciatic nerve gaps of a rat model with a peripheral nerve injury. The study revealed enhanced nerve fiber regeneration and myelin repair, as well as increased cell count due to the open structure which provided migration/penetration into the scaffolds [102]. Aligned glycosaminoglycans (from aorta porcine tissue) functionalized electrospun PCL scaffolds were used as well in peripheral nervous system repair. The scaffolds have been shown to effectively influence Schwann cells (SCs) adhesion, proliferation, and differentiation [103]. Peripheral nerve injury was also suggested to be repaired by electrospun piezoelectric polyvinylidene fluoride (PVDF) or polyvinylidene fluoride trifluoroethylene (P(VDF-TrFE)) scaffolds. These polymers are known for their piezoelectricity which stimulates cells ingrowth induced by electrical activity upon mechanical force application. Having this in mind, the scaffolds showed biocompatibility with cultured SCs and supported sensory neurite outgrowth [104]. When layered double hydroxides (LDH) nanoclay particles were incorporated into electrospun PCL/gelatin, increased viability, and proliferation of the cultured human neuroblastoma SH-SY5Y cells were observed at higher LDHs, but there was no increased differentiation [105]. Photocrosslinked gelatin methacryloyl was used for the fabrication of an aligned hydrogel electrospun microfiber bundle to
be used in the repair of spinal cord injury (SCI). The viability of the cultured bone marrow-derived mesenchymal stem cells (similar to neural stem cells) was reported to be 95%, with cell infiltration depth of $197.5 \pm 18.1 \, \mu m$ into the scaffold on the 3rd day of culture, while SCI rats were observed to have significant functional recovery of the lower limbs. Generally the in vivo study resulted in the increase of the neural stem cells, neurons, synaptic connections, and vascular endothelial cells, as well as an inhibition of glial scar formation [106]. Electrospun (fiber aligned) aminated PLA, loaded with nerve growth factor, was grafted with liposomes pDNA vehicles to be used as well in SCI repair. The scaffold in the rat in vivo study performed with a great reduction of the inflammation and scar formation, while simultaneously promoting angiogenesis, neurogenic bioability and resulting in significant neuromotor function recovery of the hindlimb [107]. Nerve growth guidance and peripheral nerve regeneration were supported by electrospun PCL/collagen/nano bioglass. The in vitro study reported the promotion of human endometrial stem cells (hENSCs) adhesion and proliferation [108]. Scaffolds were also fabricated by combining several techniques including electrospinning of PLA, spin coating, and ammonia-induced solid-state polymerization to obtain eumelanin-coated PLA for the treatment of neurodegenerative disorder. The scaffolds supported human-derived cell line SH-SY5Y, from neuroblastoma to survive and differentiate into a neuronal phenotype [109]. Electrospun PCL-amnion nanofibrous membranes were also proposed to be used after neurolysis and as reported it resulted in the reduction of the peripheral nerve adhesion, lessen intraneuronal macrophage invasion, high gastrocnemius muscle weight, and muscle bundle area as well as improved sense and movement of the model rats limbs [110]. Another condition proposed to be treated with electrospun biomimetic polybenzyl glutamate, was optic neuropathy which causes irreversible blindness due to retinal ganglion cell degeneration [111, 112]. Prepared scaffolds with cultured induced pluripotent stem cells promoted neurite outgrowth or neuronal differentiation, neuronal maturation, and retinal differentiation and maturation [112].

4.2.2 Nerve guidance conduits

Nerve guidance conduits (NGC) are a physical barrier and guiding tool for regenerative axons across gap lesions. In peripheral nerve injuries, NGC is frequently used as simple hollow structures, but also in a more advanced manner functionalized (or filled) with molecular (growth factors) and gene or cell-based (i.e., Schwann cells, bone marrow stromal cells, human umbilical-cord stem cells, neural stem cells, etc.) therapies [113]. Earlier multichannel conduits [114] and recently micro-channeled tubular structures, Figure 4a [115], are also proposed, as well as optimal aligned architectures with conductive features to stimulate neural regeneration [117]. PLGA electrospun yarns were encapsulated by electrospun PLGA tubular wall to form NGC which were further coated by laminin through covalent binding. As prepared nerve guidance conduits showed a synergistic effect of the 3D yarns structure and the laminin layer that resulted in significant Schwann cells (SCs) proliferation and migration, respectively [118]. Similarly, NGC was prepared by wrapping a sponge-like electrospun/freeze-dried PLCL/SF structure via electrospinning the same composition outer layer, Figure 4b. In vitro study showed that the SCs grew on the NGC surface but also infiltrated the sponge structure for 1000 in-depth on the 7th day of culture. The in vivo study in rat sciatic nerve defect model revealed good nerve regeneration, especially when compared to a hollow NGC structure [116].
Electrospun PVDF-TrFE and matrigel coated conduit, with random or aligned fibrous inner walls, cultured with SCs were used for the rat spinal cord repair in vivo. The conduits supported cell viability and axon regeneration with a greater uniform distribution in the aligned structures [119]. Mussel adhesive proteins fused with biofunctional peptides from the extracellular matrix were incorporated into PLGA to form electrospun-aligned nanofiber conduit. The scaffold supported a stable environment for both neural and Schwann cells differentiation. Dense and large axon- and endoneurium-like structures similar to one of the autografts were also observed for the fabricated scaffold which further provided volume and functional accelerated nerve regeneration [120]. Nerve guides tubular structures with microchannels and parallel fibers walls were electrospun from PCL or PLLA to act as cell delivery vehicle of stromal vascular fraction for a 10 mm nerve gap bridging. The PLLA nerve guides supported axonal regeneration but were not as good as an autologous nerve graft [115]. Dual electrospun PLGA and poly (d,l-lactic acid) (PDLLA) incorporating glial cell line-derived growth factor and nerve growth factor (NGF), respectively, were produced with an aligned fibrous topography. Rat pheochromocytoma cells (PC12) migrated on the aligned scaffolds in a well-organized manner with greater neurite sprouting and elongation. Fiber topography and biochemical cues resulted in enhanced neurite outgrowth and neural differentiation [121]. Similarly, aligned electrospun PCL/chitosan scaffolds with an immobilized effective nerve regeneration agent NGF showed elongated PC12 cell morphology with increased neuronal viability as well as enhanced differentiation and neurite outgrowth [122]. Despite the traditional application of the NGF for PC12 differentiation, authors proposed an electroconductive electrospun SF/reduced graphene oxide (rGO) scaffold that provides superior levels of cell differentiation into neural phenotypes due to electrical stimulation ability. Cell viability was >95%, while attached cells appeared with thin filopodia and neuritis. Increased differentiation of the cells was noticed in case of applied electrostimulation [123]. Good cell attachment and proliferation were obtained in a similar electroconductive scaffold PCL/gelatin incorporating graphene as well as tetracycline hydroxide drug with antibacterial properties [124].

5. Challenges and future aspects

Recent studies of electrospun nanofibrous materials for nanomedical applications consider synthetic or natural biomaterials, as well as inorganic or composite-based
multifunctional systems that most often incorporate bioactive compounds in order to offer mechanical support, cells viability, and life activities support, compatibility with ECM interactions and new tissue formation. Although there are advances in terms of materials diversity, fabrication procedure, therapeutic/healing performance, challenges are still present and need to be addressed. When new materials or bioactive compounds are encapsulated some studies mention possible cell toxicity, thus further research needs to be carried out on the issue of an optimal concentration set that will not affect cell viability. *In vitro* studies apply animal-based or commercial cell lines, some of which are cancer-derived, thus human-based cells would be a better choice in order to simulate the natural surroundings. Also, since human cells are more sensitive and slower to accommodate in a new environment, the same can reflect the original conditions more closely. There is still a lack of clinical trials, as most of the studies are conducted on rat animal models. Standardization of the procedures as well as materials ethical approval is imperative in order to transfer the product to a commercial market. Within this respect, the fabrication processes need industrialization, although many researchers have demonstrated large-scale electrospinning machines (i.e., needleless electrospinning) continuous production of a nanomedical material still remains a challenge.

6. Conclusion

The research in the field of electrospun nanofibrous materials for nanomedical applications has not decreased, it is actually still growing and the last few years have shown more challenges and frontiers. This chapter discusses selected studies, from 2017 onwards, that are dealing with the development and performance of electrospun nanofibrous materials for drug delivery, wound healing, and tissue engineering with a focus on bone and nerve tissue repair. In drug delivery systems, materials’ composition as well as fabrication technologies affect drugs’ pace mechanisms, which finally affects therapeutic performance. On demand, drug delivery materials are mainly dealing with cancer treatment, tissue repair, and some minor ailments. Wound therapeutic electrospun materials are focusing on chronic diabetic wounds and skin burn wounds while generally comprising natural or synthetic remedies with antibacterial and healing functions. Diverse tissue engineering scaffolds are designed to carry growth factors, genetic materials, or target selected vesicles to boost systems’ regenerative performance. Scaffolds are fabricated as 2D or 3D architectures via simple or modified electrospinning or in a combination with other techniques (i.e., freeze drying, L-B-L, coating, wrapping, etc.). Versatile cells are cultured on the scaffolds, after or during the fabrication procedure with a general successful result in terms of cell viability, growth, migration, and specific differentiation. *In vivo* studies are still based on animal models, although there are some clinical trials as well. Peripheral and spinal cord injuries are reported to have better outcomes in case of aligned structures with biochemical as well as electro-conductive cues for neurite outgrowth and neural differentiation. Some of the challenges and future aspects are also addressed.

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Conflict of interest

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