

Chapter 9

Electrospinning of Hydrogels for Biomedical Applications



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Abstract The field of biomedical applications for hydrogels requires the development of nanostructures with specific controlled diameter and mechanical properties. Nanofibers are ideal candidates for these advanced requirements, and one of the easiest techniques that can produce one-dimensional nanostructured materials in fibrous form is the electrospinning process. This technique provides extremely thin fibers with controlled diameter and highly porous microstructure with interconnected pores. Electrospinning demonstrates extreme versatility allowing the use of different polymers for tailoring properties and applications. It is a simple cost-effective method for the preparation of scaffolds. In this section, we will discuss recent and specific applications with a focus on their mechanisms. As such, we conclude this section with a discussion on perspectives and future possibilities on this field.

Keywords Electrospinning · Hydrogel · Tissue engineering · Drug delivery
Wound healing

1 Introduction

Electrospinning is an easy technique for the production of nanoscale polymer fibers from a variety of materials in one-dimensional, two-dimensional, and three-dimensional configurations (Li and Xia 2004; Greiner and Wendorff 2007). This technique provides extremely thin fibers with controlled diameters and highly porous microstructure with interconnected pores; versatility allows the use of various polymers for tailoring various applications requirements. The ability to

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produce nanofibers composites of blend polymers, composites with metals, and/or ceramics with high surface area than regular fibers, it provides various areas of applications such as nanocatalysis, tissue engineering, biomedical, pharmaceutical, and environmental engineering (Bhardwaj and Kundu 2010). One of the limitations of electrospinning is their low production rate which several groups are trying now to overcome this by producing multiple spinnerets arranged in an ordered position such as circle or lines (Hou et al. 2009; Persano et al. 2013).

Fields of applications on electrospinning largely studied are drug delivery, tissue engineering, and wound healing. One of the main reasons on these applications is that polymeric scaffolds produced by electrospinning have the advantage of mimicking the natural extracellular matrix (ECM). However, nanofibers produced by electrospinning on tissue engineering have irregular distribution of cells and poor migration at the interior of the scaffold on normal behaviors (Bhardwaj and Kundu 2010). Furthermore, the increase in packing density of nanofibers produced by electrospinning limits cells to enter on the inner part of the fibers. Several techniques have been performed to modify the fiber parameters to overcome these issues (Li et al. 2014) which will be discussed in this chapter.

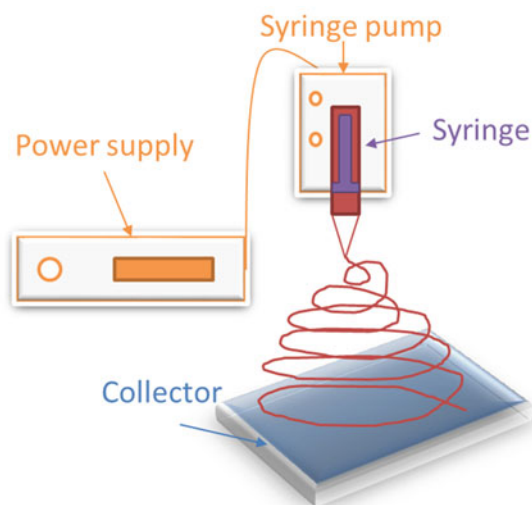
Although not yet deeply discussed, hydrogel nanofibers can overcome the limitation of simple polymeric nanofibers. Hydrogels are hydrophilic cross-linked polymers structured in three dimensions that can swell under aqueous conditions but not dissolve instantly. Hydrogels swell to a greater or lesser extent in water due to hydrophilic power of the group chains. On lower hydrophilicity, the polymer will swell in water, but with a further increase in hydrophilicity the polymer becomes water soluble (de Lima et al. 2015a, b). Hydrogel nanofibers have the advantage of combining both techniques, and it is being widely investigated in wound healing (Fogaça and Catalani 2013; Choi et al. 2015) since they can maintain a healing environment and adequate humidity on the region of the wound and absorb the exudate with exchange of minimal pain. In addition, their inherent abilities help on diffusion of extended release of drugs, in particular on the case of hydrophobic drugs (McKenzie et al. 2015).

The focus on this chapter will be treated, along with the fundamentals on electrospinning, on the polymers employed for the application intended, modifications of parameters on fibers for tissue engineering. Finally, a focus on incorporation of drugs into nanofibers and the diverse applications with novel techniques have been investigated with a perspective for future prospects.

2 Overview of Electrospinning

Electrospinning process is a simple and very controllable technique which produces fine fibers using electrostatic forces. These fibers are either produced by polymer melt or solution with fibers' diameters in the nanometer scale with a large surface area. A typical electrospinning apparatus usually involves syringe (attached with the emitter) with feed pump, a grounded collector, and power supply with high

Fig. 1 Schematic drawing of basic setup for electrospinning



voltage as described in Fig. 1 (Bhardwaj and Kundu 2010). The process of electrospinning involves applying high voltage in the emitter and collector and charging the polymeric solution. When this polymer reaches the electric emitter, the droplet that is being held by its surface tension deforms once the electric field reaches an important value to a cone formation labeled as “Taylor cone”; the polymeric solution is then expelled in a jet shape from the emitter and accelerated toward the collector which is of opposite polarity. During the traveling toward the collector, the solvent is evaporated in the air and dried fibers form at the collector. However, it is essential to adjust the electrospinning parameters due to instability of polymeric jet to obtain uniform nanofibers (Greiner and Wendorff 2007).

2.1 Influence of Process Parameters on Electrospinning

The process parameters are important when aiming to obtain continuous non-beaded fibers, and manipulating improves it when designing nanofibers; some of these processes can be governed by the solution such as surface tension, concentration, viscosity, molecular weight, and conductivity. Alternatively, processing parameters of the electrospinning apparatus also plays important roles, which are flow rate, voltage, type of collector, and collector–emitter (tip) distance. Finally, the ambient when producing nanofibers affects the morphology and structure.

2.2 *Characteristics of the Solution*

2.2.1 Concentration

Concentration in electrospinning is crucial for fiber formation because it cannot be formed until a minimum is required. According to Li and Wang (2013), there are four critical concentrations that affect the morphology of fibers: very low—nanoparticles are formed, and there is electrospray rather than electrospinning due to limited viscosity and surface tensions (Deitzel et al. 2001). At slightly increasing concentration, fibers and beads mixture occurs (Eda and Shivkumar 2007), and with a suitable concentration evenly nanofibers are obtained (Fong et al. 1999). Finally, in case of high concentrations, “helix-shaped” microribbons can be observed (Yang et al. 2004).

2.2.2 Molecular Weight (MW)

The polymeric solution entangled chains are indicative of molecular weight and along with concentration contribute to the solution viscosity and affect the morphology of fibers. Electrospinning is essential to aim for higher molecular weight since there are enough chain entanglements to stabilize the jet and form nanofibers (Bhardwaj and Kundu 2010). An equation was obtained by (Gupta et al. 2005), for the exact transition from beads to fibers as it will be discussed in Sect. 2.2.

2.2.3 Viscosity

As another crucial parameter, viscosity can also determine the fiber morphology (Larrondo and St. John Manley 1981). The balance of viscosity is crucial since low viscosity excludes the formation of continuous fibers and just beads are normally obtained, whereas high viscosity makes difficult the jet formation of polymers on the emitter. For melt electrospinning, the variation of polymer viscosity varies depending on the spinning (Bhardwaj and Kundu 2010). The viscosity is also connected to the concentration and molecular weight parameters. Various works investigated the effect of viscosity onto electrospinning polymeric solutions (Geng et al. 2005; Kim et al. 2010; Binulal et al. 2014).

2.2.4 Surface Tension

Surface tension values might be different for different solvents. Higher values of surface tension might inhibit the electrospinning generating unsteady droplets (Moses et al. 2001). A lower surface tension values on the other hand strongly depend on the other parameters; for example, electrospinning can be formed on low

electric field with low values of surface tension (Rogina 2014). According to Bhardwaj et al., the surface tension determines the boundary of nanofibers' condition on electrospinning if all other variables are held constant.

2.2.5 Conductivity/Surface Charge Density

With a few exceptions, polymers are polyelectrolyte and this ability highly influences the jet formation. Usually, higher values of conductivity of the solution decrease the nanofiber diameter and lower conductivity results in non-uniform fibers with beads (Chuachamsai et al. 2008). Increasing conductivity can be achieved by adding ionic salts on the polymeric solution like NaCl or KH_2PO_4 (Li and Xia 2004) resulting in fibers with decreasing diameters and beadless fibers (Huang et al. 2006).

2.3 Processing Parameters

2.3.1 Voltage

Voltage is one of the most important parameters since electric jets released from the emitter only occur after a voltage threshold. Higher voltage on polymers for electrospinning influences fiber diameter, but it depends on the concentration and the emitter-to-collector distance (Deitzel et al. 2001; Li and Wang 2013).

2.3.2 Flow Rate

Flow rate affects the velocity of the jet and the amount of polymer transferred. Lower flow rate is generally required since it leads to more time for polarization and evaporation of the polymeric solution (Yuan et al. 2004). Higher values of flow rate may induce the formation of bead fibers with thick diameter due to short drying period before reaching the collector (Zhang et al. 2005).

2.3.3 Type of Collector

Collectors are conductive substrates that collect the charged fibers during the electrospinning process. The simplest collector is aluminum foil, but it is difficult to remove the fibers on this type of collector, so different arrangements have been performed such as conductive paper, gridded bar, rotating rod, and wheel. Such collectors can also contribute to the alignment of fibers which are useful in tissue engineering (Vaquette and Cooper-White 2011).

2.3.4 Distance Between the Collector and Emitter (Tip)

The distance between the emitter and collector also affects the fiber diameter and structure. The required distance is usually minimal so that fibers dry before it reaches the collector, otherwise beaded fibers will be formed (Ki et al. 2005).

2.4 Ambient Parameters

As explained previously, the ambient conditions affect the morphology of the nanofibers. Humidity seems to have a great impact on some polymers in which after a critical value it can dissolve in the cross-points of the structure and fuse together forming a dispersal layer (Yao et al. 2013). On the other hand, it has been shown that lower temperatures led to a slower evaporation of the solvent and fibers could not be formed. The average diameter of the nanofibers has a complex relationship in terms of temperatures (De Vrieze et al. 2009) since the formation of nanofibers on electrospinning depends on the solvent and rigidity of the polymeric chains.

2.5 Theoretical Foundation for Electrospinning Polymers Capable of Physical Gelation

The process formation of fibers via electrospinning is affected by various parameters such as flow rate (Uchko et al. 1999), voltage (Yuan et al. 2004; Zhang et al. 2005), polymer molecular weight (MW) (Casper and Stephens 2004; Tao and Shivkumar 2007), and concentration (Fong et al. 1999; Deitzel et al. 2001; Eda and Shivkumar 2007; Felice et al. 2015). To tailor these parameters to obtain a window for range of fiber formations is not straightforward, since these processes are interdependent on each other. For these reasons, an integrated approach must be used to identify the range of fiber formation. For gel polymers, the nanofiber formation is dependent on the entanglements of the structure of the gel and the solution (Shenoy et al. 2005a). For this reason, a semiempirical method, described by Shenoy et al. (2005a), can presume the shift over electrospaying to spinning based on the amount of chain entanglements—physical link of polymeric chains which are similarly to chemical cross-links (Shenoy et al. 2005b).

Equation (1) correlates the polymer MW to its entanglement solution MW. Due to the preparation method of polymers, normally the average MW is considered.

$$(n_e)_{soln} = \frac{M_w}{(M_e)_{soln}} = \frac{\phi M_w}{M_e} \quad (1)$$

For polymers solutions, its entanglement value is dependent on the solution concentration and the polymer volume fraction ϕ , described in Eq. (2)

$$\phi_p = \frac{\rho_s W_p}{\rho_s W_p + (1 - W_p)\rho_p} \quad (2)$$

where ρ_p and ρ_s denote the densities of polymer and solvent and W_p is polymer weight concentration of the solution.

With these equations, it is possible to obtain a single value (n_e) which corresponds to viability of formation of fibers in electrospinning based on their polymeric chain entanglements (Shenoy et al. 2005a; Husain et al. 2016).

The number of chain entanglements, due to variations of polymer solution concentration (C) and molecular weight, causes morphology transitions on most electrospinnable polymers (Felice et al. 2015). This variation of chain entanglement leads to alteration of viscosity (Bock et al. 2012) and can be used as a determinant for solution regimes of polymers (Gupta et al. 2005). The different solution regimes, particles to fiber, can be defined by the Berry in Eq. (3) (Hager and Berry 1982) which correlates the polymer concentration with the intrinsic viscosity:

$$B_e = [\eta]C \quad (3)$$

where B_e is the berry number, ($[\eta] = \lim_{c \rightarrow 0} \frac{\eta_{sp}}{C}$) the intrinsic viscosity; η_{sp} is the specific viscosity, and C is the polymer concentration.

The solution regimes are classified according to the critical overlap concentration (C^*) and the chain entanglement concentration (C_e) described as diluted, semi-diluted unentangled, and semi-diluted entangled also represented in Fig. 2 (Gupta et al. 2005). Chain overlap is absent in dilute system, and thus, chain entanglement does not exist, limiting the system with significantly weak entanglements (Shenoy et al. 2005a). When the concentration of the solution is equal to the concentration inside a single macromolecular chain, the critical concentration overlap occurs, A \rightarrow B process in Fig. 2.

As the concentration increases, the chain reaction overlap occurs, but it is not enough to produce a degree of entanglement. Although some entanglements are observed, the chain entanglements within the drop formed on electrospray are not enough to stabilize the particle structure formation and these are not optimum as it leads to inferior and non-reproducible morphology since they lose their shape when impacting over the collector showing a beaded and non-continuous fiber formation (Husain et al. 2016). For entangled systems, $B_e > 4$ or C_e is generally accepted as the formation of pure fibers and the effect is due to the increase in entanglement chains so the jet formation can be stabilized through jet breakup inhibition because of the increased surface tension (Felice et al. 2015; Husain et al. 2016).

In practice, electrospun beaded fibers occur unexpectedly, but it was reported in the literature (Taepaiboon et al. 2006; Husain et al. 2016). Formation of beads, as explained before, usually is dependent on the parameters of the polymeric solution, which include the polymer structure, concentration, and salt content (Li and Wang 2013).

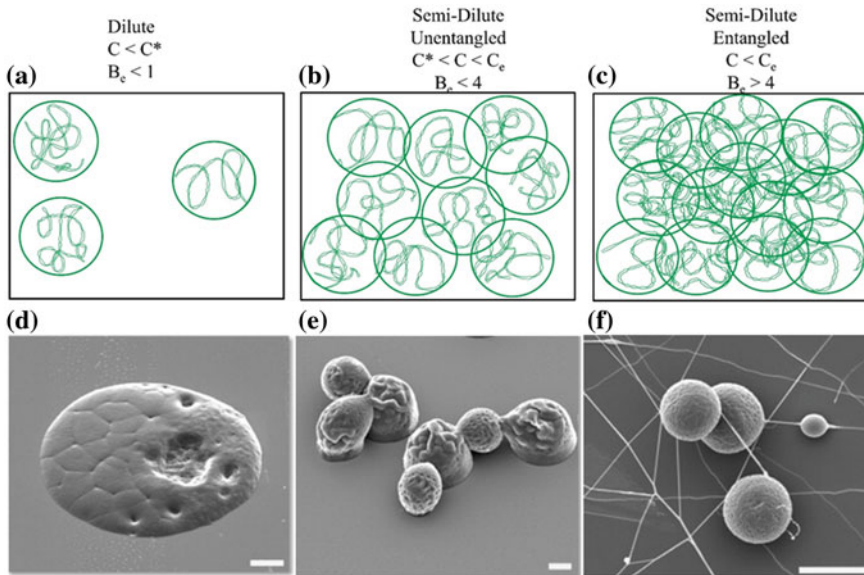


Fig. 2 Physical representation of the three solutions regimes with corresponding SEM images. **a, d** dilute; **b, e** semi-dilute unentangled; **c, f** semi-dilute entangled. $C^* = 1/[\eta]$. Adapted with permission from Bock et al. (2012). Copyright (2016), Elsevier

3 Applications

3.1 Tissue Engineering Applications

Tissue engineering creates artificial materials for regeneration of tissues based on the approach from materials engineering and life science (Ma 2004; Lanza et al. 2011; Okamoto and John 2013). Mostly, the repair or replacement of failing organs and tissues is facilitated by tissue engineering creating biological substitutes, like the growing of cells on scaffolds to support the regeneration of the desired tissue (Okamoto and John 2013). Cell interactions are extremely important for cell growth since it can change the cell functions via complex pathways (Kai et al. 2013; Temenoff and Mikos 2014).

Seeding of cells on scaffolds normally progresses with attachment followed by proliferation and differentiation. The cell agility to proliferate is one of the most important factors for tissue regeneration. With faster proliferation, the development of the injured tissue is improved and reduces scar tissue formation in vivo (Prakash et al. 2010; Kai et al. 2013).

Electrospinning for tissue engineering is one of the most used techniques since its fibrous structure is comparable to the tissue extracellular matrix (ECM) (Kim et al. 2005; Li et al. 2014; Guarino et al. 2015; Weng and Xie 2015). Ito et al. (2005) have shown that the attachment of fibroblast-like cell line (COS-7) was

higher to nanofiber mats of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) than on regular scaffolds of the same material after a short incubation time. The increased surface area of nanofibers helped the improvement on cell attachment due to its 3D features (Ito et al. 2005). Moreover, Chua et al. (2006) also demonstrated that nanofiber scaffolds containing amine groups had higher cell proliferation and adhesion, in comparison with films containing amine groups.

3.1.1 Choice of Polymer Hydrogel for Tissue Engineering

The behavior of cells can be adjusted by focal adhesion and signaling complexes (Wozniak et al. 2004), and such behaviors are intimately related to the properties of the scaffold (Kai et al. 2013). In addition, high-surface area nanofibrous scaffolds are preferably used on tissue engineering and different cells react different to the surface where it is attached (Leung and Ko 2011; Kai et al. 2015). Moreover, materials have to be biocompatible—the body must not reject the implant or scaffolds and must interact with it, so the spreading of cells is achieved faster (Yang et al. 2010; Van Vlierberghhe et al. 2011; Rogina 2014). Furthermore, it must not elicit inflammatory response and cytotoxicity with a three-dimensional environment for cell proliferation and adhesion (Langer and Peppas 2003; Leung and Ko 2011; Parratt and Yao 2013). For these reasons, the choices of polymer and/or hydrogel designed for tissue engineering are important. Figure 3 shows the different polymers employed in electrospinning along with its properties. Currently, biodegradable scaffolds are the most investigated materials for production of nanofibers via electrospinning tissue engineering (Rogina 2014). Biodegradable nanofibers can have tailored degradation rate in the body so that it will be metabolized or excreted. The degradation mechanism normally consists of chemical degradation, and the most important parameters are the polymer structure and the environment which can also influence the degradation rate such as the pH and chemical structure (Simionescu and Ivanov 2016).

3.1.2 Natural Polymer Hydrogel Nanofibers for Tissue Engineering

Natural-based hydrogels/polymers are normally obtained from living plants and animals and are hydrophilic in nature; they can be extracted on polysaccharides and cellulose from plants (Simionescu and Ivanov 2016). Although most are obtained from vegetal sources, microorganisms can also synthesize biodegradable polymers. Examples are: fish—fish skin serves as a collagen; crustaceans—shells have large amounts of chitin; corals-algae—rich source of polysaccharides. These polymers are biocompatible, biodegradable, and non-toxic. In addition, natural polymers have an organized structure and it helps on cell viability and tissue ingrowth (Wolf et al. 2015; Simionescu and Ivanov 2016).

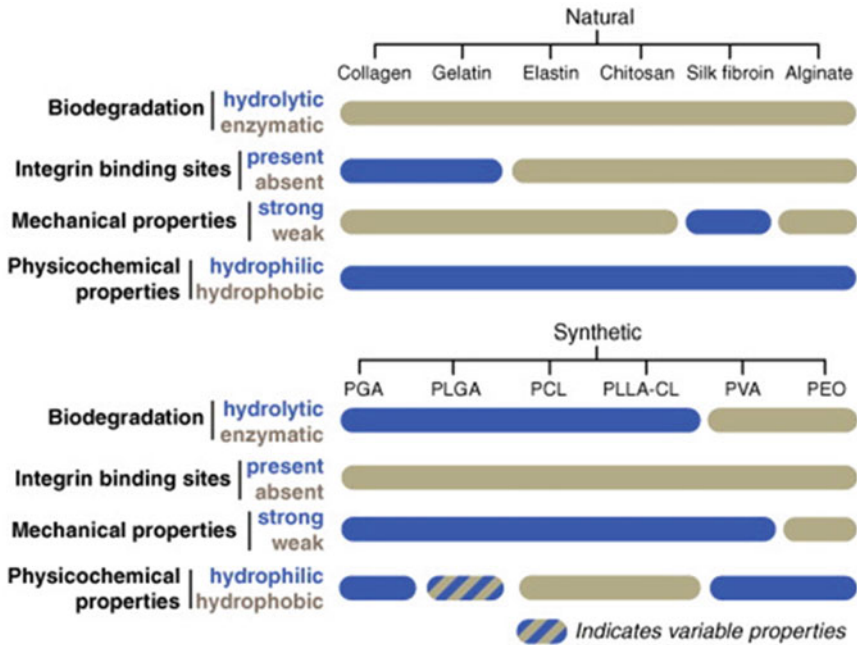


Fig. 3 Most common used natural and synthetic polymers on electrospinning along with its biological, mechanical, and physicochemical properties. Reprinted with permission from Gunn and Zhang (2010). Copyright (2016), Elsevier

The main advantages of natural polymers (collagen, chitosan, silk fibroin, gelatin, etc.) are their inherent cellular interaction and similar chemical versatility—greatly mimicking the extracellular matrix structure (ECM) for bone cell support matrix, which encourages protein adsorption and cellular adhesion, surface migration, and proliferation (Lai et al. 2014). However, ECM of different tissues has unique characteristics (Li et al. 2014; Khorshidi et al. 2015).

Collagen nanofiber scaffold can be used as a matrix for osteogenic progenitor cells to adhere, proliferate, and differentiate into osteoblasts (Chen and Lv 2015). Some studies performed with collagen nanofibers exhibited an adhesion of over 45% for mesenchymal stem cell population in a quickly response time of 30 min at room temperature (Chan et al. 2009).

In addition, recent studies suggest that stiffness plays an important part in bone tissue engineering for nanofiber scaffolds. Collagen nanofibers when tested under MG63 osteoblast-like cells produce bone-ECM proteins such as osteocalcin, responsible for ECM deposition and mineralization; leading to superior values of cell maturation and their cellular adhesion as well as response is increased based on the value of stiffness of the scaffold (Torres-Giner et al. 2009; Tsai et al. 2012).

Chitosan, which is biocompatible and biodegradable, presents low toxicity and is widely investigated on electrospinning as nanofibers (Rogina 2014). However, pure electrospun chitosan fibers are difficult to obtain (Rogina 2014) and chemical modifications into derivatives that are soluble in common organic solvents are used (Neamark et al. 2006). The morphology of chitosan fibers is altered by the acetic acid concentration, whereas an increase in the solvent changes the chain entanglements and is easy to form uniform fibers (Geng et al. 2005). The properties of chitosan nanofibers for bone regeneration have been studied (Shin et al. 2005), and cells MG63 proliferated on the nanofiber with collagen and osteocalcin induction after two weeks *in vitro*. In addition, chitosan can also maintain its integrity for as long of six weeks and enhance bone regeneration without inflammatory reaction due to its antifungal and antibacterial properties, which can be improved by UV irradiation (Shin et al. 2005). Charged reactions can occur on chitosan, leading to a network between polymeric chains (Berger et al. 2004). This network acts as a hydrogel. However, one of the drawbacks is its poor mechanical strength and, therefore, it is normally used with other material or cross-linked with a copolymer.

Alginate, a naturally biodegradable polysaccharide material, is obtained from brown seaweed and is biocompatible, non-toxic, and non-immunogenic. However, it is hard to obtain continuous and uniform nanofiber scaffolds by electrospinning due to the rigid and extended chain conformation in aqueous solution and lack of chain entanglement (Chen and Lv 2015). Therefore, the addition of another copolymer is usually performed on alginate nanofibers. The ability of alginates to absorb and retain water is superior to that of natural gums (Berger et al. 1953).

However, nanofibers composed of natural polymers are compared poorly in terms of their mechanical properties with low resistance to aqueous solutions that limits their use as tissue engineering. (Frenot and Chronakis 2003; Khadka and Haynie 2012). Many researchers reported a number of cross-linking procedures to stabilize the nanofibers synthesized using a wide range of natural polymers and their blends (Delmar and Bianco-Peled 2016; Jalaja et al. 2016). The effect of cross-linking on nanofibers creates a network of 3D polymer chains which can possibly enhance fiber stability and other physical and mechanical properties (Miraftab et al. 2015; Laha et al. 2016). Cross-linking on different natural polymers have been performed (Torres-Giner et al. 2009; Gualandi et al. 2016; Jalaja et al. 2016), such as gelatin in order to decrease its solubility for being able to use in long term (Zhang et al. 2006a). Laha et al. (2016) developed a gelatin with saturated vapor of glutaraldehyde as cross-link. The effect of cross-link induces the nanofibers to a more hydrogellic state (Fig. 4).

3.1.3 Synthetic Hydrogels/Polymer for Tissue Engineering

One of the drawbacks of using natural polymers is their inherent brittleness, in addition to their restricted flexibility (Chen and Lv 2015). Additionally, synthetic polymers can be easily modified in contrast to natural polymers which have

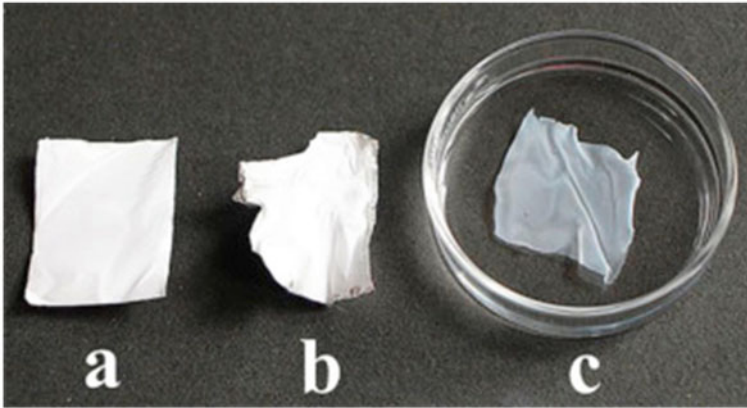


Fig. 4 Digital images representing **a** non-cross-linked gelatin, **b** gelatin after cross-link, and **c** gelatin with cross-link immersed in water. Reprinted with permission from Laha et al. (2016). Copyright (2016), Elsevier

sensitivity to processing conditions such as pH or UV radiations, water. (Simionescu and Ivanov 2016).

Synthetic polymers are, as the name suggests, synthesized in the laboratory. Between the synthetic nanofibers, the most attractive ones used in tissue engineering include polyvinyl alcohol (PVA), poly(ethylene glycol) (PEG) and poly(ethylene oxide) (PEO), polycaprolactone (PCL), poly(Lactic Acid) (PLA), and poly-(N-vinyl-2-pyrrolidone) (PVP) (Wolf et al. 2015). With most of the biodegradable synthetic materials approved by FDA, the interest in using these materials has drawn great attention.

PVA polyvinyl alcohol is created as a result of free radical polymerization of vinyl acetate with subsequent hydrolysis of acetate groups to hydroxyl moieties resulting in a wide molecular weight distribution (Hassan and Peppas 2000). PVA is biocompatible material and non-toxic with useful mechanical properties for tissue engineering and has the ability to swell to a large extent in solutions similar to those of human tissues. Nanofibers of PVA can be used as single scaffold (Felice et al. 2015) or combined (Yang et al. 2008; Vashisth and Pruthi 2016), especially for drug delivery systems and tissue engineering (Felice et al. 2015). PVA can be easily dissolved in aqueous solutions and produced as nanofibers via electrospinning. Furthermore, cross-linking approaches have been performed to produce PVA hydrogels, such as chemical cross-linking, freeze/thawed, and UV irradiation (Franco et al. 2012; Canillas et al. 2015). The cross-linking via methanol and chemical with glutaraldehyde seems to be the mostly used method for PVA nanofiber hydrogel. However, glutaraldehyde and chemical cross-links seem to have toxicity problems, which could impact and damage cells. Therefore, authors tried to elaborate different physical and chemical cross-linking methods (Torres-Giner et al. 2009).

PEG and PEG-containing block copolymers are used in many synthetic forms, due to its non-degradability by simple swelling and its limited metabolism in the body. In addition, PEG with molecular weight inferior of 50 kDa is used in tissue engineering applications (Yamaoka et al. 1994) so that they can be totally degraded on the kidneys (<30 kDa) or the liver (>30 kDa) (Veronese and Pasut 2005).

PCL nanofibers have been extensively used (Torres-Giner et al. 2009) due to their bioresorb ability. Aliphatic polyesters are associated with low cost and slow degradation. Mesenchymal stem cells (MSCs), which show potential to treat large bone defects (Quarto et al. 2001), proliferate and grow well on PCL scaffold (Yoshimoto et al. 2003), showing bone-like appearance when implanted on rat models (Shin et al. 2004). In addition, in comparison with normal PCL substrates, PCL nanofibers support higher MSC adhesion and viability (Ruckh et al. 2010). In addition, PCL nanofiber demonstrates the deposition of HAp on simulated body fluid (SBF) (Araujo et al. 2008).

Poly-(N-vinyl-2-pyrrolidone) (PVP) has excellent biocompatibility with high ability to absorb water. PVP nanofibers are excellent candidates for fabrication of nanofibers with non-spinnable materials due to various inorganic ions that can be produced and its ability to disperse particles acting as covering agent, which makes it a polymer of choice for the fabrication of electrospun fibers with non-spinnable materials. However, PVP nanofibers are very soluble in water showing poor properties as hydrogel (Lubasova et al. 2015). Consequently, PVP hydrogel nanofibers with further cross-linking are required for improvements and acting as hydrogels. Recent methods have been performing through Fenton reaction and UV irradiation (Fogaça and Catalani 2013), also with polyacrylic acid, since this reaction forms a strong hydrogen bond interaction (Lubasova et al. 2015).

3.1.4 Blend of Natural and Synthetic Polymer Nanofibers and Integration of Nanofibers with Hydrogels for Tissue Engineering

The polyblend of natural biodegradable polymers (chitosan and silk fibroin) with synthetic polymers offers a major advancement in tissue engineering by the simple and economical approach of the favorable biological properties on natural polymers and the excellent mechanical properties of the synthetic polymers that favor cell growth and proliferation (Gunn and Zhang 2010; Abdal-Hay et al. 2016). Various polyblend polymers have been researched in the past years (Cosme et al. 2016; Hu et al. 2016a; Mahoney et al. 2016; Zhijiang et al. 2016; Ziaee et al. 2016).

A common polyblend scaffold is made from PCL/gelatin mixture and demonstrates increased hydrophilicity and promotes bone osteogenesis and mineralization of MSCs in vitro (Alvarez Perez et al. 2012). In addition, with the support of PCL the scaffold provided improved mechanical and biochemical properties to guide bone regeneration. Currently, various types of polyblends have been researched for the application intended, such as polyester urethane urea (PEUU) with gelatin for application in myocardial tissue engineering. Since cardiac tissue challenges are the

development of scaffold with suitable Young's modulus, the polyblend PEUU/gelatin provided relatively desirable values for the application intended. In addition, cardiomyocytes were able to proliferate and grow in this nanofiber scaffold (Jamadi et al. 2016).

The combination of nanofibers and pure hydrogels may offer the advantages of incorporating both structures and minimize these problems. Although this concept is in early stages, some researchers developed different designs for tissue engineering applications (Bosworth et al. 2013; Xu et al. 2015).

Laminated composites The easiest way to incorporate both structures is to fabricate individually and mix them by the layer-by-layer method, and this method is adjustable by the layers, class of fibers, and hydrogels which can be tuned to the morphology and mechanical properties required. Another technique is to cross-link the hydrogels directly onto nanofiber films, dropping the solution onto the nanofiber (Quinn et al. 2007; Manna and Patil 2009; Shi et al. 2015). In this application, the voids that separate each nanofiber are filled with hydrogels. Yang et al. (2011) developed a layer by layer of oriented nanofibers of PLA with collagen type 1 hydrogels. These were separated by filter paper with cells deposited onto the fibers and incubated before adding another layer. The authors investigated the different fiber directions on the arrangement of the layers. The results found that there was a difference in direction of cells which were dependent on the orientation of the deposited fiber. These suggested further studies were possible into developing complicated structures to simulate ECM found in some tissues, such as skin and cartilages.

Encapsulating fibers in hydrogel Controlled placement of fibers with an ordered structure can be achieved by encapsulating the fibers in hydrogel. McMahon et al. (2011) achieved a nanotubular scaffold with nanofibers of PEUU (poly(ester urethane) urea and PEG-fibrin hydrogel (McMahon et al. 2011) for the application of coronary artery bypass grafts. Basically, rectangular segments of aligned electrospun fibers were revolved around latex mandrels. Smooth muscular progenitor cells were embedded onto the fibers and incubated for two days. After incubation, the fibers were revolved again through a latex tube with the cells facing outwards. The tube was added in a hollow Teflon cylinder, and a thrombin/fibrinogen cell was added to encapsulate the fibrous layers before polymerization and support enough mechanical strength so that after the removal of the latex, the composite hydrogel would be intact. After incubation, the latex and Teflon tubes were removed and the final composite was immersed in diacrylate-derivatized polyethylene glycol (PEG) solution for the final construct of PEG on fibrin gel. Finally, polymerization was achieved by UV. This structure was hypothesized to mimic the coronary artery vessels, showing a biphasic layer of hydrogel fibers and collagen. Suture strength results showed that this construct has similar values to those of human artery. In addition, smooth muscle cells were able to proliferate and migrate on this hydrogel nanofiber construct.

Injectable Composites A recently technique has been developed by Brown et al. (2011) named as melt electrospinning writing which can produce complex porous fiber structure using an automated stage, and this technique can create scaffolds by stacking melt electrospun fibers on top of each other which is similar to melt extrusion based on direct writing but in a sub-micrometer magnitude. (Visser et al. 2015) use the innovation of this technique to produce scaffolds for cartilage tissue and via an injection mold prepared a reinforced hydrogel scaffold nanofiber by adding the polymer GelMA with an etched PCL nanofiber scaffold produced by melt electrospinning. These constructs have increased stiffness compared with hydrogels or nanofiber scaffolds alone approaching that of articular cartilage tissue. The scaffolds were also embedded with human chondrocytes and show viable responses, retaining their morphology, and can respond to biological regime in terms of matrix production and gene expression, making it a feasible material to culture cells in various environments mechanically diverse.

3.2 Control of Fiber Parameters for Tissue Engineering

With recent progress of cells interactions and tissue microenvironment, important investigations on the structural nanofiber scaffolds on different cells environment have been performed (Liu et al. 2012; Li et al. 2014). For the application intended, a control of the fiber parameters is important. Between these parameters, four majors, as pointed by a great recent article Xu et al. (2013), have been deeply investigated: fiber diameter, packing, orientation, and 3D shape.

Researchers have been trying to control the nanofiber diameter (Du et al. 2008) since it can regulate cell behavior influence like adhesion, proliferation, migration, differentiation, and protein adsorption (Christopherson et al. 2009). Currently, controllable diameter size of the electrospun fibers produced has a range of 150 nm–5 μm (Ishii et al. 2008; Nasouri et al. 2012). These ranges of fiber are in much smaller size than those produced by conventional electrospun methods including some cells which help facilitate contact guidance of cells (Wang et al. 2010a). Normally, the size controls are dependent on the polymer solution parameters (Zhang et al. 2005) and processing conditions (Deitzel et al. 2001).

The conventional electrospun method forms 3D tightly packed structures, and studies indicate that cells can only grow and migrate on the superficial surface, resulting in a 2D membrane rather than a 3D structure. Additionally, these scaffolds restrict cell infiltration and limit nutrient exchange. This effect results in loss of cells and the unsuccessful or partial regeneration of tissues (Li et al. 2014). To overcome this issue, the control of fiber packing is important when designing the structure for tissue engineering culture. One strategy is to increase the pore size and porous structure of these scaffolds (Baker et al. 2008; Kim et al. 2008). Various techniques to increase the porosity and pore sizes have been developed such as increasing the diameter of nanofibers (Rnjak-Kovacina and Weiss 2011), evaporating constituents

of a mixed polymer after electrospun process (Wu et al. 2014). These allow a low packing density of nanofibers which helps the cells to infiltrate the scaffold.

Researchers are trying to obtain oriented fibers since the extracellular matrix in tissues of human body has anisotropic architectures, so the scaffold needs to display the same anisotropic behavior for the tissue application intended (Li et al. 2014). In addition, cell migration and extension are improved when nanofibers are oriented to a single-axis direction, such as neural cells, in which oriented nanofibers help direct the growth of axons in healing process on neural tissue engineering. However, random orientation is typical in electrospun fibers which are attributed to the bending instability related to the spinning jet. To overcome this, fiber orientation can be produced on electrospun fibers by using two grounded rods (Li et al. 2003) or a rotating drum (Kim and Reneker 1999). A rotating drum at high speed can be used to obtain aligned fibers, but their orientation is not perfect, and disk collectors have also been used (Xu et al. 2004). Usually, on this configuration the electric field is higher at the disk edge and the fibers are well aligned along the edge of the collector. Another technique is the use of two conductive strips separated by a void gap, and due to this void gap, which acts as an insulated region, it results in electrostatic interactions on the nanofibers, and they are stretched to form a parallel array across the gap.

Since then, different designs have been developed to improve this system such as conductive coil for the collector (Lee et al. 2016) and addition of finite-length hollow cylindrical electrode along the jet trajectory, to suppress the coil formation. Parallel-plate electrodes in between the collector and a cylindrical electrode to orientate the nanofiber scaffold at the collector have also been used (Karatay et al. 2014).

Furthermore, research is ongoing to produce fibers with similar morphologies and characteristics of the native tissue ECM. As an example, a nanotubular scaffold—that simulates the muscle layer of blood vessel while mimicking elasticity, mechanical strength, and high surface area—is possible to be obtained through electrospinning. Tubular electrospinning structures give aligned fibrous scaffolds with a high surface area that can induce the proliferation and adhesion of loads of cells for a faster and complete healing of tissues (Wang et al. 2014). In addition, recent studies have shown that patterned nanofibers in 3D tubular scaffolds can be produced easily, using designed collector templates. The collector template can be designed based on varying nanopatterns with different shapes, producing various nanofiber structures that can be tailored by the collector template (Daming and Jiang 2008). These specific controlling parameters tend to be important for specific tissue engineering.

3.2.1 Control of Fibers for Neural Tissue Engineering

Neural cells are affected by the 3D shape of electrospun membranes (Christopherson et al. 2009; He et al. 2010; Wang et al. 2010a), and its fiber diameter affects adhesion, proliferation, migration of rat hippocampus-derived adult neural stem cells (rNSC) (Christopherson et al. 2009; He et al. 2010; Li et al. 2014). Studies

performed by (Meng et al. 2015) tried to simulate the ectoplasm of nerve (polyanionic nanofibrous cortical layer) by producing a tubular-shape PAA nanofiber hydrogels. The results from Meng et al. concludes that PAA fibrillar structure could be a potential candidate for aligned fibers that can mimic the cortical layer structure.

The effect of alignment was reported by several authors (He et al. 2010; Wang et al. 2010a; Hu et al. 2016b), and aligned fibers appear to enhance Schwann cell maturation more than randomly oriented fibers (Wang et al. 2010a).

Finally, hydrogels seem to affect the neural tissue. In the innovative work of Hodde et al. (2015), layers of oriented PCL nanofibers were embedded with fibrin hydrogel. Fibrin was selected because it could act as targeting tissue healing, depositing fibrin at the site of the injury and acting as extracellular matrix for migration and proliferation of perineural fibroblasts, Schwann cells, and regenerating axons during nerve healing (Weis et al. 1994). The hydrogel fibrin nanofiber structure was similar to the ECM of peripheral nerves. In addition, the fiber hydrogel on 2D structures retained the deficient simple flattened, unipolar morphologies of Schwann cells, where the 3D construct had a complex, highly branched morphology similar to neuron-like morphology, and the maximum outgrowth was observed after one day of incubation. In addition, Schwann cells were oriented to the direction of PCL fibers (Hodde et al. 2015).

3.2.2 Control of Fibers for Vascular Tissue Engineering

Alignment of fibers seems to improve the proliferation of vascular cells (Del Gaudio et al. 2009; Ma et al. 2012; Li et al. 2014; Shalumon et al. 2015; Ercolani et al. 2015). Shalumon et al. (2015) studied PLLA/gelatin electrospun aligned fibers in smooth muscle cells (SMCs), and its results indicate that aligned fibers support SMCs cells and improve the proliferation (Shalumon et al. 2015).

3D shape of electrospun fibers also seems to strongly affect vascular tissue cells (Ma et al. 2012; Merkle et al. 2015) with a preferable tubular shapes for the reason that it mimics the natural blood vessels (Stitzel et al. 2006).

Electrospun fibers produced in a core-shell design promote NIH 3T3 fibroblasts (FBs) and rat smooth muscle cells (rSMC) viability (Merkle et al. 2014, 2015). In addition, the packing of fibers impacts on the overall effect, and according to Zilla et al. (2007), tubular scaffolds must possess a porous structure with pore diameter of 10 μm in average and 20–80 μm^2 minimum area to allow penetration of cells so as to obtain a fast regeneration of vascular tissues (Zilla et al. 2007). Vascular tissue grafts also need to possess proper mechanical properties and a confluent endothelialized lumen to resist thrombosis (Lin 2011). Hydrogel-based systems such as hydrogel nanofiber scaffolds are generally more biocompatible in the peritoneum than hydrophobic polymeric devices (Yeo et al. 2007). Stefani et al. produced a novel hydrogel nanofiber with PCL with copolymer of acrylated poly((l-lactide-co-trimethylene carbonate), aPLA-co-TMC, the mixing of the two incompatible polymers as melts with UV-cross-link produced core-shell tubular fibers and the scaffolds supported the migration, alignment, and proliferation of

human mesenchymal stem cells (hMSCs). In addition, cells followed the fiber alignment; random fibers give raise to diverse migration and adhesion, and more spread and disorganized cell orientation, while aligned fibers promoted cell elongation with high organized and oriented pattern (Stefani and Cooper-White 2016).

3.2.3 Control of Fibers for Bone Tissue Engineering

Diameter of fibers influence bone forming cell behavior, Badami et al., investigated the use of electrospun mats on MC3T3-E1 cells and found that the optimum range of fibers diameters for cell proliferation is usually between 0.14 and 2.1 μm and they are likely to reproduce on larger diameter fibers; optimization of the fiber dimension helped in the regeneration of bone tissues (Badami et al. 2006). The fiber packing also affects bone tissue, and enhanced porosities significantly improve the cell penetration and distribution (Baker et al. 2008; Vaquette and Cooper-White 2011). The alignment of fibers takes an important place in bone tissue because the bone ECM is oriented in the same direction of the collagen nanofibers in basic structures of the bone (Cai et al. 2012). The orientation and pattern of the fibrous scaffold have to resemble the fibrous structure of the natural extracellular matrix (ECM) because it can improve osteoblast cell migration, proliferation and simulate the ECM structure (Wang et al. 2009a, 2010b).

Hydrogel nanofibers with PVA/gelatin followed by cross-linking based on methanol, for the improvement in the mechanical structure, show a well-spaced 3D structure with growth and proliferation of MG-63 (human osteosarcoma cells) (Linh and Lee 2012). Recently, Pangon et al. (2016) developed a chitosan/chitin whisker with HAp hydrogel nanofiber for the objective of promote bone cell response, and the results indicate that after the simulated body fluid (SBF) the samples were randomly mineralized with Ca-deficient HAp. In addition, the hydrogel presented non-toxicity to osteoblast cells with proliferation and viability enhanced by increasing the chitin whisker (Pangon et al. 2016).

3.2.4 Control of Fibers for Ligament and Tendon

Alignment of electrospun nanofibers structure is important on ligaments and tendons because it mimics the dimensionality of collagen fibrils that comprise native tendons and ligaments (Li et al. 2007; Choi et al. 2008). In this case, it is extremely important that the orientation of the nanofibers is optimized with the mechanical properties, since it has to mimic the native tissue structure. Deepthi et al. aligned PCL nanofibers coated with a hydrogel chitosan-hyaluronic acid in a cross-link of N,N-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC) and lyophilized by stacking multiple nanofiber mats. The cell results with rabbit ligament fibroblasts exhibited better migration, attachment, and proliferation along the direction of alignment of fibers with elongation in comparison with PCL random ones where cells just spread onto the fibers (Deepthi et al. 2015). However, the results from

Deepthi et al. (2015) showed that PCL fibers with random orientation infiltrated more onto the scaffolds owing to the increased porosity. However, ligament tissues require strong scaffolds and the random PCL fibers exhibit poor mechanical properties. In addition, cell arrangement along the direction of the acting force is a prerequisite for ligament tissue engineering and the mechanical strengths of most of the scaffolds presented in the literature are yet inferior compared to the ligament tissue (ACL) (Liu et al. 2012; Deepthi et al. 2015).

3.2.5 Control of Fibers for Skin Tissue Engineering

Skin tissue consists of multilayers categorized in terms of the epidermis, dermis, and hypodermis. These diverse tissue layers comprised of diverse cells and diverse functions, so complex structured scaffolds are needed for this tissue engineering. The effect of electrospun nanofibers has been extensively studied (Cui et al. 2008; Huang and Fu 2010). Studies have been showed that fibroblasts proliferated best at 350–1100 nm. Few results have been reported on the parameters for fiber orientation and fiber packing on skin regeneration (Li et al. 2014). Hydrogel nanofibers containing gellan/PVA and its effects on human dermal fibroblast (3T3L1) cells were investigated showing positive results (Vashisth and Pruthi 2016). Various similar results have been reported (Cui et al. 2008; Loh et al. 2010).

3.2.6 Control of Fibers for Cartilage Tissue Engineering

Cartilage wounds can advance to osteoarthritis and are acute challenges for regenerative medicine (McCullen et al. 2012; Steele et al. 2014). One of the unique features of cartilage tissues is that they have anisotropic mechanical properties due to differences in density and structural arrangements (Becerra et al. 2010). This leads to three distinct zones with collagen fibers varying their orientation, developing from aligned in the surface regions, to random and orientating perpendicular to deep zones (Steele et al. 2014). These profiles for cartilage zones contribute in terms of mechanical properties (Klein et al. 2009; Becerra et al. 2010).

Authors tried to mimic this cartilage unique zone behavior. Steele et al. developed trilayered electrospun fibers (Fig. 5) with scaffold nanofibers regions by using the same polymer with varying the alignment, packing, and diameter of fibers. The combination of the two distinct zones is designed to yield an anisotropic scaffold with a smooth articulating surface and a more porous region for ECM deposition. The morphological changes were able to provide desired functionality, in terms of mechanical stability, while impacting both chondrocyte gene expression and ECM accumulation. Hydrogels with PLA and chitosan have also been successfully reported for the regeneration of cartilage tissue (Mallick et al. 2016). The water adsorption of hydrogel nanofiber is a significant parameter during the chondrocyte culture and cartilage regeneration (Mallick et al. 2016). Chitosan has a similar structure than of glycosaminoglycan (GAG)—a natural biopolymer found in tissues

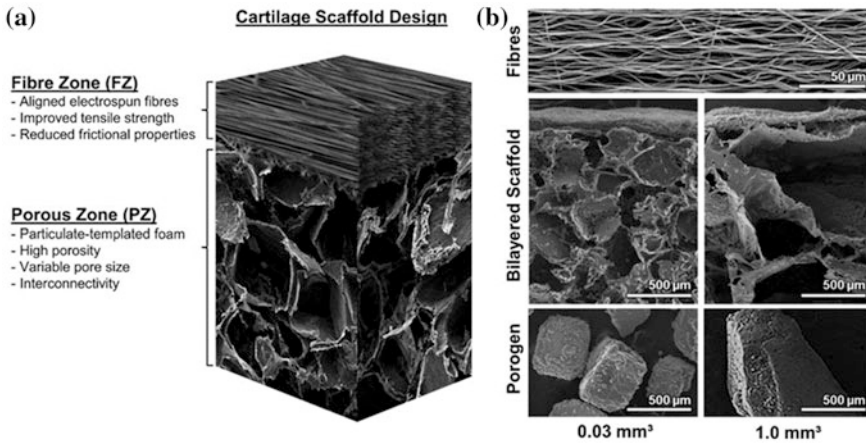


Fig. 5 Bilayered cartilage scaffold schematic. **a** A diagram illustrating the electrospun fiber zone (FZ) and a porous zone (PZ). **b** SEM images of (top) the aligned fiber zone that is shared between both scaffold varieties, (middle) the complete bilayered scaffolds with 0.03 mm³ (left) and 1.0 mm³ (right) pores and (bottom) the sodium chloride porogens used to produce higher porous zones. Reprinted from Steele et al. (2014)

and ECM. Results from Mallick et al. (2016) using nanofiber scaffolds for cartilage engineering show that rabbit chondrocytes can attach well and proliferate throughout the nanofibers. In addition, the glycosaminoglycan values resulted from chondrocyte culture from a specific design scaffold exhibited a desired enhancement in the GAG release, which the authors suggest it might be due to suitable modulation and maturation of the chondrocytes (Mallick et al. 2016).

3.3 Dressings for Wound Healing

Wounds, if exposed and untreated, are susceptible to water loss, toxins, and bacterial infections and could promote unnecessary and continued inflammatory response that limits the regeneration process. In this way, wound dressing materials are used for regeneration and repair of the dermal tissues, protecting it mainly against microorganism (Mogoşanu and Grumezescu 2014).

Ideal dressings must contain certain characteristics, including absorption ability of wound exudates, bacterial barrier, functional adhesion—which can adhere to healthy tissue but not adhere to wound tissue, ease of removal, and low cost (Thomas 1990; Bhardwaj and Kundu 2010).

Hydrogel nanofibers for wound dressing applications meet most of the requirements as dressing material due to their microfibrillar and/or nanofibrillar structure related to the electrospinning, producing a moist environment and helping the regeneration of skin with no scar (Alvarez et al. 1983). In addition, hydrogels have great ventilation ability and it can be suitable and efficient on absorption of

contaminated exudates (Dumville et al. 2013). Furthermore, electrospun nanofibers can prevent and control microbial biofilms, cleanse the injured tissue, and eliminate/minimalize pain (Lee et al. 2003; Mogoşanu and Grumezescu 2014).

Xu et al. (2016) electrospun a mixture of chitosan/PLA and PEG, and the formed nanofibers were evaporated to remove the solvent at 60 °C. The cross-link of nanofibers was done with Glutaraldehyde vapor at room temperature followed by 0.1 M glycine aqueous solution to block unreacted aldehyde groups. These fibers demonstrated high wicking rates and equilibrium water absorptions. These fibers can hold excess exudates and create a wet wound healing environment for the wound. The swollen fibers reduced the size of the pores and permeability of air, but the cross-linked reaction allowed the ingress of oxygen and carbon dioxide. Finally, Xu et al. demonstrated that these hydrogel nanofiber mats showed good antibacterial activities (Xu et al. 2016).

3.3.1 Choice of Polymer for Wound Healing

Natural polymers are widely used for wound and burn dressing due to their biocompatible properties and similarity to ECM. Natural polymers can stimulate the healing process and repair the damaged tissues and skin regeneration (Huang and Fu 2010). Between the natural polymers, the most common used are cellulose—used in chronic wound dressing (Hunt et al. 1984; Montesano and Orci 1988), chitin and chitosan—anti-inflammatory and wound healing properties (Anitha et al. 2014; Mogoşanu and Grumezescu 2014), alginates—hemostatic properties in exudation/bleeding wounds and burns (Wang et al. 2002; Paul and Sharma 2004). Numerous hydrophilic polymers such as polyethylene glycol (PEG) have the potential hydrogel properties. Due to the 3D cross-linked networks, polymeric hydrogels are extensively used in pharmaceutical and biomedical area, tissue engineering, drug delivery (Peppas and Sahlin 1996; Peppas 2000; Samchenko et al. 2011). Therefore, hydrogels cross-linked natural polymers can be used for wound and burn dressings (Mogoşanu and Grumezescu 2014; Wolf et al. 2015). Synthetic polymers on the other hand are usually selected as carriers for drugs (Peppas 2000; Chaterji et al. 2007; Nguyen and Alsberg 2014; de Lima et al. 2015a, b) and can be designated for the choice as hydrogel blend.

3.4 Drug Delivery Applications

3.4.1 Methods of Drug Loading unto Electrospun fibers

Several methods can be used in order to incorporate antibacterial drugs into nanofibers.

1. One of the most common methods is to mix the drug with the polymer solution directly following the electrospun fibers. This method does not require any

additional steps and is one of the simplest systems to obtain effective nanofibers as long as the drug and the polymer lipophilic or hydrophilic interactions are considered (Zeng et al. 2005).

2. The drug is mixed with the polymer solution, as per method 1, and another polymer electrospun layer is added to encapsulate the drug and act as a shell. This method is particularly useful for sensitive drugs. In addition, shell layers improve the sustainable release of the drug and overcome the initial rush initial release typical on drug delivery systems of nanofibers produced with electrospinning. This method is effective for the delivery of active pharmaceutical ingredients and permits a biphasic drug release (Miao and Liu 2015). The effective prolonged release of core-shell structure is demonstrated by Zhang et al. (2006b), and core-shell nanofibers BSA loaded onto PEG slow the release of BSA for one month. In addition, this technique shows improved adhesion to fibers allowing uniform fiber structure and the protection of the drug in the early activity with the biological ambient (Miao and Liu 2015).
3. Another method is where nanoparticles of drug are loaded onto the polymer and finally electrospun forming the fiber matrix. Due to the specific properties that are obtained by some materials at nanoscale, such as silver nanoparticles (Zhao et al. 2012) and bioactive europium-doped hydroxyapatite (Hap:Eu3+) (Hou et al. 2009), it is necessary to process these materials to obtain nanoparticles before processing the electrospinning.
4. Adsorption of the drug by immersing the fiber mats into a required amount of drug. This method can be achieved by using nanofiber mats that have a high surface, resulting in greater drug loading amount. This method allows immediate release of drugs from the surface of the scaffold and allows facile dosage control (Yoo et al. 2009). Chen et al. (2007) developed a PLA nanofiber immersed in TiO₂ nanoparticles. Subsequently, the authors immersed these nanofiber mats in daunorubicin drug, for the treatment of cancer. The AFM results show that after immersed in daunorubicin, the TiO₂ nanoparticles and drug packed together and formed spherical particles on PLA nanofibers. This surface incorporated with anticancer drug can adhere to the surface of the targeted cancer cells and approach the damaged cell surface slightly improving the metabolic system.
5. Immobilization of the drug using surface activation on the polymer mats and following immersion in a required amount of drug (Yoo et al. 2009). Immobilization of bioactive molecules on the exterior of electrospinning nanofibers is also performed to produce reactive functional groups. Owing to benefits of polymers process, greater selection of molecules with distinct biological features can be immobilized onto the nanofiber mat without compromising the bulk properties. Chemical immobilization reduces release rate of the biomolecule, but also allows a precise control (Goonoo et al. 2014). The immobilization can be performed either by physical and chemical methods (Yoo et al. 2009); however, it is usually done with chemical method since the drugs are covalently attached to nanofibers and they are not easily removed from this modified nanofiber mat when incubated over long periods of time. Zomer Volpato et al. (2012)

tested chitosan nanofiber mats where it was surface activated and coated with heparin-containing polyelectrolyte complex nanoparticles (PCN) which presents basic fibroblast growth factor (FGF-2). The PCN helps protect FGF-S for over 30 days, and it could be modulated.

6. Drug nanoparticles and the polymer solutions are electrospun in a side-by-side method to form a biphasic layer of fiber mats. In this method, two liquids (polymer and drug solutions) are loaded in two parallel metal capillaries. These form an interesting morphology behavior (Liu et al. 2007). Such fibers are also called Janus fibers (Yu et al. 2016). However, with different nozzles, the fiber is formed with the junction of the drug and the polymer. In addition, the drug is trapped between each fiber connection.

Yu et al. (2016) tested a new design of using a Teflon barrier between the nozzles in the side-by-side method, and it was possible to observe for the same fiber two different morphologies with a poorly soluble drug amorphaously distributed, with biphasic controlled release and achieving an initial burst and a slower sustained release phase.

All these methods are different approaches that can be used to incorporate various active pharmaceutical ingredients (API) in electrospun fibers that can control the release profile through changes in the fibers morphology, porosity, and composition.

3.4.2 Choice of Polymer/Hydrogels for Nanofibers in Drug Delivery Systems

Target-drug delivery nanofibers can be produced by using matrices with either biodegradable or non-degradable polymers. The drug release mechanism may vary depending of the type of polymer, diffusion for non-degradable and matrix erosion for biodegradable (Pillay et al. 2013). The attainable delivery of the drug can be achieved depending on the polymer used. However, the parameters polymer type, solvent, and drug compatibility are important process variables when designing stable nanofibers (Zeng et al. 2005; Pillay et al. 2013). However, recent studies have shown that it is possible to design hydrophobic drug in electrospun carriers (Laha et al. 2016) without losing the properties of the polymer matrix.

The release of drug in nanofibers produced by electrospinning is controlled by diffusion of drug and/or degradation of the polymer matrix (Cui et al. 2006; Loh et al. 2010; Laha et al. 2016). However, Laha et al. (2016) tested the effect of cross-link on hydrophobic drug-loaded gelatin nanofibers. Laha et al. (2016) found that nanofibers in the polymer matrix, without cross-linking, usually led to deficient exchanges with the poorly water-soluble drug molecules and as such, the hydrophilic nanofiber mat result in rapid release of drug within few hours. When cross-link was achieved on the nanofiber mats, their swelling nature and osmotic behavior provided the principal mechanism for delivery of the hydrophobic drug in the medium and consequently, even at longer periods of time, and there was

sustained release of drug as it diffused to the release medium through the carrier gradually (Laha et al. 2016).

3.4.3 Electrospun Nanofibers that Contain Natural Products for Drug Delivery Systems and Tissue Engineering Applications

Recently, blended nanofibers with plant-derived natural biomaterials have gathered great interest since it is possible to incorporate the curative, regenerative, antimicrobial, and anti-inflammatory properties of plants with the incorporation of good mechanical properties and slow biodegradation of synthetic polymers. One of the advantages of blending plant-derived materials into polymers is that plants have usually large molecular sizes and most compounds are unable to cross the lipid membranes of the cells which results in poor adsorption and loss of bioavailability and efficacy (Venugopal et al. 2014). Electrospun fibers deliver the active ingredients of the plants at sufficient concentration during the entire treatment period to the host site (Venugopal et al. 2014).

Many plants have been tested in electrospun nanofibers for drug delivery, and as example there is *Aloe vera*—antioxidant having good medicinal properties for tissue engineering. Nanofibers with *Aloe vera* show that human dermal fibroblasts can have better and faster attachment, proliferation, and guided growth (Tam et al. 2014). Moreover, it can accelerate the healing of open wounds in type 2 diabetic radiation-exposed rats (Venugopal et al. 2014).

Asian ginseng (Panax ginseng root) has numerous applications for central nervous systems, cardiovascular and human skin applications (Lee et al. 2007). Panax ginseng extracts can also promote collagen in human dermal fibroblast cells (Lee et al. 2007; Pajoumshariati et al. 2015) and positive effect on osteogenesis and cell proliferation. On nanofiber scaffolds, (Pajoumshariati et al. 2015) results indicate that ginseng extracts show an improvement in cell attachment and proliferation, and it also enhanced the MSCs osteogenic differentiation with high level of calcium content deposited on the surface of fibers which shows a potential candidate for bone tissue engineering.

The range of nanofibers medicinal plant is vast, and this field has enormous potential.

3.4.4 Electrospun Nanofibers with Drugs for Tissue Engineering Applications

In addition to bone regeneration that nanofibers can induce, drug loading can be added. This is of interest since the number of patients with infections is rising owing to the risk of bacterial contamination on the implant (Zimmerli et al. 2004). Infections associated with guided tissue regeneration (GTR) and guided bone regeneration (GBR) implants are mainly caused by anaerobic bacterial infections (Ulubayram et al. 2015). In this way, nanofiber scaffolds have been currently used

as an anti-infection barrier with loadings of various different drugs such as metronidazole (MNA) and silver nanoparticles, and since the barrier had a sustainable release of those drugs, the membranes maintained its antibacterial effect for a long term (Xue et al. 2014). In addition, recent studies have shown that it is also possible to obtain a biphasic release kinetics with good antibiotic encapsulation ($\sim 75\text{--}100\%$) on PLGA electrospun fibers; the researchers used 10% (w:w) fusidic acid and 5% (w:w) rifampicin which help reduce the number of adherent bacteria by 99.9% in an in vivo rodent model of implant associated infection (Gilchrist et al. 2013; Ulubayram et al. 2015).

3.4.5 Drug-Encapsulated Nanofibers for Wound Recovery

Nanofiber scaffolds and hydrogel nanofibers have been successfully employed as vehicles for antibacterial agents for wound recovery (Lee and Yoo 2008; Choi et al. 2015; Vashisth et al. 2016). Antimicrobial agents are preferred to tailor the role in the wound healing process, and preferably such products usually must protect against gram-negative, gram-positive, and antibiotic-resistant bacteria. One natural product that has protection from gram-negative and gram-positive is propolis (de Lima et al. 2015b), and from our knowledge, it has not been overlooked as nanofiber scaffolds. On the other hand, strong antibiotics have been encapsulated into the nanofiber scaffolds, such as neomycin (Nitanan et al. 2013), ampicillin (Sabitha and Rajiv 2015), ciprofloxacin (Canillas et al. 2015). Cefixime is a very effective antibactericidal antibiotic for *Escherichia coli* and *Staphylococcus aureus* bacterial strains, which are very common in wound infections (Bergeron and Turcotte 1986; Arshad et al. 2012). Shahzad et al. produced nanofiber mats of chitosan, PVA, and HAp with Cefixime for wound healing, and the nanofibers were cross-linked via freeze-thawed method, freezing the mats at $-80\text{ }^{\circ}\text{C}$ for 24 h; freeze dried to form porous scaffolds and finally heat treated at $80\text{ }^{\circ}\text{C}$ for 10 min. Shahzad et al. demonstrated that heat treatment affects the structure of the mats, has excellent interconnected porous structure, high swelling capabilities with sustained release of Cefixime, inhibition against *S. aureus* and *E. coli* and cytocompatibility with VERO cell line (Shahzad et al. 2015). Ciprofloxacin has also been studied with PVA and PVA/PAA hydrogel structures for the objective of reducing infection against osteomyelitis (Canillas et al. 2015); however, its investigation still needs to be analyzed for nanofibers.

4 Recent Strategy Developments in Electrospinning for Drug Delivery

Although many works have been described in terms of drug delivery on wound healing and tissue engineering, it still needs more investigation in terms of poorly water-soluble drugs and localized targeting delivery. The effect of initial burst

release also needs to be improved, so the next session describes innovations on recent fronts of targeting and poorly water-soluble drugs.

4.1 *Multilayered Nanofibers*

The ability to engineer drug release produced by nanofibers can also be improved or modified by the polymers matrix. If the drug is incorporated in separate nanofiber matrix, the diffusion is different and can promote a controlled release of the drug (Wang et al. 2010d; Huang et al. 2012). In this manner, complex nanofiber mats can be produced with various polymers to attain multiphased drug delivery. In this configuration, after the first layer of electrospun is deposited with the first polymer, another polymer is sequentially deposited on the same collector. This process can be repeated multiple times to produce meshes of multilayered fibers with ordered structure and different kinds of polymer. Recently, controlled release systems for oral delivery of poorly water-soluble drug have been studied with multilayered nanofibers, such as ketoprofen (KET) incorporated in a trilayered electrospun with two different polymers (Huang et al. 2012).

In addition, a recently new triaxial electrospinning strategy has been adopted with a gradual layered structure mesh that is dependent on the various working fluids containing varied concentrations of the drug which was designed to incrementally increase the content of drug moving from the exterior of the fibers inwards resulting in a gradient distribution of the drug—linear release of KET. By incorporating this formulation into an enteric-coated capsule, a linear release colon-targeted oral drug delivery system can be produced as shown in Fig. 6.

4.2 *Hollow and Core–Shell Electrospun Fibers*

In contrast to solid nanofibers, the hollow cores have interesting advantages in terms of higher specific surface area, lower density, and multiphase interfaces (Wu et al. 2011). Hollow spheres as compared to normal nanoscaffolds have gathered interest as drug delivery systems owing to this hollow core can encapsulate large amounts of drugs. In addition, it also controls the release rate, to prevent the initial burst and short-term release that occurs in solid nanofibers (Wang et al. 2010c). Wu et al. created a hollow hydroxyapatite fiber for protein delivery systems, the hydroxyapatite nanofibers produced an ultrafine fiber diameter with interconnected pores providing large specific surface area and demonstrated great protein adsorption ability with long-term sustained release. However, hollow fibers have poor mechanical properties (Kang et al. 2015). To overcome the deficiencies of this technique, core–shell nanofibers have been formed on the exterior of the hollow

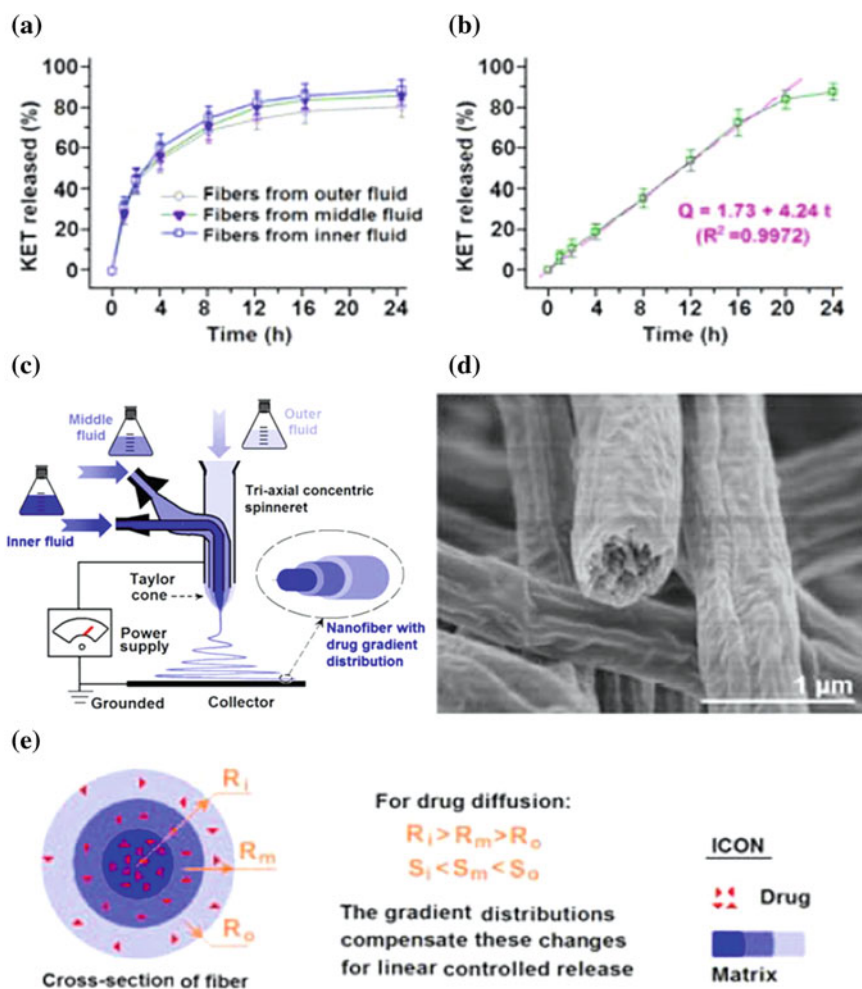


Fig. 6 **a** in vitro dissolution test results for KET incorporated in each monolithic nanofibers and **b** the tri-layer nanofibers, **c** a schematic of the tri-axial electrospinning process **d** FESEM images of the tri-layer nanofibers after release of all the KET loading, and **e** a diagram explaining how the gradient drug distribution can yield a linear release profile. Adapted with permission from Yu et al. (2015). Copyright (2016) American Chemical Society

fibers (Kang et al. 2015). The principle behind using core-shell fibers as a layer on hollow fibers was that since large quantities of drugs can be encapsulated onto the hollow fibers, it might be useful to protect them, in which the core-shell technique preserves the biological activity of the drug (Su et al. 2012; Zhang et al. 2013).

4.3 *Patterned and Alignment Structures of Nanofibers*

There are several methods to produce nanofibers with controllable patterns (Zhang and Chang 2007), and as a simple method, it is based on the theory that the orientation of nanofibers is affected by the topography of the collector, so a patterned nanofibrous scaffold can be generated by using a patterned conductive collector (Zhang and Chang 2007; Li et al. 2014). Alternating the patterned collector and distribution, nanofibers can be assembled into well-ordered nanofiber meshes with both types of topographies, random and parallel alignment existing in the same mesh (Daming and Jiang 2008; Wang et al. 2009b).

The orientation effect and pattern on nanofiber have also been investigating for drug delivery applications. Results show that the drug delivery compartment can be adjusted by the surface wettability of the drug carrier. Meng et al. (2011) showed that aligned scaffolds of nanofibers had a lower release rate compared to random orientation, suggesting that alignment of fibers could also influence the drug release.

5 **Conclusion and Future Perspective**

Nanofibers produced by electrospinning are versatile materials that can have many applications in the biomedical field. Nevertheless, polymer jets are relatively unstable, so controlling the solution and electrospinning parameters is vitally important to obtain uniform nanofibers.

The electrospun nanofiber scaffolds mimic the natural ECM, and this feature suggests that the materials are ideal candidates for tissue engineering. Presently, the focus and specific knowledge on different tissues of the body is helping for further progression in this field immensely. Such knowledge is helping to achieve regeneration of tissues at a relatively fast rate. Nonetheless, the designed scaffold needs appropriate properties for the application intended, so a deep understanding of the nanofibrous scaffold material is crucial to application of the technologies. Currently, the blend of natural with synthetic polymers offers the appropriate properties for biomedical applications. Furthermore, the incorporation of nanofibers with hydrogels seems to be a solution for the current problems and challenges in this particular field.

The control of the nanofiber diameter, packing, orientation, and 3D shape impacts on different tissues environment. This will direct effect cell behaviors such as attachment, orientation, proliferation, and migration. For example, cartilage has three different layers and requires a complex nanofibrous scaffold with varying porosities and alignment. However, this field still needs further investigation for better understanding on how tissue regeneration is impacted by physiological signals.

Nanofibers can also incorporate drugs by different methods, and it can not only help in terms of tissue engineering by creating antimicrobial barriers (Huang et al. 2012; Xue et al. 2014) but also help on wound healing. Hydrogel nanofibers are suitable candidates for wound healing applications, and their swelling ability coupled with permeability for gaseous transfers can promote a perfect condition for healing environment. In this manner, the ability to encapsulate drugs and control the release rate can reduce infections. As technology advances and studies progress, novel techniques for incorporation of drugs in specific target delivery will be at the forefront. The field of drug delivery on nanofibers impacts on the main current problems on biomedical field such as poorly water-soluble drugs and biofilms of bacteria (Ahire et al. 2015; Paaver et al. 2015).

References

- Abdal-Hay A, Hussein KH, Casertari L et al (2016) Fabrication of novel high performance ductile poly(lactic acid) nanofiber scaffold coated with poly(vinyl alcohol) for tissue engineering applications. *Mater Sci Eng, C* 60:143–150. <https://doi.org/10.1016/j.msec.2015.11.024>
- Ahire JJ, Neveling DP, Hattings M, Dicks LMT (2015) Ciprofloxacin-Eluting nanofibers inhibits biofilm formation by *Pseudomonas aeruginosa* and a methicillin-resistant *Staphylococcus aureus*. *PLoS ONE* 10:1–13. <https://doi.org/10.1371/journal.pone.0123648>
- Alvarez Perez MA, Guarino V, Cirillo V, Ambrosio L (2012) In vitro mineralization and bone osteogenesis in poly(ϵ -caprolactone)/gelatin nanofibers. *J Biomed Mater Res A* 100:3008–3019. <https://doi.org/10.1002/jbm.a.34233>
- Alvarez OM, Mertz PM, Eaglstein WH (1983) The effect of occlusive dressings on collagen synthesis and re-epithelialization in superficial wounds. *J Surg Res* 35:142–148
- Anitha A, Sowmya S, Kumar PTS et al (2014) Chitin and chitosan in selected biomedical applications. *Prog Polym Sci*. <https://doi.org/10.1016/j.progpolymsci.2014.02.008>
- Araujo JV, Martins A, Leonor IB, et al (2008) Surface controlled biomimetic coating of polycaprolactone nanofiber meshes to be used as bone extracellular matrix analogues. *J Biomater Sci Polym Ed* 19:1261–78. <https://doi.org/10.1163/156856208786052335>
- Arshad HM, Mohiuddin OA, Bilal M (2012) Comparative in vitro antibacterial analysis of different brands of cefixime against clinical isolates of *Staphylococcus aureus* and *Escherichia coli*. 02:109–113
- Badami AS, Kreke MR, Thompson MS et al (2006) Effect of fiber diameter on spreading, proliferation, and differentiation of osteoblastic cells on electrospun poly(lactic acid) substrates. *Biomaterials* 27:596–606. <https://doi.org/10.1016/j.biomaterials.2005.05.084>
- Baker BM, Gee AO, Metter RB et al (2008) The potential to improve cell infiltration in composite fiber-aligned electrospun scaffolds by the selective removal of sacrificial fibers. *Biomaterials* 29:2348–2358. <https://doi.org/10.1016/j.biomaterials.2008.01.032>
- Becerra J, Andrades JA, Guerado E et al (2010) Articular cartilage: structure and regeneration. *Tissue Eng Part B Rev* 16:617–627
- Berger FM, Ludwig BJ, Wielich KH (1953) The hydrophilic and acid binding properties of alginates. *Am J Dig Dis* 20:39–42
- Berger J, Reist M, Mayer JM et al (2004) Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. *Eur J Pharm Biopharm* 57:19–34. [https://doi.org/10.1016/S0939-6411\(03\)00161-9](https://doi.org/10.1016/S0939-6411(03)00161-9)

- Bergeron MG, Turcotte A (1986) penetration of cefixime into fibrin clots and in vivo efficacy against *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. *Antimicrob Agents Chemother* 30:913–916
- Bhardwaj N, Kundu SC (2010) Electrospinning: a fascinating fiber fabrication technique. *Biotechnol Adv* 28:325–347. <https://doi.org/10.1016/j.biotechadv.2010.01.004>
- Binulal NS, Natarajan A, Menon D et al (2014) PCL-gelatin composite nanofibers electrospun using diluted acetic acid-ethyl acetate solvent system for stem cell-based bone tissue engineering. *J Biomater Sci Polym Ed* 25:325–340. <https://doi.org/10.1080/09205063.2013.859872>
- Bock N, Dargaville TR, Woodruff MA (2012) Electrospaying of polymers with therapeutic molecules: state of the art. *Prog Polym Sci* 37:1510–1551. <https://doi.org/10.1016/j.progpolymsci.2012.03.002>
- Bosworth LA, Turner LA, Cartmell SH (2013) State of the art composites comprising electrospun fibres coupled with hydrogels: a review. *Nanomed Nanotechnol Biol Med* 9:322–335. <https://doi.org/10.1016/j.nano.2012.10.008>
- Brown TD, Dalton PD, Hutmacher DW (2011) Direct writing by way of melt electrospinning. *Adv Mater* 23:5651–5657. <https://doi.org/10.1002/adma.201103482>
- Cai YZ, Zhang GR, Wang LL, et al (2012) Novel biodegradable three-dimensional macroporous scaffold using aligned electrospun nanofibrous yarns for bone tissue engineering. *J Biomed Mater Res A* 100:1187–1194. <https://doi.org/10.1002/jbm.a.34063>
- Canillas M, de Lima GG, Rodríguez MA, et al (2015) Bioactive composites fabricated by freezing-thawing method for bone regeneration applications. *J Polym Sci Part B Polym Phys*. <https://doi.org/10.1002/polb.23974>
- Casper CL, Stephens JS (2004) Controlling surface morphology of electrospun polystyrene fibers: effect of humidity and molecular weight in electrospinning process. *Macromolecules* 37:573–578
- Chan CK, Liao S, Li B et al (2009) Early adhesive behavior of bone-marrow-derived mesenchymal stem cells on collagen electrospun fibers. *Biomed Mater* 4:035006. <https://doi.org/10.1088/1748-6041/4/3/035006>
- Chaterji S, Kwon IK, Park K (2007) Smart polymeric gels: redefining the limits of biomedical devices. *Prog Polym Sci* 32:1083–1122. <https://doi.org/10.1016/j.progpolymsci.2007.05.018>
- Chen C, Lv G, Pan C et al (2007) Poly(lactic acid) (PLA) based nanocomposites—a novel way of drug-releasing. *Biomed Mater* 2:L1–L4. <https://doi.org/10.1088/1748-6041/2/4/L01>
- Chen G, Lv Y (2015) Immobilization and application of electrospun nanofiber scaffold-based growth factor in bone tissue engineering. *Curr Pharm Des* 21:1967–1978
- Choi JS, Kim HS, Yoo HS (2015) Electrospinning strategies of drug-incorporated nanofibrous mats for wound recovery. *Drug Deliv Transl Res* 5:137–145. <https://doi.org/10.1007/s13346-013-0148-9>
- San Choi J, Lee SJ, Christ GJ, et al (2008) The influence of electrospun aligned poly (ϵ -caprolactone)/collagen nanofiber meshes on the formation of self-aligned skeletal muscle myotubes. *Biomaterials* 29:2899–2906. <https://doi.org/10.1016/j.biomaterials.2008.03.031>
- Christopherson GT, Song H, Mao HQ (2009) The influence of fiber diameter of electrospun substrates on neural stem cell differentiation and proliferation. *Biomaterials* 30:556–564. <https://doi.org/10.1016/j.biomaterials.2008.10.004>
- Chua K-N, Chai C, Lee P-C et al (2006) Surface-aminated electrospun nanofibers enhance adhesion and expansion of human umbilical cord blood hematopoietic stem/progenitor cells. *Biomaterials* 27:6043–6051. <https://doi.org/10.1016/j.biomaterials.2006.06.017>
- Chuachamsai A, Lertviriyasawat S, Danwanichakul P (2008) Spinnability and defect formation of chitosan/ poly vinyl alcohol electrospun nanofibers. *Water* 13:24–29
- Cosme JGL, Silva VM, Nunes RRC, Picciani PHS (2016) Development of biobased poly (lactic acid)/epoxidized natural rubber blends processed by electrospinning: morphological, Structural and thermal properties. 210–219

- Cui W, Jin Y, Zhu X, Li X (2008) Electrospun fibrous mats with high porosity as potential scaffolds for skin tissue engineering. *Biomacromol* 9:1795–1801. <https://doi.org/10.1021/bm800476u>
- Cui W, Li X, Zhu X et al (2006) Investigation of drug release and matrix degradation of electrospun poly (DL-lactide) fibers with paracetamol inoculation. *Biomacromol* 7:1623–1629. <https://doi.org/10.1021/bm060057z>
- Daming Z, Jiang C (2008) Electrospinning of three-dimensional nanofibrous tubes with controllable architectures. *Nano Lett* 8:3283–3287. <https://doi.org/10.1021/nl801667s>
- de Lima GG, De Souza RO, Bozzi AD et al (2015a) Extraction method plays critical role in antibacterial activity of propolis-loaded hydrogels. *J Pharm Sci* 105:1248–1257. <https://doi.org/10.1016/j.xphs.2015.12.027>
- de Lima GG, Kanwar D, Macken D, et al (2015) Smart hydrogels: therapeutic advancements in hydrogel technology for smart drug delivery applications. In: Thakur VK, Thakur MK (eds) *Handbook of polymers for pharmaceutical technologies*, 1st edn. Wiley, New York, pp 1–16
- De Vrieze S, Van Camp T, Nelvig A et al (2009) The effect of temperature and humidity on electrospinning. *J Mater Sci* 44:1357–1362. <https://doi.org/10.1007/s10853-008-3010-6>
- Deepthi S, Jeevitha K, Nivedhitha Sundaram M et al (2015) Chitosan-hyaluronic acid hydrogel coated poly(caprolactone) multiscale bilayer scaffold for ligament regeneration. *Chem Eng J* 260:478–485. <https://doi.org/10.1016/j.cej.2014.08.106>
- Deitzel J, Kleinmeyer J, Harris D, Beck Tan N (2001) The effect of processing variables on the morphology of electrospun nanofibers and textiles. *Polymer (Guildf)* 42:261–272. [https://doi.org/10.1016/S0032-3861\(00\)00250-0](https://doi.org/10.1016/S0032-3861(00)00250-0)
- Del Gaudio C, Bianco A, Folin M et al (2009) Structural characterization and cell response evaluation of electrospun PCL membranes: micrometric versus submicrometric fibers. *J Biomed Mater Res A* 89A:1028–1039. <https://doi.org/10.1002/jbm.a.32048>
- Delmar K, Bianco-Peled H (2016) Composite chitosan hydrogels for extended release of hydrophobic drugs. *Carbohydr Polym* 136:570–580. <https://doi.org/10.1016/j.carbpol.2015.09.072>
- Du J, Shintay S, Zhang X (2008) Diameter control of electrospun polyacrylonitrile/iron acetylacetonate ultrafine nanofibers. *J Polym Sci, Part B: Polym Phys* 46:1611–1618
- Dumville JC, O'Meara S, Deshpande S, Speak K (2013) Hydrogel dressings for healing diabetic foot ulcers
- Eda G, Shivkumar S (2007) Bead-to-fiber transition in electrospun polystyrene. *J Appl Polym Sci* 106:475–487
- Ercolani E, Del Gaudio C, Bianco A (2015) Vascular tissue engineering of small-diameter blood vessels: reviewing the electrospinning approach. *J Tissue Eng Regen Med* 9:861–888. <https://doi.org/10.1002/term.1697>
- Felice B, Prabhakaran MP, Zamani M et al (2015) Electrospayed poly(vinyl alcohol) particles: preparation and evaluation of their drug release profile. *Polym Int* 64:1722–1732. <https://doi.org/10.1002/pi.4972>
- Fogaça R, Catalani LH (2013) PVP hydrogel membranes produced by electrospinning for protein release devices. *Soft Mater* 11:61–68. <https://doi.org/10.1080/1539445X.2011.580411>
- Fong H, Fong H, Chun I et al (1999) Beaded nano bers formed during electrospinning. *Polymer (Guildf)* 40:4585–4592
- Franco RA, Min YK, Yang HM, Lee BT (2012) On stabilization of PVPA/PVA electrospun nanofiber membrane and its effect on material properties and biocompatibility. *J Nanomater.* <https://doi.org/10.1155/2012/393042>
- Frenot A, Chronakis IS (2003) Polymer nanofibers assembled by electrospinning. *Curr Opin Colloid Interface Sci* 8:64–75
- Geng X, Kwon OH, Jang J (2005) Electrospinning of chitosan dissolved in concentrated acetic acid solution. *Biomaterials* 26:5427–5432. <https://doi.org/10.1016/j.biomaterials.2005.01.066>

- Gilchrist SE, Lange D, Letchford K et al (2013) Fusidic acid and rifampicin co-loaded PLGA nanofibers for the prevention of orthopedic implant associated infections. *J Control Release* 170:64–73. <https://doi.org/10.1016/j.jconrel.2013.04.012>
- Goonoo N, Bhaw-Luximon A, Jhurry D (2014) Drug loading and release from electrospun biodegradable nanofibers. *J Biomed Nanotechnol* 10:2173–2199. <https://doi.org/10.1166/jbn.2014.1885>
- Greiner A, Wendorff JH (2007) Electrospinning: a fascinating method for the preparation of ultrathin fibers. *Angew Chemie—Int Ed* 46:5670–5703. <https://doi.org/10.1002/anie.200604646>
- Gualandi C, Torricelli P, Panzavolta S et al (2016) An innovative co-axial system to electrospin in situ crosslinked gelatin nanofibers. *Biomed Mater* 11:025007. <https://doi.org/10.1088/1748-6041/11/2/025007>
- Guarino V, Cirillo V, Altobelli R, Ambrosio L (2015) Polymer-based platforms by electric field-assisted techniques for tissue engineering and cancer therapy. *Expert Rev Med Devices* 12:113–129. <https://doi.org/10.1586/17434440.2014.953058>
- Gunn J, Zhang M (2010) Polyblend nanofibers for biomedical applications: perspectives and challenges. *Trends Biotechnol* 28:189–197. <https://doi.org/10.1016/j.tibtech.2009.12.006>
- Gupta P, Elkins C, Long TE, Wilkes GL (2005) Electrospinning of linear homopolymers of poly (methyl methacrylate): exploring relationships between fiber formation, viscosity, molecular weight and concentration in a good solvent. *Polymer (Guildf)* 46:4799–4810. <https://doi.org/10.1016/j.polymer.2005.04.021>
- Hager BL, Berry GC (1982) Moderately concentrated solutions of polystyrene. I. Viscosity as a function of concentration, temperature, and molecular weight. *J Polym Sci Polym Phys Ed* 20:911–928
- Hassan CM, Peppas N (2000) Structure and morphology of freeze/thawed PVA hydrogels. *Macromolecules* 33:2472–2479. <https://doi.org/10.1021/ma9907587>
- He L, Liao S, Quan D et al (2010) Synergistic effects of electrospun PLLA fiber dimension and pattern on neonatal mouse cerebellum C17.2 stem cells. *Acta Biomater* 6:2960–2969. <https://doi.org/10.1016/j.actbio.2010.02.039>
- Hodde D, Gerardo-Nava J, Wöhlk V et al (2015) Characterisation of cell-substrate interactions between Schwann cells and three-dimensional fibrin hydrogels containing orientated nanofibre topographical cues. *Eur J Neurosci* 43:376–387. <https://doi.org/10.1111/ejn.13026>
- Hou Z, Yang P, Lian H et al (2009) Multifunctional hydroxyapatite nanofibers and microbelts as drug carriers. *Chem—A Eur J* 15:6973–6982. <https://doi.org/10.1002/chem.200900269>
- Hu J, Li H-Y, Williams GR et al (2016a) Electrospun poly(N-isopropylacrylamide)/ethyl cellulose nanofibers as thermoresponsive drug delivery systems. *J Pharm Sci* 105:1104–1112. [https://doi.org/10.1016/S0022-3549\(15\)00191-4](https://doi.org/10.1016/S0022-3549(15)00191-4)
- Hu J, Tian L, Prabhakaran MP et al (2016b) Fabrication of nerve growth factor encapsulated aligned poly (ϵ -caprolactone) nanofibers and their assessment as a potential neural tissue engineering scaffold. *Polymers (Basel)* 8:54
- Huang C, Chen S, Lai C et al (2006) Electrospun polymer nanofibres with small diameters. *Nanotechnology* 17:1558
- Huang LY, Branford-White C, Shen XX et al (2012) Time-engineered biphasic drug release by electrospun nanofiber meshes. *Int J Pharm* 436:88–96. <https://doi.org/10.1016/j.ijpharm.2012.06.058>
- Huang S, Fu X (2010) Naturally derived materials-based cell and drug delivery systems in skin regeneration. *J Control Release* 142:149–159. <https://doi.org/10.1016/j.jconrel.2009.10.018>
- Hunt TK, Knighton DR, Thakral KK et al (1984) Studies on inflammation and wound healing: angiogenesis and collagen synthesis stimulated in vivo by resident and activated wound macrophages. *Surgery* 96:48–54
- Husain O, Lau W, Edirisinghe M, Parhizkar M (2016) Investigating the particle to fibre transition threshold during electrohydrodynamic atomization of a polymer solution. *Mater Sci Eng, C* 65:240–250. <https://doi.org/10.1016/j.msec.2016.03.076>

- Ishii Y, Sakai H, Murata H (2008) A new electrospinning method to control the number and a diameter of uniaxially aligned polymer fibers. *Mater Lett* 62:3370–3372. <https://doi.org/10.1016/j.matlet.2008.03.038>
- Ito Y, Hasuda H, Kamitakahara M et al (2005) A composite of hydroxyapatite with electrospun biodegradable nanofibers as a tissue engineering material. *J Biosci Bioeng* 100:43–49. <https://doi.org/10.1263/jbb.100.43>
- Jalaja K, Naskar D, Kundu SC, James NR (2016) Potential of electrospun core-shell structured gelatin-chitosan nanofibers for biomedical applications. *Carbohydr Polym* 136:1098–1107. <https://doi.org/10.1016/j.carbpol.2015.10.014>
- Jamadi ES, Ghasemi-Mobarakeh L, Morshed M et al (2016) Synthesis of polyester urethane urea and fabrication of elastomeric nanofibrous scaffolds for myocardial regeneration. *Mater Sci Eng, C* 63:106–116. <https://doi.org/10.1016/j.msec.2016.02.051>
- Kai D, Jin G, Prabhakaran MP, Ramakrishna S (2013) Electrospun synthetic and natural nanofibers for regenerative medicine and stem cells. *Biotechnol J* 8:59–72. <https://doi.org/10.1002/biot.201200249>
- Kai D, Liow SS, Loh XJ (2015) Biodegradable polymers for electrospinning: towards biomedical applications. *Mater Sci Eng, C* 45:659–670. <https://doi.org/10.1016/j.msec.2014.04.051>
- Kang MS, Kim JH, Singh RK et al (2015) Therapeutic-designed electrospun bone scaffolds: mesoporous bioactive nanocarriers in hollow fiber composites to sequentially deliver dual growth factors. *Acta Biomater* 16:103–116. <https://doi.org/10.1016/j.actbio.2014.12.028>
- Karatay O, Dogan M, Uyar T et al (2014) An alternative electrospinning approach with varying electric field for 2-D-aligned nanofibers. *IEEE Trans Nanotechnol* 13:101–108. <https://doi.org/10.1109/TNANO.2013.2293704>
- Khadka DB, Haynie DT (2012) Protein- and peptide-based electrospun nanofibers in medical biomaterials. *Nanomed Nanotechnol Biol Med* 8:1242–1262. <https://doi.org/10.1016/j.nano.2012.02.013>
- Khorshidi S, Solouk A, Mirzadeh H, et al (2015) A review of key challenges of electrospun scaffolds for tissue-engineering applications
- Ki CS, Baek DH, Gang KD et al (2005) Characterization of gelatin nanofiber prepared from gelatin-formic acid solution. *Polymer (Guildf)* 46:5094–5102. <https://doi.org/10.1016/j.polymer.2005.04.040>
- Kim ES, Kim SH, Lee CH (2010) Electrospinning of polylactide fibers containing silver nanoparticles. *Macromol Res* 18:215–221. <https://doi.org/10.1007/s13233-010-0316-4>
- Kim J, Reneker DH (1999) Polybenzimidazole nanofiber produced by electrospinning. *Polym Eng Sci* 39:849–854. <https://doi.org/10.1002/pen.11473>
- Kim KH, Jeong L, Park HN et al (2005) Biological efficacy of silk fibroin nanofiber membranes for guided bone regeneration. *J Biotechnol* 120:327–339. <https://doi.org/10.1016/j.jbiotec.2005.06.033>
- Kim TG, Chung HJ, Park TG (2008) Macroporous and nanofibrous hyaluronic acid/collagen hybrid scaffold fabricated by concurrent electrospinning and deposition/leaching of salt particles. *Acta Biomater* 4:1611–1619. <https://doi.org/10.1016/j.actbio.2008.06.008>
- Klein TJ, Malda J, Sah RL, Huttmacher DW (2009) Tissue engineering of articular cartilage with biomimetic zones. *Tissue Eng Part B Rev* 15:143–157
- Laha A, Yadav S, Majumdar S, Sharma CS (2016) In-vitro release study of hydrophobic drug using electrospun cross-linked gelatin nanofibers 105:481–488
- Lai G-J, Shalumon KT, Chen S-H, Chen J-P (2014) Composite chitosan/silk fibroin nanofibers for modulation of osteogenic differentiation and proliferation of human mesenchymal stem cells. *Carbohydr Polym* 111:288–297. <https://doi.org/10.1016/j.carbpol.2014.04.094>
- Langer R, Peppas NA (2003) Advances in biomaterials, drug delivery, and bionanotechnology. *AIChE J* 49:2990–3006
- Lanza R, Langer R, Vacanti JP (2011) Principles of tissue engineering. Academic press
- Larrondo L, St. John Manley R (1981) Electrostatic fiber spinning from polymer melts. I. Experimental observations on fiber formation and properties. *J Polym Sci Polym Phys Ed* 19:909–920

- Lee J, Jung E, Lee J et al (2007) Panax ginseng induces human Type I collagen synthesis through activation of Smad signaling. *J Ethnopharmacol* 109:29–34. <https://doi.org/10.1016/j.jep.2006.06.008>
- Lee JH, Shin DW, Nam KB et al (2016) Continuous bundles of aligned electrospun PAN nano-fiber using electrostatic spiral collector and converging coil. *Polymer (Guildf)* 84:52–58. <https://doi.org/10.1016/j.polymer.2015.11.046>
- Lee JI, Yoo HS (2008) Biodegradable microspheres containing poly (epsilon-caprolactone)-Pluronic block copolymers for temperature-responsive release of proteins. *Colloids Surf B Biointerfaces* 61:81–87
- Lee P-Y, Li Z, Huang L (2003) Thermosensitive hydrogel as a Tgf- β 1 gene delivery vehicle enhances diabetic wound healing. *Pharm Res* 20:1995–2000
- Leung V, Ko F (2011) Biomedical applications of nanofibers. *Polym Adv Technol* 22:350–365
- Li D, Wang Y, Xia Y (2003) Electrospinning of polymeric and ceramic nanofibers as uniaxially aligned arrays. *Nano Lett* 3:1167–1171. <https://doi.org/10.1021/nl0344256>
- Li D, Xia Y (2004) Electrospinning of nanofibers: reinventing the wheel? *Adv Mater* 16:1151–1170. <https://doi.org/10.1002/adma.200400719>
- Li HY, Xu YC, Xu H, Chang J (2014) Electrospun membranes: control of the structure and structure related applications in tissue regeneration and drug delivery. *J Mater Chem B* 2:5492–5510. <https://doi.org/10.1039/c4tb00913d>
- Li WJ, Mauck RL, Cooper JA et al (2007) Engineering controllable anisotropy in electrospun biodegradable nanofibrous scaffolds for musculoskeletal tissue engineering. *J Biomech* 40:1686–1693. <https://doi.org/10.1016/j.jbiomech.2006.09.004>
- Li Z, Wang C (2013) Effects of working parameters on electrospinning. In: *One-dimensional nanostructures*. Springer, pp 15–28
- Lin T (2011) Nanofibers-production, properties and functional applications. InTech
- Linh NTB, Lee B-T (2012) Electrospinning of polyvinyl alcohol/gelatin nanofiber composites and cross-linking for bone tissue engineering application. *J Biomater Appl* 27:255–266. <https://doi.org/10.1177/0885328211401932>
- Liu W, Thomopoulos S, Xia Y (2012) Electrospun nanofibers for regenerative medicine. *Adv Healthc Mater* 1:10–25. <https://doi.org/10.1002/adhm.201100021>
- Liu Z, Sun DD, Guo P, Leckie JO (2007) An efficient bicomponent TiO₂/SnO₂ nanofiber photocatalyst fabricated by electrospinning with a side-by-side dual spinneret method. *Nano Lett* 7:1081–1085. <https://doi.org/10.1021/nl061898e>
- Loh XJ, Peh P, Liao S et al (2010) Controlled drug release from biodegradable thermoresponsive physical hydrogel nanofibers. *J Control Release* 143:175–182. <https://doi.org/10.1016/j.jconrel.2009.12.030>
- Lubasova D, Niu H, Zhao X, Lin T (2015) Hydrogel properties of electrospun polyvinylpyrrolidone and polyvinylpyrrolidone/poly(acrylic acid) blend nanofibers. *RSC Adv* 5:54481–54487. <https://doi.org/10.1039/C5RA07514A>
- Ma G, Fang D, Liu Y et al (2012) Electrospun sodium alginate/poly(ethylene oxide) core-shell nanofibers scaffolds potential for tissue engineering applications. *Carbohydr Polym* 87:737–743. <https://doi.org/10.1016/j.carbpol.2011.08.055>
- Ma PX (2004) Scaffolds for tissue fabrication. *Mater Today* 7:30–40. [https://doi.org/10.1016/S1369-7021\(04\)00233-0](https://doi.org/10.1016/S1369-7021(04)00233-0)
- Mahoney C, Conklin D, Waterman J, et al (2016) Electrospun Nanofibers of Poly (ϵ -caprolactone)/Depolymerized Chitosan for Respiratory Tissue Engineering Applications. *J Biomater Sci Polym Ed* 1–21
- Mallick SP, Pal K, Rastogi A, Srivastava P (2016) Evaluation of poly(L-lactide) and chitosan composite scaffolds for cartilage tissue regeneration. *Des Monomers Polym* 19:271–282. <https://doi.org/10.1080/15685551.2015.1136535>
- Manna U, Patil S (2009) Borax mediated layer-by-layer self-assembly of neutral poly(vinyl alcohol) and chitosan. *J Phys Chem B* 113:9137–9142. <https://doi.org/10.1021/jp9025333>

- McCullen SD, Autefage H, Callanan A et al (2012) Anisotropic fibrous scaffolds for articular cartilage regeneration. *Tissue Eng Part A* 18:2073–2083. <https://doi.org/10.1089/ten.TEA.2011.0606>
- McKenzie M, Betts D, Suh A et al (2015) Hydrogel-based drug delivery systems for poorly water-soluble drugs. *Molecules* 20:20397–20408. <https://doi.org/10.3390/molecules201119705>
- McMahon RE, Qu X, Jimenez-Vergara AC, et al (2011) Hydrogel—electrospun mesh composites for coronary artery bypass grafts. <https://doi.org/10.1089/ten.tec.2010.0427>
- Meng L, Klinkajon W, K-hasuwan PR et al (2015) Electrospun crosslinked poly(acrylic acid) fiber constructs: towards a synthetic model of the cortical layer of nerve. *Polym Int* 64:42–48. <https://doi.org/10.1002/pi.4793>
- Meng ZX, Zheng W, Li L, Zheng YF (2011) Fabrication, characterization and in vitro drug release behavior of electrospun PLGA/chitosan nanofibrous scaffold. *Mater Chem Phys* 125:606–611. <https://doi.org/10.1016/j.matchemphys.2010.10.010>
- Merkle VM, Tran PL, Hutchinson M et al (2015) Core-shell PVA/gelatin electrospun nanofibers promote human umbilical vein endothelial cell and smooth muscle cell proliferation and migration. *Acta Biomater* 27:77–87. <https://doi.org/10.1016/j.actbio.2015.08.044>
- Merkle VM, Zeng L, Slepian MJ, Wu X (2014) Core-shell nanofibers: integrating the bioactivity of gelatin and the mechanical property of polyvinyl alcohol. *Biopolymers* 101:336–346. <https://doi.org/10.1002/bip.22367>
- Miao Y-E, Liu T (2015) Electrospun biopolymer nanofibers and their composites for drug delivery applications. *Biodegrad Polyesters* 275–298. <https://doi.org/10.1002/9783527656950.ch11>
- Shin Michael, Yoshimoto H, Vacanti JP (2004) In vivo bone tissue engineering using mesenchymal stem cells on a novel electrospun nanofibrous scaffold. *Tissue Eng* 10:33–41. <https://doi.org/10.1089/107632704322791673>
- Mirafteb M, Saifullah AN, Çay A (2015) Physical stabilisation of electrospun poly(vinyl alcohol) nanofibres: comparative study on methanol and heat-based crosslinking. *J Mater Sci* 50:1943–1957. <https://doi.org/10.1007/s10853-014-8759-1>
- Mogoşanu GD, Grumezescu AM (2014) Natural and synthetic polymers for wounds and burns dressing. *Int J Pharm* 463:127–136. <https://doi.org/10.1016/j.ijpharm.2013.12.015>
- Montesano R, Orci L (1988) Transforming growth factor beta stimulates collagen-matrix contraction by fibroblasts: implications for wound healing. *Proc Natl Acad Sci* 85:4894–4897
- Moses H, Gregory R, Michael P (2001) Electrospinning and electrically forced jets. II, Applications
- Nasouri K, Bahrambeygi H, Rabbi A et al (2012) Modeling and optimization of electrospun PAN nanofiber diameter using response surface methodology and artificial neural networks. *J Appl Polym Sci* 126:127–135
- Neamark A, Rujiravanit R, Supaphol P (2006) Electrospinning of hexanoyl chitosan. *Carbohydr Polym* 66:298–305. <https://doi.org/10.1016/j.carbpol.2006.03.015>
- Nguyen MK, Alsberg E (2014) Bioactive factor delivery strategies from engineered polymer hydrogels for therapeutic medicine. *Prog Polym Sci*. <https://doi.org/10.1016/j.progpolymsci.2013.12.001>
- Nitanan T, Akkaramongkolporn P, Rojanarata T et al (2013) Neomycin-loaded poly(styrene sulfonic acid-co-maleic acid) (PSSA-MA)/polyvinyl alcohol (PVA) ion exchange nanofibers for wound dressing materials. *Int J Pharm* 448:71–78. <https://doi.org/10.1016/j.ijpharm.2013.03.011>
- Okamoto M, John B (2013) Synthetic biopolymer nanocomposites for tissue engineering scaffolds. *Prog Polym Sci* 38:1487–1503. <https://doi.org/10.1016/j.progpolymsci.2013.06.001>
- Paaver U, Heinämäki J, Laidmäe I, et al (2015) Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs. *Int J Pharm* 479:252–260. <https://doi.org/10.1016/j.ijpharm.2014.12.024>
- Pajoumshariati S, Yavari SK, Shokrgozar MA (2015) Physical and biological modification of polycaprolactone electrospun nanofiber by panax ginseng extract for bone tissue engineering application. *Ann Biomed Eng* 44:1808–1820. <https://doi.org/10.1007/s10439-015-1478-1>

- Pangon A, Saesoo S, Saengkrit N et al (2016) Hydroxyapatite-hybridized chitosan/chitin whisker bionanocomposite fibers for bone tissue engineering applications. *Carbohydr Polym* 144:419–427. <https://doi.org/10.1016/j.carbpol.2016.02.053>
- Parratt K, Yao N (2013) Nanostructured biomaterials and their applications. *nanomaterials* 3:242–271. <https://doi.org/10.3390/nano3020242>
- Paul W, Sharma CP (2004) Chitosan and alginate wound dressings: a short review. *Trends Biomater Artif Organs* 18:18–23
- Peppas N (2000) Hydrogels in pharmaceutical formulations. *Eur J Pharm Biopharm* 50:27–46. [https://doi.org/10.1016/S0939-6411\(00\)00090-4](https://doi.org/10.1016/S0939-6411(00)00090-4)
- Peppas N a., Sahlin JJ (1996) Hydrogels as mucoadhesive and bioadhesive materials: a review. *Biomaterials* 17:1553–1561. [https://doi.org/10.1016/0142-9612\(95\)00307-x](https://doi.org/10.1016/0142-9612(95)00307-x)
- Persano L, Camposeo A, Tekmen C, Pisignano D (2013) Industrial upscaling of electrospinning and applications of polymer nanofibers: a review. *Macromol Mater Eng* 298:504–520. <https://doi.org/10.1002/mame.201200290>
- Pillay V, Dott C, Choonara YE, et al (2013) A review of the effect of processing variables on the fabrication of electrospun nanofibers for drug delivery applications 22. <https://doi.org/10.1155/2013/789289>
- Prakash S, Khan A, Paul A (2010) Nanoscaffold based stem cell regeneration therapy: recent advancement and future potential. *Expert Opin Biol Ther* 10:1649–1661. <https://doi.org/10.1517/14712598.2010.528387>
- Quarto R, Mastrogiacomo M, Cancedda R et al (2001) Repair of large bone defects with the use of autologous bone marrow stromal cells. *N Engl J Med* 344:385–386
- Quinn JF, Johnston APR, Such GK et al (2007) Next generation, sequentially assembled ultrathin films: beyond electrostatics. *Chem Soc Rev* 36:707–718. <https://doi.org/10.1039/b610778h>
- Rnjak-Kovacina J, Weiss AS (2011) Increasing the pore size of electrospun scaffolds. *Tissue Eng B, Rev* 17:365–372. <https://doi.org/10.1089/ten.teb.2011.0235>
- Rogina A (2014) Electrospinning process: versatile preparation method for biodegradable and natural polymers and biocomposite systems applied in tissue engineering and drug delivery. *Appl Surf Sci* 296:221–230. <https://doi.org/10.1016/j.apsusc.2014.01.098>
- Ruckh TT, Kumar K, Kipper MJ, Popat KC (2010) Osteogenic differentiation of bone marrow stromal cells on poly(ϵ -caprolactone) nanofiber scaffolds. *Acta Biomater* 6:2949–2959. <https://doi.org/10.1016/j.actbio.2010.02.006>
- Sabitha M, Rajiv S (2015) Preparation and characterization of ampicillin-incorporated electrospun polyurethane scaffolds for wound healing and infection control. *Polym Eng Sci* 55:541–548
- Samchenko Y, Ulberg Z, Korotych O (2011) Multipurpose smart hydrogel systems. *Adv Colloid Interface Sci* 168:247–262. <https://doi.org/10.1016/j.cis.2011.06.005>
- Shahzad S, Yar M, Siddiqi SA et al (2015) Chitosan-based electrospun nanofibrous mats, hydrogels and cast films: novel anti-bacterial wound dressing matrices. *J Mater Sci Mater Med* 26:1–12. <https://doi.org/10.1007/s10856-015-5462-y>
- Shalumon KT, Deepthi S, Anupama MS, et al (2015) Fabrication of poly (l-lactic acid)/gelatin composite tubular scaffolds for vascular tissue engineering. *Int J Biol Macromol* 72:1048–1055. <https://doi.org/10.1016/j.ijbiomac.2014.09.058>
- Shenoy SL, Bates WD, Frisch HL, Wnek GE (2005a) Role of chain entanglements on fiber formation during electrospinning of polymer solutions: good solvent, non-specific polymer-polymer interaction limit. *Polymer (Guildf)* 46:3372–3384. <https://doi.org/10.1016/j.polymer.2005.03.011>
- Shenoy SL, Bates WD, Wnek G (2005b) Correlations between electrospinnability and physical gelation. *Polymer (Guildf)* 46:8990–9004. <https://doi.org/10.1016/j.polymer.2005.06.053>
- Shi Q, Fan Q, Ye W et al (2015) Binary release of ascorbic acid and lecithin from core-shell nanofibers on blood-contacting surface for reducing long-term hemolysis of erythrocyte. *Colloids Surfaces B Biointerfaces* 125:28–33. <https://doi.org/10.1016/j.colsurfb.2014.11.013>
- Shin S-Y, Park H-N, Kim K-H et al (2005) Biological evaluation of chitosan nanofiber membrane for guided bone regeneration. *J Periodontol* 76:1778–1784

- Simionescu BC, Ivanov D (2016) Natural and synthetic polymers for designing composite materials. *Handb Bioceram Biocomposites* 233–286
- Steele JAM, McCullen SD, Callanan A et al (2014) Combinatorial scaffold morphologies for zonal articular cartilage engineering. *Acta Biomater* 10:2065–2075. <https://doi.org/10.1016/j.actbio.2013.12.030>
- Stefani I, Cooper-White JJ (2016) Development of an in-process UV-crosslinked, electrospun PCL/aPLA-co-TMC composite polymer for tubular tissue engineering applications. *Acta Biomater* 36:231–240. <https://doi.org/10.1016/j.actbio.2016.03.013>
- Stitzel J, Liu J, Lee SJ et al (2006) Controlled fabrication of a biological vascular substitute. *Biomaterials* 27:1088–1094. <https://doi.org/10.1016/j.biomaterials.2005.07.048>
- Su Y, Su Q, Liu W et al (2012) Controlled release of bone morphogenetic protein 2 and dexamethasone loaded in core-shell PLLACL-collagen fibers for use in bone tissue engineering. *Acta Biomater* 8:763–771. <https://doi.org/10.1016/j.actbio.2011.11.002>
- Taepaiboon P, Rungsardthong U, Supaphol P (2006) Drug-loaded electrospun mats of poly(vinyl alcohol) fibres and their release characteristics of four model drugs. *Nanotechnology* 17:2317–2329. <https://doi.org/10.1088/0957-4484/17/9/041>
- Tam K, Cheyyatraviendran S, Venugopal J et al (2014) A nanoscaffold impregnated with human wharton's jelly stem cells or its secretions improves healing of wounds. *J Cell Biochem* 115:794–803
- Tao J, Shivkumar S (2007) Molecular weight dependent structural regimes during the electrospinning of PVA. *Mater Lett* 61:2325–2328. <https://doi.org/10.1016/j.matlet.2006.09.004>
- Temenoff JS, Mikos AG (2014) *Biomaterials: the intersection of biology and materials science*
- Thomas S (1990) *Wound management and dressings*. Pharmaceutical Press
- Torres-Giner S, Gimeno-Alcañiz JV, Ocio MJ, Lagaron JM (2009) Comparative performance of electrospun collagen nanofibers cross-linked by means of different methods. *ACS Appl Mater Interfaces* 1:218–223. <https://doi.org/10.1021/am800063x>
- Tsai SW, Liou HM, Lin CJ et al (2012) MG63 osteoblast-like cells exhibit different behavior when grown on electrospun collagen matrix versus electrospun gelatin matrix. *PLoS ONE* 7:1–11. <https://doi.org/10.1371/journal.pone.0031200>
- Uchko CJ, Chen LC, Shen Y, Martina DC (1999) Processing and microstructural characterization of porous biocompatible protein polymer thin films. *Polymer (Guildf)* 40:7397–7407. [https://doi.org/10.1016/S0032-3861\(98\)00866-0](https://doi.org/10.1016/S0032-3861(98)00866-0)
- Ulubayram K, Calamak S, Shahbazi R, Eroglu I (2015) Nanofibers based antibacterial drug design, delivery and applications. *Curr Pharm Des* 21:1930–1943
- Van Vlierberghe S, Dubrue P, Schacht E (2011) Biopolymer-based hydrogels as scaffolds for tissue engineering applications: a review. *Biomacromol* 12:1387–1408. <https://doi.org/10.1021/bm200083n>
- Vaquette C, Cooper-White JJ (2011) Increasing electrospun scaffold pore size with tailored collectors for improved cell penetration. *Acta Biomater* 7:2544–2557. <https://doi.org/10.1016/j.actbio.2011.02.036>
- Vashisth P, Pruthi V (2016) Synthesis and characterization of crosslinked gellan/PVA nanofibers for tissue engineering application. *Mater Sci Eng, C* 67:304–312. <https://doi.org/10.1016/j.msec.2016.05.049>
- Vashisth P, Srivastava AK, Nagar H et al (2016) Drug functionalized microbial polysaccharide based nanofibers as transdermal substitute. *Nanomed Nanotechnol Biol Med* 12:1375–1385. <https://doi.org/10.1016/j.nano.2016.01.019>
- Venugopal JR, Sridhar S, Ramakrishna S (2014) Electrospun plant-derived natural biomaterials for tissue engineering. *Plant Sci Today* 1:151–154. <https://doi.org/10.14719/pst.2014.1.3.65>
- Veronese FM, Pasut G (2005) PEGylation, successful approach to drug delivery. *Drug Discov Today* 10:1451–1458. [https://doi.org/10.1016/S1359-6446\(05\)03575-0](https://doi.org/10.1016/S1359-6446(05)03575-0)
- Visser J, Melchels FPW, Jeon JE et al (2015) Reinforcement of hydrogels using three-dimensionally printed microfibrils. *Nat Commun* 6:6933. <https://doi.org/10.1038/ncomms7933>

- Wang HB, Mullins ME, Cregg JM et al (2010a) Varying the diameter of aligned electrospun fibers alters neurite outgrowth and Schwann cell migration. *Acta Biomater* 6:2970–2978. <https://doi.org/10.1016/j.actbio.2010.02.020>
- Wang J, Valmikinathan CM, Liu W et al (2010b) Spiral-structured, nanofibrous, 3D scaffolds for bone tissue engineering. *J Biomed Mater Res A* 93:753–762. <https://doi.org/10.1002/jbm.a.32591>
- Wang KW, Zhu YJ, Chen XY et al (2010c) Flower-like hierarchically nanostructured hydroxyapatite hollow spheres: facile preparation and application in anticancer drug cellular delivery. *Chem—Asian J* 5:2477–2482. <https://doi.org/10.1002/asia.201000463>
- Wang L, Khor E, Wee A, Lim LY (2002) Chitosan-alginate PEC membrane as a wound dressing: assessment of incisional wound healing. *J Biomed Mater Res* 63:610–618
- Wang Q, Ogawa K, Toma K, Tamiaki H (2009a) Smart pH sensitive luminescent hydrogel based on Eu(III) β -diketonate complex and its enhanced photostability. *J Photochem Photobiol A Chem* 201:87–90. <https://doi.org/10.1016/j.jphotochem.2008.10.005>
- Wang Y, Shi H, Qiao J, et al (2014) Electrospun tubular scaffold with circumferentially aligned nano fibers for regulating smooth muscle cell growth. doi:<http://pubs.acs.org/doi/abs/10.1021/am405556x>
- Wang Y, Wang B, Qiao W, Yin T (2010d) A novel controlled release drug delivery system for multiple drugs based on electrospun nanofibers containing nanoparticles. *J Pharm Sci* 99:4805–4811. <https://doi.org/10.1002/jps.22189>
- Wang Y, Wang G, Chen L et al (2009b) Electrospun nanofiber meshes with tailored architectures and patterns as potential tissue-engineering scaffolds. *Biofabrication* 1:15001–15009. <https://doi.org/10.1088/1758-5082/1/1/015001>
- Weis J, May R, Schröder JM (1994) Fine structural and immunohistochemical identification of perineurial cells connecting proximal and distal stumps of transected peripheral nerves at early stages of regeneration in silicone tubes. *Acta Neuropathol* 88:159–165
- Weng L, Xie J (2015) Smart electrospun nanofibers for controlled drug release : recent advances and new perspectives. 1944–1959. <https://doi.org/10.2174/1381612821666150302151959>
- Wolf MT, Dearth CL, Sonnenberg SB et al (2015) Naturally derived and synthetic scaffolds for skeletal muscle reconstruction. *Adv Drug Deliv Rev* 84:208–221. <https://doi.org/10.1016/j.addr.2014.08.011>
- Wozniak MA, Modzelewska K, Kwong L, Keely PJ (2004) Focal adhesion regulation of cell behavior. *Biochim Biophys Acta (BBA)-Mol Cell Res* 1692:103–119
- Wu J, Huang C, Liu W et al (2014) Cell infiltration and vascularization in porous nanoyarn scaffolds prepared by dynamic liquid electrospinning. *J Biomed Nanotechnol* 10:603–614
- Wu L, Dou Y, Lin K et al (2011) Hierarchically structured nanocrystalline hydroxyapatite assembled hollow fibers as a promising protein delivery system. *Chem Commun (Camb)* 47:11674–11676. <https://doi.org/10.1039/c1cc14709a>
- Xu CY, Inai R, Kotaki M, Ramakrishna S (2004) Aligned biodegradable nanofibrous structure: a potential scaffold for blood vessel engineering. *Biomaterials* 25:877–886. [https://doi.org/10.1016/S0142-9612\(03\)00593-3](https://doi.org/10.1016/S0142-9612(03)00593-3)
- Xu H, Li H, Chang J (2013) Controlled drug release from a polymer matrix by patterned electrospun nanofibers with controllable hydrophobicity. *J Mater Chem B* 1:4182. <https://doi.org/10.1039/c3tb20404a>
- Xu S, Deng L, Zhang J, et al (2015) Composites of electrospun-fibers and hydrogels: a potential solution to current challenges in biological and biomedical field. *J Biomed Mater Res B Appl Biomater* 1–17. <https://doi.org/10.1002/jbm.b.33420>
- Xu X, Zhou G, Li X et al (2016) Solution blowing of chitosan/PLA/PEG hydrogel nanofibers for wound dressing. *Fibers Polym* 17:205–211. <https://doi.org/10.1007/s12221-016-5800-9>
- Xue J, He M, Liu H et al (2014) Drug loaded homogeneous electrospun PCL/gelatin hybrid nanofiber structures for anti-infective tissue regeneration membranes. *Biomaterials* 35:9395–9405. <https://doi.org/10.1016/j.biomaterials.2014.07.060>

- Yamaoka T, Tabata Y, Ikada Y (1994) Distribution and tissue uptake of poly(ethylene glycol) with different molecular weights after intravenous administration to mice. *J Pharm Sci* 83:601–606. <https://doi.org/10.1002/jps.2600830432>
- Yang C, Xu L, Zhou Y et al (2010) A green fabrication approach of gelatin/CM-chitosan hybrid hydrogel for wound healing. *Carbohydr Polym* 82:1297–1305. <https://doi.org/10.1016/j.carbpol.2010.07.013>
- Yang Q, Zhenyu LI, Hong Y et al (2004) Influence of solvents on the formation of ultrathin uniform poly(vinyl pyrrolidone) nanofibers with electrospinning. *J Polym Sci B: Polym Phys* 42:3721–3726. <https://doi.org/10.1002/polb.20222>
- Yang X, Liu Q, Chen X et al (2008) Investigation of PVA/ws-chitosan hydrogels prepared by combined γ -irradiation and freeze-thawing. *Carbohydr Polym* 73:401–408. <https://doi.org/10.1016/j.carbpol.2007.12.008>
- Yang Y, Wimpenny I, Ahearne M (2011) Portable nanofiber meshes dictate cell orientation throughout three-dimensional hydrogels. *Nanomed Nanotechnol Biol Med* 7:131–136. <https://doi.org/10.1016/j.nano.2010.12.011>
- Yao S, Wang X, Liu X et al (2013) Effects of ambient relative humidity and solvent properties on the electrospinning of pure hyaluronic acid nanofibers. *J Nanosci Nanotechnol* 13:4752–4758. <https://doi.org/10.1166/jnn.2013.7197>
- Yeo Y, Adil M, Bellas E et al (2007) Prevention of peritoneal adhesions with an in situ cross-linkable hyaluronan hydrogel delivering budesonide. *J Control Release* 120:178–185. <https://doi.org/10.1016/j.jconrel.2007.04.016>
- Yoo HS, Kim TG, Park TG (2009) Surface-functionalized electrospun nanofibers for tissue engineering and drug delivery. *Adv Drug Deliv Rev* 61:1033–1042. <https://doi.org/10.1016/j.addr.2009.07.007>
- Yoshimoto H, Shin YM, Terai H, Vacanti JP (2003) A biodegradable nanofiber scaffold by electrospinning and its potential for bone tissue engineering. *Biomaterials* 24:2077–2082. [https://doi.org/10.1016/S0142-9612\(02\)00635-X](https://doi.org/10.1016/S0142-9612(02)00635-X)
- Yu DG, Li XY, Wang X et al (2015) Nanofibers fabricated using triaxial electrospinning as zero order drug delivery systems. *ACS Appl Mater Interfaces* 7:18891–18897. <https://doi.org/10.1021/acsami.5b06007>
- Yu D-G, Yang C, Jin M et al (2016) Medicated Janus fibers fabricated using a Teflon-coated side-by-side spinneret. *Colloids Surfaces B Biointerfaces* 138:110–116
- Yuan XY, Zhang YY, Dong C, Sheng J (2004) Morphology of ultrafine polysulfone fibers prepared by electrospinning. *Polym Int* 53:1704–1710. <https://doi.org/10.1002/pi.1538>
- Zeng J, Yang L, Liang Q et al (2005) Influence of the drug compatibility with polymer solution on the release kinetics of electrospun fiber formulation. *J Control Release* 105:43–51. <https://doi.org/10.1016/j.jconrel.2005.02.024>
- Zhang C, Yuan X, Wu L et al (2005) Study on morphology of electrospun poly(vinyl alcohol) mats. *Eur Polym J* 41:423–432. <https://doi.org/10.1016/j.eurpolymj.2004.10.027>
- Zhang D, Chang J (2007) Patterning of electrospun fibers using electroconductive templates. *Adv Mater* 19:3662–3667. <https://doi.org/10.1002/adma.200700896>
- Zhang H, Jia X, Han F et al (2013) Dual-delivery of VEGF and PDGF by double-layered electrospun membranes for blood vessel regeneration. *Biomaterials* 34:2202–2212. <https://doi.org/10.1016/j.biomaterials.2012.12.005>
- Zhang YZ, Venugopal J, Huang ZM et al (2006a) Crosslinking of the electrospun gelatin nanofibers. *Polymer (Guildf)* 47:2911–2917. <https://doi.org/10.1016/j.polymer.2006.02.046>
- Zhang YZ, Wang X, Feng Y et al (2006b) Coaxial electrospinning of (fluorescein isothiocyanate-conjugated bovine serum albumin)-encapsulated poly(ϵ -caprolactone) nanofibers for sustained release. *Biomacromol* 7:1049–1057
- Zhao Y, Zhou Y, Wu X et al (2012) A facile method for electrospinning of Ag nanoparticles/poly(vinyl alcohol)/carboxymethyl-chitosan nanofibers. *Appl Surf Sci* 258:8867–8873. <https://doi.org/10.1016/j.apsusc.2012.05.106>

- Zhijiang C, Yi X, Haizheng Y et al (2016) Poly (hydroxybutyrate)/cellulose acetate blend nanofiber scaffolds: preparation, characterization and cytocompatibility. *Mater Sci Eng, C* 58:757–767
- Zhou F, Gong R, Porat I (2009) Mass production of nanofibre assemblies by electrostatic spinning. *Polym Int* 58:331–342
- Ziaee M, Zahedi P, Abdouss M et al (2016) Electrospun poly (N-isopropylacrylamide-co-acrylic acid)/cellulose laurate blend nanofibers containing adapalene: morphology, drug release, and cell culture studies. *Int J Polym Mater Polym Biomater* 65:477–486
- Zilla P, Bezuidenhout D, Human P (2007) Prosthetic vascular grafts: wrong models, wrong questions and no healing. *Biomaterials* 28:5009–5027. <https://doi.org/10.1016/j.biomaterials.2007.07.017>
- Zimmerli W, Trampuz A, Ochsner PE (2004) Prosthetic-joint infections. *N Engl J Med* 351:1645–1654
- Zomer Volpato F, Almodóvar J, Erickson K et al (2012) Preservation of FGF-2 bioactivity using heparin-based nanoparticles, and their delivery from electrospun chitosan fibers. *Acta Biomater* 8:1551–1559. <https://doi.org/10.1016/j.actbio.2011.12.023>