Chapter 5
Electrospun Nanofibers as Carriers in Dermal Drug Delivery

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Contents

Abstract Nanotechnology has opened a new direction in biomedical sciences. Nanomedicine and nanodelivery systems offer multiple benefits in treatment of diseases by site-specific and target-oriented delivery of many drugs. Among the various forms of nanocarrier systems, nanofibers have recently proved to be a versatile carrier system for drug delivery applications due to their attractive properties such as target-specific, prolonged delivery of drugs, and ease of fabrication. Polymeric nanofibers can be produced using several techniques such as phase separation, self-assembly, and electrospinning. Electrospinning is a versatile, cost-effective, and scalable technique using electrostatic forces to produce fine fibers from polymer solutions or melts. The nanofiber production by electrospinning enables higher drug loading and entrapment efficiency compared to other nanodelivery systems prepared by other methods. Electrospun nanofibers can be fabricated from a wide variety of solutions of either natural or synthetic polymers, as well as combinations thereof. The type of the polymer can be chosen depending on the treatment, on the nature of the drug, and on the compatibility with the biological environment. During

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the last several decades, polymeric nanofibers have been explored as controlled drug delivery systems for dermal, transdermal, oral, oromucosal, parenteral, and ocular routes. Recently, electrospun nanofibers have gained more popularity for the topical and transdermal drug delivery and wound dressing applications. Especially, the unique architectural properties like nanoscale morphology, porous structure, and flexibility of electrospun nanofibers make them a suitable option for developing novel wound dressings. However, despite the numerous attractive features of nanofiber composites in drug delivery applications, there are certain major drawbacks which need to be overcome. Drug stability, initial burst release, and scale-up problems foremost require to be solved before bringing nanofiber technology into mainstream drug delivery technologies. In this chapter, first, the basic concepts of electrospinning process and the characterization techniques of electrospun nanofibers are discussed. Then, the most widely used polymers in the composition of drug-loaded nanofibers are presented, and recent applications of nanofibers in dermal drug delivery and wound healing are described.

Keywords Electrospinning · Nanofibers · Polymers · Topical drug delivery · Transdermal drug delivery · Wound healing

5.1 Introduction

Novel drug delivery systems are used to improve the efficiency and safety of active compounds by carrying them on the site of action at a specific rate (Vasita and Katti 2006; Akduman et al. 2016). Particularly, nanocarriers like liposomes, nanoparticles, and nanoemulsions have demonstrated increased drug absorption, penetration, half-life, bioavailability, and stability. Among the many forms of nanocarrier systems, nanofibers have recently proved to be a versatile carrier system for drug delivery applications due to their remarkable properties such as high drug-loading capacity, high encapsulation efficiency, target-specific, prolonged delivery of drugs, and ease of fabrication (Ravikumar et al. 2017).

Polymeric nanofibers are defined as solid fibers with a nanoscale diameter. They can be produced using several techniques such as phase separation, self-assembly, and electrospinning (Melanko et al. 2009). Among these techniques, electrospinning is the mostly preferred one because of its versatility for adaptation to both laboratory- and industrial-scale production processes (Akduman et al. 2016). Electrospun nanofibers can be fabricated from a wide variety of solutions of either natural or synthetic polymers, as well as combinations thereof (Zanin et al. 2011). Natural polymers offer the advantage of being very similar to the macromolecules present in the extracellular matrix (ECM). They are usually biodegradable and biocompatible. Synthetic polymers, on the other hand, have great flexibility in synthesis and modification. In most cases, it is preferable to fabricate composite nanofibers comprising both natural and synthetic polymers (Hu et al. 2014).

The unique properties of electrospun nanofibers such as high surface area to volume ratio and high porosity make them suitable carriers for both hydrophilic and lipophilic drugs, and research studies have been especially focused on topical wound healing and tissue engineering applications recently (Kyzioł et al. 2017). Concerning dermal drug delivery, electrospun nanofibers provide an opportunity for encapsulation of different active agents such as antifungal and antimicrobial therapeutics, antibiotics, proteins, and growth factors (Karthikeyan et al. 2015; Zhao et al. 2016). Drug release rate from nanofiber mats can be tailored by modulation of nanofiber morphology, porosity, and composition. Nanofiber mats can provide sustained drug release, which reduces the application frequency, and consequently increase the patient compliance to the treatment (Goyal et al. 2016; He et al. 2014).

In this chapter, first, the basic concepts of electrospinning process and the characterization techniques of electrospun nanofibers are discussed. Then, the most widely used polymers in the composition of drug-loaded nanofibers are presented, and recent applications of nanofibers in dermal drug delivery and wound healing are described.

5.2 Electrospinning of Nanofibers

Electrospinning is a versatile, cost-effective, and scalable technique using electrostatic forces to produce fine fibers from polymer solutions or melts. Electrospinning was patented firstly by Formhals in 1934 (Frenot and Chronakis 2003). It is a top-down nanomanufacturing process and usually conducted at room temperature with atmosphere conditions. A classical electrospinning setup, shown in Fig. 5.1, consists of three basic components: a syringe pump fitted with a metallic spinneret, a high voltage supply, and a conductive collector (Bhardwaj and Kundu 2010; Liao et al. 2008).

In the electrospinning process, a high voltage is applied to the polymer solution, and with the use of the syringe pump, the polymer solution is delivered to the tip of spinneret at a constant rate (Kamble et al. 2017; Zanin et al. 2011; Zamani et al. 2013). When the electrostatic charge is larger than the surface tension of the polymer droplet at the tip of the nozzle, the droplet elongates to form the "Taylor cone." Then, a fiber jet extrudes from the cone and moves toward the fiber collector (He et al. 2014; Seif et al. 2015). As the solvent evaporates during this process, a mat of ultrafine solid nanofibers is collected as a final product. The evaporation patterns determine the porosity of the nanofibers (Sharma et al. 2015; Frenot and Chronakis 2003).

The nanofiber production by electrospinning enables higher drug loading and entrapment efficiency compared to other nanodelivery systems prepared by other methods (Pelipenko et al. 2015). Among all the developed methods for drug loading into nanofibers, mixing the drug with a polymer solution prior to electrospinning remains the most predominant. Generally, lipophilic drugs are loaded in lipophilic polymers, while hydrophilic drugs are loaded in hydrophilic polymer solutions

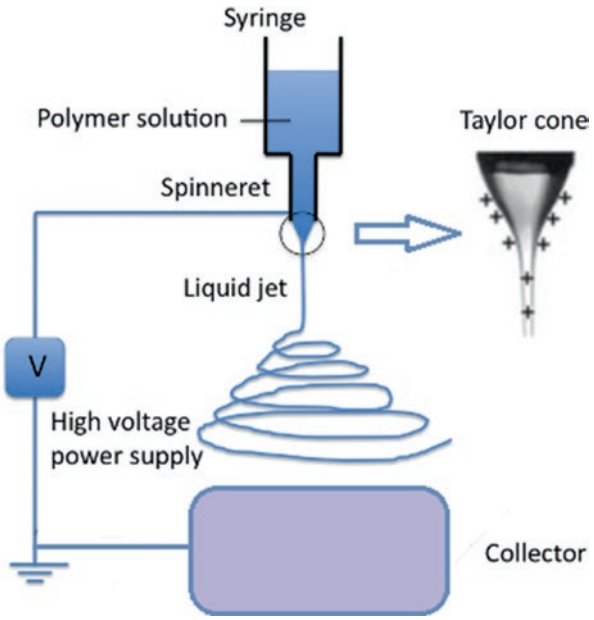

Fig. 5.1 Schematic representation of the electrospinning process

(Kamble et al. 2017; Zamani et al. 2013). For this purpose, the drug is dissolved or dispersed in the polymer solution to achieve encapsulated drug through a single-phase electrospinning procedure. A common problem in this technique is the loss of activity of the incorporated biological molecules (e.g., enzymes and growth factors) during the electrospinning process (Mickova et al. 2012). Therefore, several electrospinning techniques have been developed to obtain nanofibers with different shapes and structural characteristics (He et al. 2014).

Coaxial electrospinning is a modified version of electrospinning that enables production of drug-loaded fibers with core–shell morphology (Zamani et al. 2013) (Fig. 5.2). The coaxial configuration involves two capillaries which permit simultaneous electrospinning of two separate polymer solutions into core–shell structured nanofiber (Zanin et al. 2011). The shell polymer improves sustained and prolonged release of the active agent. It also prevents the direct contact of the drug with the external environment. Therefore, to encapsulate specific materials such as biological agents and growth factors, coaxial electrospinning is preferred (Manuel et al. 2016). Mickova et al. (2012) produced core–shell nanofibers with embedded liposomes. They have suggested that the liposomes remained intact during and after coaxial electrospinning in contrast with blend electrospinning. The main drawbacks of coaxial electrospinning are the need for a specialized electrospinning setup and the complication of controlling of multiple feed rates (Canbolat et al. 2013).

Emulsion electrospinning is another method for the encapsulation of the drugs into core–shell structured nanofibers. Briefly, this technique involves the emulsification of drug solution in the polymer solution and the electrospinning of the obtained emulsion. The application of emulsion electrospinning process has been resulted in

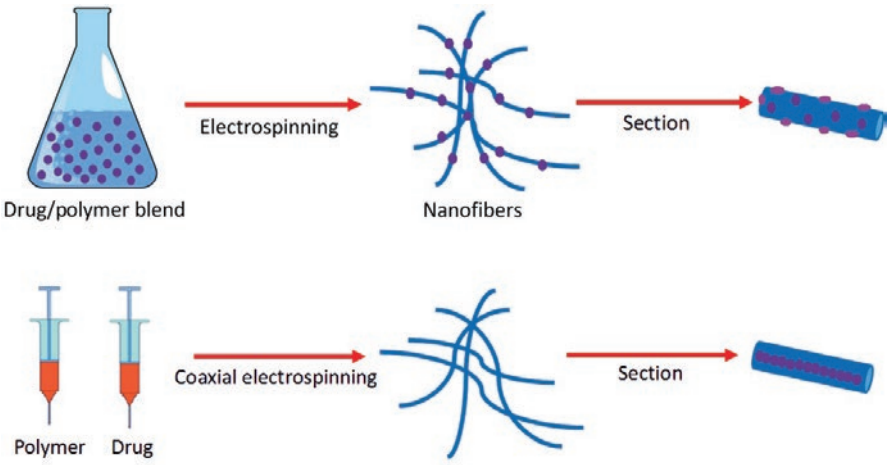

Fig. 5.2 The difference between the blend (conventional) and coaxial electrospinning processes

the controlled release of drugs and enhanced bioactivity of sensitive compounds (Nikmaram et al. 2017). The primary advantage of this technique is the absence of organic solvent usage (Manuel et al. 2016). On the other hand, emulsion electrospinning requires the inclusion of surfactants, which may generate toxicity to the biological systems (Zhang et al. 2018).

Other techniques to incorporate drugs into nanofibers could be listed as (a) physical adsorption by immersing electrospun nanofibers into drug solution wherein electrostatic interactions occur; (b) chemical method, which involves modifying the surface properties of nanofibers and covalent bounding of drug molecules to the surface of preformed nanofibers; and (c) bioconjugating drug molecules such as enzymes, DNA, or growth factors to nanofiber surfaces (Pelipenko et al. 2015; Sharma et al. 2015; Kamble et al. 2017).

It can be found in the literature that certain techniques such as phase separation and self-assembly have also been used to prepare drug-loaded polymeric nanofibers. However, the obvious disadvantages of these techniques can be listed as material limitation and time-consuming and complex processing (Table 5.1) (Morie et al. 2016; Zanin et al. 2011). Compared with other methodologies, electrospinning can be used for many formulations and is more reproducible when system and process parameters are controlled (Manuel et al. 2016).

Conventional electrospinning is accepted as an easy and efficient method; however, the big problem limiting its industrial applications is the electrospinning production rate versus commercial fiber production rate. Multineedle electrospinning and needleless electrospinning came to the forefront among the several methods which have been developed to increase the productivity of solution electrospinning process (Valipouri 2017; Zhao et al. 2016). Multineedle electrospinning technique is based on multiplication of the jets using multineedle constructions. Jets instability and mutual interference have been reported as the main limitations of this method

Table 5.1 Advantages and disadvantages of phase separation, self-assembly, and electrospinning techniques

Nanofiber production technique	Advantage	Disadvantage
Phase separation	Minimum equipment requirement Process can directly fabricate a nanofiber matrix Batch-to-batch consistency is achieved easily Mechanical properties of the matrix can be tailored by adjusting polymer concentration	Limited to specific polymers Laboratory-scale process Fiber dimensions cannot be controlled
Self-assembly	Process can fabricate smaller nanofibers	Complex and laboratory-scale process Fiber dimensions cannot be controlled
Electrospinning	Cost-effective Long, continuous nanofibers can be produced Scale-up possibility	Jet instability

(Dubský et al. 2012). The needleless electrospinning technology however created an opportunity for the scale-up the conventional electrospinning process to an industrial production level (Zhao et al. 2016). The setup which consists of a rotating drum immersed into a bath of a liquid polymer has been commercialized under the brand name Nanospider™. Nanospider™ technology is a patented, needle-free, high-voltage, free liquid surface electrospinning process and is able to fabricate polymeric nanofibers in diameter range of 50–300 nm into nonwovens (Petrik 2011; Kamble et al. 2017).

5.3 Factors Affecting Electrospinning

Although electrospinning is considered to be a simple production technique, a number of parameters can influence the formation and structure of the obtained fibers. The process parameters and the system parameters known to affect nanofiber properties are shown in Fig. 5.3. By appropriately adjusting all or some of these parameters, fibers with desired morphology and diameter can be obtained (Frenot and Chronakis 2003; Supaphol et al. 2012).

The physicochemical properties of the polymer solution have a significant impact on the final morphology and characteristics of the formed electrospun fibers (Morie et al. 2016; Bhardwaj and Kundu 2010). The polymer concentration influences both the viscosity and the surface tension of the solution. Within the optimal concentration range of the solutions, uniform fibers can be obtained (Supaphol et al. 2012). It was reported that the fiber diameter increases with an increase in the polymer solution concentration (Huang et al. 2003). A low viscosity favors an efficient stretching of the polymer jet and thus the formation of thinner fibers. However, the viscosity of the polymer solution must be high enough to prevent the jet from collapsing into

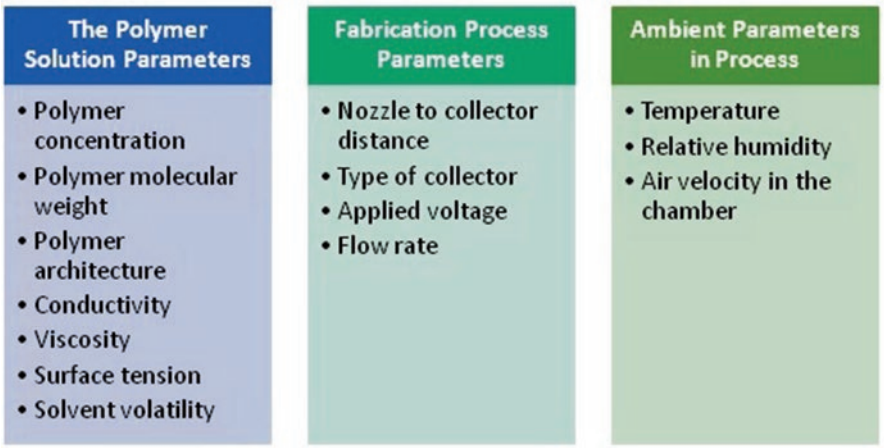

Fig. 5.3 Process parameters and system parameters affecting nanofiber production by electrospinning method

droplets before the solvent has evaporated (Frenot and Chronakis 2003; Gomes et al. 2015).

The vapor pressure of the solvent should be suitable so that it evaporates quickly enough for the fiber to maintain its integrity when it reaches the collector (Ramakrishna et al. 2005). Solvent volatility has been reported to affect the porosity of fibers (Morie et al. 2016). The conductivity of the polymer solution can be altered by adding ionic salts. A low conductivity leads to a decrease in stretching behavior of the jet and to thicker nanofibers (Gomes et al. 2015). It was suggested that the radius of the fiber jet is inversely related to the cube root of the solution conductivity (Supaphol et al. 2012). The surface tension of polymer solution is another significant parameter, and electrospinnability could be enhanced by reduction in the surface tension (Huang et al. 2003; Wali et al. 2018).

Fabrication process parameters can greatly affect fiber formation and structure. The applied voltage, polymer flow rate, nozzle to collector distance, and type of the collector can influence the formation of nanofibers with bead-like defects (Bhardwaj and Kundu 2010; He et al. 2014). The distance between the capillary and the fiber collector has an impact on fiber drying and should be kept at minimum. If the distance is too long, the electrostatic force cannot overcome the surface tension, and electrospraying instead of electrospinning occurs (Thakkar and Misra 2017). Polymer flow rate also has an impact on fiber size and can influence fiber porosity as well as fiber geometry. At high flow rates, significant amounts of bead defects can be observed (Supaphol et al. 2012). The applied voltage has been found to influence the macroscale morphology of the nanofibers. The fiber diameter usually decreases using high voltage and low flow rate. The power supply should be adequate to overcome the viscosity and surface tension of the polymer solution to form and sustain the jet from the pipette (Frenot and Chronakis 2003; Ramakrishna et al. 2005; Sharma et al. 2015).

Ambient parameters in the production are likewise important in controlling the formation of nanofibers. Temperature, relative humidity, and air velocity in the electrospinning chamber play a major role in the properties of the polymeric solution and, consequently, modulate the nanofiber formation. It has been reported that high environmental temperature leads to an increase in solvent evaporation rate and as a result thicker nanofibers occur (Esentürk et al. 2016; Melanko et al. 2009; Pelipenko et al. 2015).

Taking all parameters into account, the choice of optimum electrospinning conditions depends on the selected polymer or polymers blend along with the intended use of the resulting nanofibers. By appropriately varying all or some of these parameters, fibers with desired morphologies can be obtained. However, the optimization of the process and system parameters is complex, and keeping close conditions in industrial scale is still a challenge.

5.4 Characterization of Nanofibers

During the preparation of polymeric nanofibers, it is crucial to monitor the basic properties such as nanofiber morphology, molecular structure, and mechanical characteristics. The average fiber diameter, porosity, and hydrophobic property are related to the morphology of the nanofibrous membrane. The molecular structure affects the optical, thermal, and mechanical behavior of electrospun nanofibers. Mechanical properties of nanofibers are important especially in biomedical applications such as wound dressings. The most commonly used techniques for the characterization of nanofibers are summarized in Table 5.2.

The morphological characterization of nanofibrous materials requires a complex approach and evaluation of the results of various methods. SEM, FE-SEM, TEM, and AFM have been used as complementary measurements in morphological characterization of the nanofibrous samples (Viana et al. 2015). SEM is the most used technique to evaluate the fiber diameter, diameter distribution, and surface morphology of prepared nanofibers (Fig. 5.4). FE-SEM is recommended to investigate biodegradable polymer-based nanofibers with poor heat resistance (Melanko et al. 2009; Širc et al. 2012; Vashisth et al. 2016).

The pore size of nanofibers and its distribution can be measured by using electron microscopy techniques and AFM. However porosity cannot be measured by these methods. The most commonly methodology to determine the porosity and pore size of nanofiber scaffolds is using mercury porosimetry (Morie et al. 2016). This method is based on the property of mercury that does not wet the surface of solid materials. During the measurement, mercury is transferred into the sample under vacuum and pressure is applied. Then, the sample porosity is calculated from the mass of mercury penetrated into the pores at highest pressure (Širc et al. 2012). The total pore volume and the total pore area can also be determined by using the same method. The total volume of pores gives foresight about the internal structure of nanofiber mats (Dubský et al. 2012). The major drawbacks of mercury

Table 5.2 Methods for nanofiber characterization

Nanofiber property	Characterization method
Fiber diameter, orientation, structure, morphology	Scanning electron microscopy (SEM), field emission SEM (FE-SEM)
Surface roughness	Atomic force microscopy (AFM)
Internal structure	Transmission electron microscopy (TEM)
Chemical functional groups Polymer–drug secondary interactions	Fourier transform infrared (FTIR) spectroscopy
Crystallographic structure and phase analysis Polymer–drug secondary interactions	X-ray diffraction (XRD) analysis
Porosity and pore size distribution	Mercury porosimetry
Specific surface area	Brunauer–Emmett–Teller (BET) analysis
Mechanical characteristics	Dynamic mechanical analysis (DMA) Tensile strength measurement
Wettability	Water contact angle measurement
Swelling behavior	Swelling index measurement
Thermal behavior	Differential scanning calorimetry (DSC) Differential thermal analysis (DTA) Thermogravimetric analysis (TGA)
Other	Drug entrapment efficiency Drug release study In vitro cell viability study In vitro cell attachment study

porosimetry are its cost and toxicity and the risk of the sample being destroyed at very high pressures.

In order to apply the nanofiber scaffolds for various biomedical applications, an appropriate mat with desirable wettability should be prepared. The hydrophilicity of electrospun nanofibrous membranes can be investigated by water contact angle measurement (Fazli and Shariatinia 2017). Hydrophilic nanofibers show low contact angle, depending on the spreadability of water across surface, while hydrophobic nanofibers show high contact angle because of the minimal contact between water droplet and nanofiber surface (Ramakrishna et al. 2005). Cross-linked nanofiber formulations based on hydrophilic polymers show an increase in the contact angle value as compared to noncross-linked counterparts which reflects the improved aqueous stability of cross-linked nanofibers (Vashisth et al. 2016).

In electrospun nanofiber membranes, the mechanical property is determined by the arrangement and packing characteristic of individual fibers that made up the membrane. As the electrospinning process is influenced by various interrelated and independent variables, it is advisable to perform mechanical testing of the nanofiber membrane when electrospinning process parameters have been altered. Moreover, in order to meet with long-life durability in biomedical applications, the mechanical properties of nanofibrous membranes should be determined. For mechanical characterization, dynamic mechanical analysis (DMA) and tensile strength measurement are the most applied techniques (Ramakrishna et al. 2005).

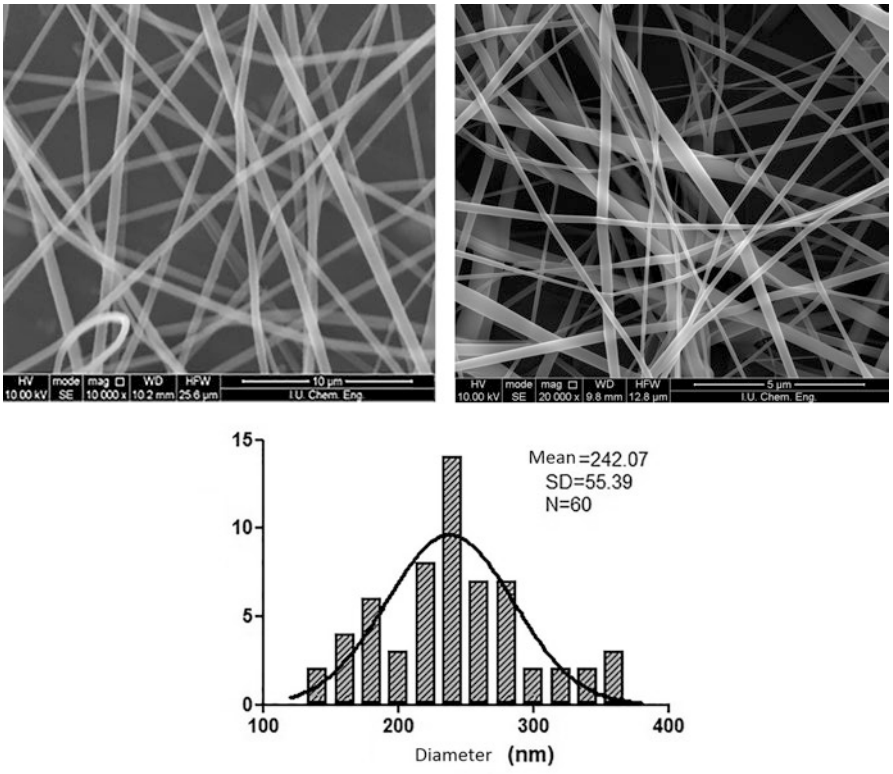

Fig. 5.4 SEM images and mean diameter of PVA/sodium alginate nanofibers (Esentürk et al. 2020)

The structures of the polymer molecules within the nanofibers, polymer–drug compatibility in drug-loaded nanofibers, and nanofiber surface chemistry can be investigated by FTIR spectroscopy. TGA and DSC can be used to study the thermal behavior of the nanofiber composites, whereas the crystallographic structure can be evaluated by XRD analysis (Melanko et al. 2009). The high evaporation rate of the solvents in electrospinning process provides the formation of a solid drug solution in polymer fibers. Therefore, amorphous form of the drug is achieved in the final nanofiber mats (Akduman et al. 2016). Since an amorphous form is thermodynamically less stable than any crystalline form, it can be a challenge to ensure physicochemical stability for the entire shelf life of the drug product (Censi and Di Martino 2015). Especially for hydrophilic drugs which are incorporated into hydrophobic polymer fibers, crystal growth of the drug on the surface of electrospun nanofibers represents a major stability challenge (Kamble et al. 2017; Seif et al. 2015).

Other than these basic physicochemical characterizations, there are a few methods which are also important to characterize nanofiber composites for drug delivery applications. Drug entrapment efficiency and the cumulative in vitro drug release should be determined in drug-loaded nanofibers. The amount of entrapped drug (%,

w/w) in nanofiber mats is usually measured by dissolving the dry mat in the electrospinning solvent. Then the amount of the drug can be measured by using an appropriate method, such as UV spectrophotometer or high-pressure liquid chromatography (HPLC). The mechanism of drug release can be elucidated by transforming and interpreting the in vitro release data into mathematical models. The nanofibers produced by conventional electrospinning from drug–polymer mixed solution usually display burst release behavior because of the short diffusion pathway (Kyziol et al. 2017). The burst release behavior is also associated with the presence of drug on the surface of the nanofibers (Hall Barrientos et al. 2017). This problem can be eliminated by a cross-linking process or by increasing the thickness of the membrane. Zhang et al. (2018) developed hybrid nanofibers for effective drug encapsulation and controlled release. Drug-loaded inorganic nanoparticles have been mixed with PLGA for subsequent electrospinning to form hybrid nanofibers. The preloading of drug molecules within nanocarriers significantly extended the drug diffusion distance; hence the formed hybrid nanofibers displayed reduced burst release profiles. It has been also shown that the electrospinning setup significantly affect the burst release profile of the drugs (Goyal et al. 2016).

The biodegradation profile, cellular compatibility, and cytotoxicity of drug-loaded nanofibers can also be assessed by using various biochemical assays. In industrial-scale production of nanofibers, it is desirable that the main techniques used for the characterization are automated and can be applied online (Pelipenko et al. 2015).

5.5 Polymers Used in Nanofiber Formation

The selection of polymer is of critical importance for the production of nanofibers. The type of the polymer can be chosen depending on the treatment, on the nature of the drug, and on the compatibility with the biological environment (Fig. 5.5) (Pelipenko et al. 2015; Sharma et al. 2015). Although synthetic polymers were the first to be electrospun, biopolymers have gained increasing attention because of their compatibility with biological tissues. Naturally occurring polymers exhibit good biocompatibility and low immunogenicity; hence they have been used widely in wound healing and skin regeneration applications (Erdal et al. 2016; Bhardwaj and Kundu 2010; Zhao et al. 2016). Synthetic polymers can be divided into biodegradable and nondegradable types. They provide many advantages over natural polymers such as wider range of properties, predictable lot-to-lot uniformity, and reliable source of raw materials. The biodegradable synthetic polyesters PLA, PGA, PLGA, and PCL have been commonly used for sustained drug release from nanofibers (Supaphol et al. 2012).

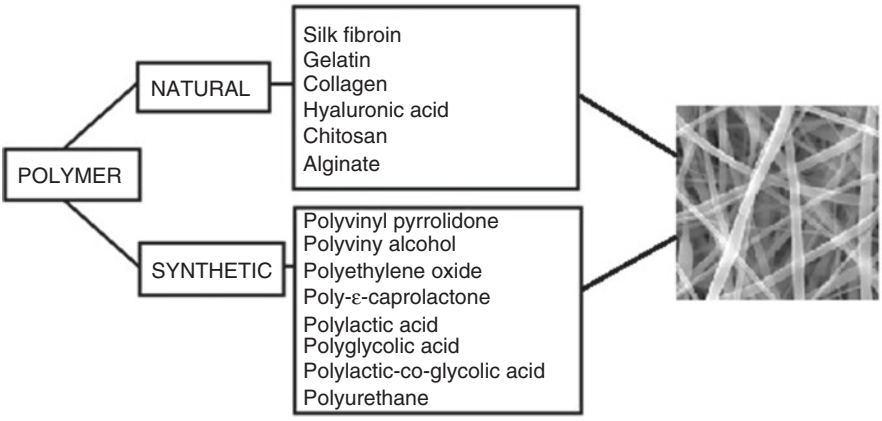

Fig. 5.5 The most widely used natural and synthetic polymers in drug-loaded electrospun nanofibers

5.5.1 Natural Polymers

Natural polymers offer the advantage of being very similar to the macromolecules present in the ECM (Melanko et al. 2009; Sharma et al. 2015). They are usually biodegradable and their biocompatibility is excellent. However, natural polymers often lack the desired physical properties, and they are difficult to electrospin on their own, so they are used mostly in combination with synthetic polymers (Supaphol et al. 2012). The most important biopolymers for the production of drug-loaded electrospun nanofibers are briefly discussed below.

Silk Fibroin Silk is a well-described natural fiber, which has been used in textile industry for ages. Silk fibroin is a main component of silk. It has excellent mechanical strength, and it is biocompatible and biodegradable (Zhao et al. 2016). Electrospun fibers from silk fibroin were found to promote cell adhesion and proliferation, and they found place in tissue engineering, wound healing, and drug delivery studies (Bhardwaj and Kundu 2010; Ramakrishna et al. 2005). Silk protein is water soluble, and therefore cross-linking treatments have been used to increase its water resistance (Kluge and Mauck 2012).

Gelatin Gelatin is obtained by partial hydrolysis of collagen. It is widely used in the pharmaceutical industry and biomedical fields due to its nontoxic nature and biodegradability (Erdal et al. 2016). Gelatin scaffolds have been engineered to facilitate the regeneration of bones, skin, muscles, and nerves (Gomes et al. 2015). However, the mechanical strength of gelatin nanofibers is low, and therefore cross-linking treatments have been used to increase their water resistance (Laha et al. 2016; Zhao et al. 2016). The blends of gelatin with natural or synthetic polymers have been used to improve the mechanical properties of nanofibers (Aldana and Abraham 2017; Laha et al. 2016). Gelatin/poly-ε-caprolactone (PCL) composite

systems showed better mechanical strength and wettability compared with gelatin or PCL alone (Vasita and Katti 2006). Gelatin nanofibers produced by needleless electrospinning accelerated wound healing in full-thickness wound model in rats (Dubský et al. 2012).

Collagen Collagen is the most abundant protein in animals and in the human body. It is a major component of the skin, cartilage, bone, tendon, and teeth. In many native tissues, type I and III collagen are the principal structural elements of the ECM (Bhardwaj and Kundu 2010; Zhao et al. 2016). Collagen as a biopolymer has been used in wound dressings. It has also been tested in skin, bone, tendon, and ligament tissue engineering. In vitro studies had shown that cells respond positively to tissue scaffold made of electrospun collagen fibers (Ramakrishna et al. 2005). The nanofibers based on collagen have been shown to be compatible with a number of cell types and offer a suitable environment for cell growth (Vasita and Katti 2006). But, electrospinning of pure collagen is difficult, and usually a stabilization procedure by cross-linking with formaldehyde or glutaraldehyde is needed (Erdal et al. 2016; Pelipenko et al. 2015).

Hyaluronic Acid Hyaluronic acid is a linear polyanionic glycosaminoglycan, and it is a natural component of the ECM of connective tissues (Bhardwaj and Kundu 2010). Due to its unique rheological properties and biocompatibility, hyaluronic acid has been used extensively in many biomedical applications such as ophthalmology, medical implants, and drug delivery (Ramakrishna et al. 2005). Hyaluronic acid nanofibers have been tested in the development of modern wound dressings. But electrospinning of hyaluronic acid alone does not allow a consistent production of fibers, and the main drawbacks of hyaluronic acid nanofibers have been reported as poor cell adhesion, mechanical instability, and rapid degradation in vivo (Pelipenko et al. 2015; Vasita and Katti 2006).

Chitosan Chitosan is a biodegradable and biocompatible polymer. Chitosan has been chosen for infection-related wound healing studies in a majority because of the rich hydrogen bonds between chitosan chains that allow a favorable swelling ability to the polymer (Wang et al. 2017). Chitosan-based nanofibers were applied for tendon, bone, and cartilage tissue engineering (Bhardwaj and Kundu 2010; Erdal et al. 2016; Pelipenko et al. 2015). Although it is possible to electrospun pure chitosan, the nonaqueous solvents, which should be used in the electrospinning process, possess very harmful characteristics. Therefore, blends of chitosan with synthetic polymers such as polyvinyl alcohol (PVA) or polyethylene oxide (PEO) have been used in order to improve the spinnability of chitosan (Zhao et al. 2016).

Alginate Alginate is a water-soluble, natural linear polysaccharide obtained from brown seaweed. It is a biopolymer which plays an important role in the design of controlled drug delivery formulations, and it shows great potential as a scaffold material in tissue engineering (Erdal et al. 2016). Alginate-based nanofiber wound dressings have been widely studied due to the specific characteristics of alginate,

including biocompatibility, nonimmunogenicity, and large water-absorbing capacity (Pelipenko et al. 2015; Zhao et al. 2016). Alginate alone could not electrospun because of its poor mechanical strength and processing difficulties. Therefore it is usually blended with appropriate polymers with a high molecular weight (Fu et al. 2016; Kyziol et al. 2017).

5.5.2 Synthetic Polymers

A wide variety of synthetic polymers has been used to fabricate nanofiber sheets by electrospinning technique (Vasita and Katti 2006). Especially, the water-soluble synthetic polymers polyvinylpyrrolidone (PVP), PVA, and PEO have been accepted as ideal candidates to fabricate nanofibers for use as drug carriers (He et al. 2014). The composite nanofibers composed of synthetic and natural polymer blends combine the favorable biological characteristics of natural polymers and the mechanical performance of the synthetic ones (Aldana and Abraham 2017).

Polyvinyl Alcohol (PVA) PVA is a nontoxic, highly hydrophilic, biodegradable, semicrystalline polymer with adhesive properties (Fu et al. 2016). It has good chemical and physical stability and has the ability to form fibers, films, and membranes (Wali et al. 2018). PVA has been widely used to produce nanofiber mats due to its good spinnability (Arthanari et al. 2016; Viana et al. 2015). The morphology of electrospun PVA nanofibers has shown to be affected by concentration of the polymer solution, ionic salt addition, applied electric potential, and pH (Ngawhirunpat et al. 2009). The elastic properties of PVA nanofibers have been found suitable for regeneration of soft tissues such as skin (Pelipenko et al. 2015). The fabrication of polyblend PVA–natural polymer nanofibers provided improved mechanical strength, bioactivity, and degradation profile to the end product and introduced scaffolds with desired properties for specific tissue regeneration and drug delivery applications (Zanin et al. 2011; Zamani et al. 2013).

Polyethylene Oxide (PEO) PEO is a unique class of nonionic water-soluble, biodegradable polymer with a linear structure and good spinnability. It shows excellent biocompatibility and very low toxicity (Kyziol et al. 2017). PEO nanofibers can be stabilized physically. Blending of PEO with biopolymers has become a popular tool for overcoming the processing limitations of less soluble or less available materials (Kluge and Mauck 2012). In the electrospinning field, PEO and PVA are often used in the preparation of nanofibers from their blend solutions (Fu et al. 2016). They are also often added to chitosan, alginate, and hyaluronic acid which are difficult to be electrospun alone (Pelipenko et al. 2015).

Poly-ε-caprolactone (PCL) PCL is an FDA-approved semicrystalline and biodegradable hydrophobic polyester which is commonly used in electrospun nanofibers for controlled release (Hall Barrientos et al. 2017). It is characterized by a high

plasticity and a slow degradation rate resulting from the hydrolysis of its ester linkages (Anjum et al. 2017; Gomes et al. 2015). The mechanical properties of PCL as well as its spinnability are excellent. PCL nanofibers are stable in an aqueous environment, but organic solvents are needed for their production (Pelipenko et al. 2015; Chou et al. 2015). Due to the limited cell specificity and high hydrophobicity of PCL, incorporation of pore-generating polymers, like PEG or gelatin, into PCL nanofibers has been shown to increase the biofunctionality (Ravikumar et al. 2017; Wang et al. 2016). Surface treatment of PCL nanofibrous scaffolds with ethanol can create a hydrophilic surface which serves for efficient cell attachment (Kluge and Mauck 2012).

Polyvinylpyrrolidone (PVP) PVP is a hydrophilic, nontoxic, biocompatible synthetic polymer (Maslakçı et al. 2017). Electrospun PVP nanofibers have been tested as a drug delivery systems and wound dressings. The water absorbability and dissolution properties of PVP nanofibers have been found to improve the dissolution profile of incorporated drugs (Yu et al. 2010).

Polylactic Acid (PLA), Polyglycolic Acid (PGA), and Polylactic-co-glycolic Acid (PLGA) The most commonly used synthetic polymers for three-dimensional tissue scaffolds are saturated biodegradable polyesters, including PLA and PGA, as well as PLGA copolymers. PGA is a hydrophilic and highly crystalline polymer with a relatively fast degradation rate. Although structurally very similar to PGA, PLA exhibits different chemical, physical, and mechanical properties. The nanofibers obtained from PLA, PGA, and PLGA have been found mechanically stable, but organic solvents are needed for their production (Kluge and Mauck 2012; Said et al. 2011).

Polyurethane (PU) PU is one of the most widely used polymers in biomedical applications especially those in contact with blood (Ramakrishna et al. 2005). PU nanofibers possess excellent mechanical properties, and they have been widely used in wound healing applications due to their oxygen permeability and barrier properties (Akduman and Kumbasar 2017).

5.6 Electrospun Nanofibers in Dermal Drug Delivery

Among the various applications of electrospun nanofibers, drug delivery plays a key role for biomedical applications. The advantages of using nanofibers in drug delivery can be considered as (a) high drug loading and encapsulation efficiency, (b) ability to modulate drug release, (c) the possibility to use a wide variety of both natural polymers and synthetic polymers, and (d) the high surface area-to-volume ratio that facilitates mass transfer and efficient delivery of both hydrophilic and hydrophobic drugs (Goyal et al. 2016; Chou et al. 2015; Manuel et al. 2016; Melanko et al. 2009). Small molecular weight drugs, proteins, DNA, genes, and

vaccines can be incorporated to the electrospun nanofibers for specific therapeutic purposes (Sharma et al. 2015; Zamani et al. 2013). During the last several decades, polymeric nanofibers have been explored as controlled drug delivery systems for dermal, transdermal, oral, oromucosal, parenteral, and ocular routes (Pelipenko et al. 2015). Recently, electrospun nanofibers have gained more popularity for the topical and transdermal drug delivery and wound dressing applications.

The use of the skin as a drug delivery route for both topical and systemic therapy is a noninvasive approach for administration of drugs. However, the remarkable barrier properties of the skin, especially of its outermost layer, stratum corneum, pose a significant challenge to administering medications via the skin either for local cutaneous effects or as systemic therapy. In order to deliver drugs through the skin, most compounds require various degrees of permeation enhancement. Nanofiber-based dermal delivery systems have been considered as tool to improve the solubility of active agents and thereby enhancing drug release and skin permeation characteristics (Kamble et al. 2017). Table 5.3 represents a selection of scientific studies dealing with the nanofiber-based dermal drug delivery in the last decade. As evident from the table, drug-loaded nanofibers have especially attracted great attention for their use in wound healing applications.

PCL poly(Ɛ-caprolactone), *PEO* poly(ethylene oxide), *PVA* poly(vinyl alcohol), *PVAc* poly(vinyl acetate), *PNIPAM* poly(-N-isopropylacrylamide), *PGS* poly(glycerol sebacate), *CA* cellulose acetate, *PVP* poly(vinylpyrrolidone), *SA* sodium alginate, *PLA* poly(lactic acid), *PLGA* poly(lactic-co-glycolic acid), *PU* poly(urethane), *HPC* hydroxypropyl cellulose, *PMMA* poly(methyl methacrylate)

Wound healing is essential for the restoration of the skin barrier after injury. It comprises of healing of dermal and epidermal tissues by their regeneration. During the wound healing process, the cells at the wound edge proliferate and migrate, leading to reepithelization of the wound surface. This is a complex and dynamic process involving five stages: hemostasis, inflammation, proliferation, migration, and maturation (Stamm et al. 2016). During this period the disturbance of wound healing can be caused by several factors, such as infection, excess of inflammatory cytokines, and necrosis (Anjum et al. 2017; Garcia-Orue et al. 2017).

The prevalence of chronic dermal wounds has increased in recent years due to the increase of the high-risk population including elderly, diabetics, and obese. The inflammation stage in chronic wounds proceeds too long, resulting in wounds that remain open for months to years. Therefore, the treatment of chronic wounds is still a significant clinical challenge (Goyal et al. 2016). Current studies to overcome this problem are focused on the development of new therapeutic approaches. Recently, the electrospun nanofibrous wound dressings have been shown to be able to enhance the wound healing process because of their potential to mimic the structure and biological function of dermal ECM (Anjum et al. 2017; Mickova et al. 2012; Wang et al. 2017).

The unique architectural properties like nanoscale morphology, porous structure, and flexibility of electrospun nanofibers make them a suitable option for developing novel wound dressings (Garcia-Orue et al. 2017). The very high porosity of the nanofibrous membranes allows cell respiration and gas permeation and prevents the

Table 5.3 Nanofiber-based dermal drug delivery studies conducted in the last decade

Polymer or polymer blend	Drug	Aim	Author and Year
PU	Doxorubicin	Wound healing	Kiliç et al. (2018)
Chitosan/PVA	Tetracycline hydrochloride	Wound healing	Alavarse et al. (2017)
Chitosan/PVA	Ampicillin	Wound healing	Wang et al. (2017)
Chitosan/PEO	Cefazolin and cefazolin loaded nanoparticles	Wound healing	Fazli and Shariatinia (2017)
Chitosan/PCL	Ferulic acid and resveratrol	Wound healing	Poornima and Korrapati (2017)
Nanochitosan/PCL	Curcumin	Wound healing	Cr et al. (2018)
Gelatin	*Centella asiatica* extract	Wound healing	Yao et al. (2017)
Gelatin/silk fibroin	Thyme essential oil and doxycycline	Wound dressing	Dadras Chomachayi et al. (2017)
Gelatin/PCL	Cerium oxide nanoparticles	Wound healing	Rather et al. (2017)
Gelatin/PGS	Ciprofloxacin	Wound healing	Shirazaki et al. (2017)
Gelatin/PVA/PCL	Bromelain and salvianolic acid	Wound healing	Shoba et al. (2017)
SA, chitosan, PCL, collagen, PEO	Doxycycline	Wound healing	Tort et al. (2017)
SA/PEO	Ciprofloxacin	Wound healing	Kyziol et al. (2017)
PLGA	Recombinant human epidermal growth factor and *Aloe vera*	Wound healing	Garcia-Orue et al. (2017)
PLGA	Growth factors	Skin tissue regeneration	Lee et al. (2017)
PLA	Ibuprofen	Wound healing	Mohiti-Asli et al. (2017)
PVP/dextran	Ibuprofen and acetylsalicylic acid	Antimicrobial wound dressing	Maslakçı et al. (2017)
PVA/SA	Dexpanthenol	Wound healing	Tamizi et al. (2017)
PVA/calcium alginate	Papain	Wound healing	Dutra et al. (2017)
Eudragit RL/RS	Gentamicin sulfate and recombinant human epidermal growth factor	Wound healing	Dwivedi et al. (2018)
PCL–PEG–PCL triblock copolymer	Magnetic iron oxide nanoparticles	Skin tissue engineering	Zhang et al. (2017)
PCL/PVA	Silver sulfadiazine	Antimicrobial wound dressing	Mohseni et al. (2016)
PCL/gum tragacanth	Curcumin	Wound healing	Ranjbar-Mohammadi et al. (2016)
PCL/hyaluronan	Epidermal growth factor	Wound healing	Wang et al. (2016)
PVP	Chloramphenicol and suberin fatty acids	Wound healing	Tamm et al. (2016)

(continued)

Table 5.3 (continued)

Polymer or polymer blend	Drug	Aim	Author and Year
PMMA/PVA	Ciprofloxacin	Wound healing	Zupančič et al. (2016a)
Chitosan/PEO	Metronidazole	Wound healing	Zupančič et al. (2016b)
PU/dextran	β-Estradiol	Post-menopausal wound care	Unnithan et al. (2015)
Collagen/hyaluronic acid	Multiple angiogenic growth factors	Wound healing	Lai et al. (2014)
Chitosan/PEO	Blood-derived growth factors	Wound healing	Bertoncelj et al. (2014)
SA/PVA	Ciprofloxacin	Wound healing	Kataria et al. (2014)
SA/PVA	Gatifloxacin	Wound healing	Arthanari et al. (2016)
PVA/PCL	Horseradish peroxidase	Wound healing	Mickova et al. (2012)
PVA/PVAc	Ciprofloxacin	Wound healing	Jannesari et al. (2011)
PLGA	Fusidic acid	Wound dressing	Said et al. (2011)
PLGA	Rhodamine B	Tissue engineering scaffold	Liao et al. (2008)
PU/HPC	Donepezil hydrochloride	Transdermal drug delivery system	Gencturk et al. (2017)
Chitosan/ phospholipid	Curcumin, diclofenac, and vitamin B12	Transdermal drug delivery system	Mendes et al. (2016)
PLGA	Daidzein-loaded lipid nanocarriers	Transdermal drug delivery system	Song et al. (2016)
PVP	Curcumin	Transdermal drug delivery system	Wang et al. (2015)
PVA	Prazosin hydrochloride	Transdermal drug delivery system	Shen et al. (2014)
CA/PVP	Ibuprofen	Transdermal drug delivery system	Shi et al. (2013)
PVA/CA	Capsicum extract	Transdermal drug delivery system	Opanasopit et al. (2013)
PVA	Meloxicam	Transdermal drug delivery system	Ngawhirunpat et al. (2009)
PU	Naproxen	Topical drug delivery system	Akduman et al. (2016)
PCL	Linezolid	Topical antibacterial	Tammaro et al. (2015)
PVA/PNIPAM	Levothyroxine (T_4)	Sustained topical delivery of T_4	Azarbayjani et al. (2010)

wound from bacterial penetration and dehydration (Mickova et al. 2012). Most of the studies have shown that electrospun nanofibrous scaffolds might be capable of supporting cell adhesion, proliferation, and maturation (Anjum et al. 2017; Frenot and Chronakis 2003). Generally, the hydrophilic natural polymers provide sites for cell adhesion, while synthetic polymers add mechanical strength and slow the degradation rate (Gomes et al. 2015). Upon proper polymer selection nanofibers can also provide an optimum barrier for appropriate healing of the wound (Kamble et al. 2017; Sharma et al. 2015; Zanin et al. 2011). The local delivery of drugs via bioactive nanofiber mats is one of the effective approaches to accelerate the wound healing process more efficiently (Kataria et al. 2014). Drug-loaded nanofibers composed of chitosan–PEO (Bertoncelj et al. 2014; Fazli and Shariatinia 2017), chitosan–PVA (Alavarse et al. 2017), chitosan–PCL (Poornima and Korrapati 2017), and gelatin–PCL (Rather et al. 2017) blends or hydrophilic synthetic polymers such as PVA (Shoba et al. 2017), PLA (Mohiti-Asli et al. 2017), and PVP (Tamm et al. 2016) have been specifically engineered to promote wound healing and skin regeneration.

5.7 Conclusions

Among the different nanotechnology-based drug delivery systems, electrospun nanofibers have been considered as promising novel carriers due to their efficiency on drug delivery in a controlled manner. The nanofiber scaffolds composed of biocompatible polymers are widely studied as effective alternatives for skin wound treatment and dermal drug delivery. On the other hand, the scale-up to industrial production and the clinical studies of drug-loaded nanofibers are still limited. Further studies have to be performed to overcome the technical challenges to ensure industrial production of uniform nanofibers. Furthermore, the effect of drug release kinetics on therapeutic efficiency as well as possible toxic effects should be clarified by in vivo studies.

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