CHAPTER

ELECTROSPINNING OF POLYMERS FOR TISSUE ENGINEERING

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3.1 INTRODUCTION

Electrospinning was introduced centuries before and it gained popularity in the beginning of the twenty-first century, since the researchers from all over the world have been showing increased interest toward the nanoscale properties and technologies [1,2]. The term "electrospinning" was coined in the year 1994, prior to this, it was known as "electrostatic spinning," [3] and was patented 60 years earlier by Formhals [4]. Academic and industrial research on nanofibers is an area of intense global interest in terms of both fundamental and applied science [5]. Here comes the importance of electrospinning. One-dimensional (1D) nanostructures or nanofibers have been a subject of intensive research due to their unique properties and intriguing applications [6] in different fields such as air and water filtration [7], drug delivery [8], tissue engineering, and regenerative medicine [9], besides many others involving active materials for photonics or electronics [10].

A large number of synthetic and fabrication techniques are used for the production of 1D nanostructure. Some of them include polymerization against porous templates [11], self-assembly [12], melt blowing [13], and various patterning approaches belonging to soft lithography [14]. However, electrospinning is a unique technology which provides incomparable operational simplicity and inexpensive nature that allows for the production of polymer fibers with both solid and hollow interiors that are extremely long in length, uniform in diameter, and diversified in composition [5,9].

The basic principle behind the formation of very thin fibers through electrospinning is due to the uniaxial stretching or elongation of a viscoelastic jet derived from a polymer solution or melt. This technique is similar to the commercial process of drawing microscale fibers, but it uses the electrostatic repulsion between surface charges to continuously reduce the diameter of a viscoelastic jet or a glassy filament than a mechanical or shear force. The main advantage of electrospinning over mechanical drawing is that the generation of fibers with much thinner diameters, since the elongation can be accomplished via a contactless scheme through the application of an external electric field. But the similarity between mechanical drawing and electrospinning is that both are continuous process and should work for high-volume production [6].

Electrospinning is closely related to the technology of electrospraying [15]. Both of these techniques involve the use of a high voltage to induce the formation of a liquid jet and to reduce the

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size of the fibers or droplets. In electrospraying, small droplets of particles are formed as a result of the varicose breakup of the electrified jet that is often present with a solution of low viscosity. In electrospinning, a solid fiber is generated as the electrified jet (composed of a highly viscous polymer solution) that is continuously stretched due to the electrostatic repulsion between the surface charges and the evaporation of the solvent [6].

Electrospinning gained substantial academic attention in the 1990s, which was partially initiated by the activities of the Reneker group [16]. One reason for the fascination with the subject is the combination of both fundamental and application-oriented research from different science and engineering disciplines. These research efforts usually target complex and highly functional systems, which could certainly be applied on a commercial level. Fiber systems in which the macroscopic properties (i.e., specific chemical, physical, or biological combinations of properties) can be targeted through modifications on the molecular level are of particular interest. The scope of possibilities presented by electrospinning encompasses a multitude of new and interesting concepts, which are developing at breakneck speed. This rapid development is reflected by the skyrocketing numbers of scientific publications and patents [17].

3.2 HISTORY OF ELECTROSPINNING

Electrospinning has its foundation in early studies. For the first inventor of the electrospinning process, it is necessary to understand the effect of electrostatics on liquid. In 1745, Bose described that on the application of high electric potentials to drops of fluids can generate aerosols [18]. In 1882, Lord Rayleigh studied the quantity of charges that are needed to overcome the surface tension of a drop [19]. In the late 1800s, electrodynamics was used to explain the excitation of dielectric liquid under the influence of an electric charge [20]. This probably led to the invention of electrospinning to produce fibers in the early 1900s [21].

The crucial patent, in which the electrospinning of plastics was described for the first time, appeared in 1934 with Anton Formhals from Mainz, as the author (and can be traced back to a German patent filing in 1929) [4]. Despite these early discoveries, the procedure was not utilized commercially. In the 1970s, Simm et al. patented the production of fibers with diameters of <1 mm [22]. However, this work, which was followed by other patents, also remained unnoticed. Moreover, there have been patents filed for various electrospinning setups since the 1900s, it is only in the last decade that academia has been looking into using electrospinning to fabricate various nanofibrous assemblies [1].

3.3 EXPERIMENTAL SETUP AND BASIC PRINCIPLE

Interest in electrospinning has recently increased due to the ability to produce materials with nanoscale properties [6]. The formation of nanofibers through electrospinning is based on the uniaxial stretching of a viscoelastic solution. In order to understand and appreciate the main process that enables the fabrication of various nanofiber assemblies, the principles of electrospinning and the different parameters that can affect the process have to be studied. Compared to conventional fiber spinning methods like dry

spinning and melt spinning, electrospinning make use of electrostatic forces to stretch the solution as it solidifies. Similar to conventional fiber spinning methods, the drawing of the solution to form the fiber will continue as long as there is enough solution to feed the electrospinning jet. Thus, without any disruption to the electrospinning jet the formation of the fiber will be continuous.

At first glance, electrospinning gives the impression of being a very simple and, therefore, easily controlled technique for the production of fibers with dimensions down to the nanometer range. There are lot of parameters that should be taken care before electrospinning. First, polymers will be surveyed as fiber-forming materials. Later, materials such as metals, ceramics, and glasses will be considered as fiber precursors. A typical electrospinning setup consists of three major components: a high-voltage power supply, a spinneret (a metallic needle), and a collector (a grounded collector). Figure 3.1 shows schematic illustration of the conventional setup of electrospinning.

In a typical electrospinning experiment in a laboratory, a polymer solution is first fed through a spinneret. The nozzle simultaneously acts as an electrode, to which a high electric field is applied. A high voltage is always applied to the solution such that at a critical voltage, typically more than 5 kV, the repulsive force within the charged solution is larger than its surface tension and a jet would erupt from the tip of the spinneret. As the solvent evaporates, it soon enters a bending instability stage with further stretching of the solution jet under the electrostatic forces in the solution. Generally, a grounded target that can act as counter electrode, which is used to collect the resultant fibers that are deposited in the form of a nonwoven mesh, either in rotating or static collectors. In a laboratory system, the distance to the counter electrode is usually 10−25 cm and the currents that flow during electrospinning range from a few hundred nanoamperes to microamperes [23].

The applied voltage causes a cone-shaped deformation of the drop of polymer solution, in the direction of the counter electrode [24]. During electrospinning, the cone angle is about 308. If higher voltages are applied, a jet is formed from the deformed drop, which moves toward the counter electrode and becomes narrower in the process. As the solvent reaches the counter electrode, it evaporates and solid fibers with diameters ranging from micrometers to nanometers are formed with

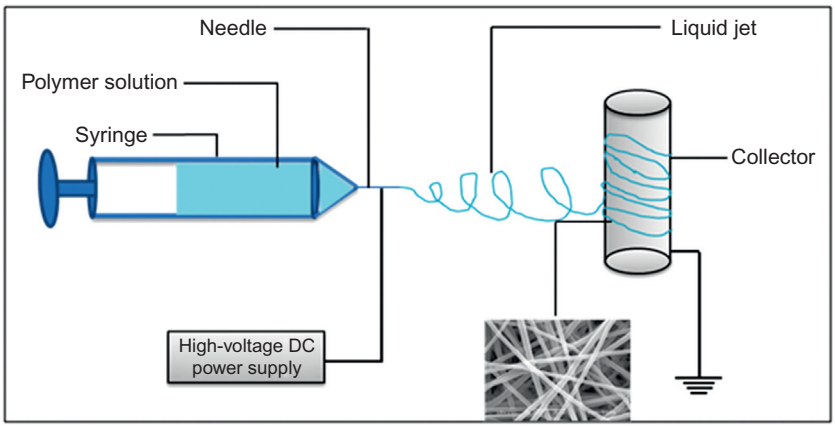

FIGURE 3.1

The schematic of conventional electrospinning setup.

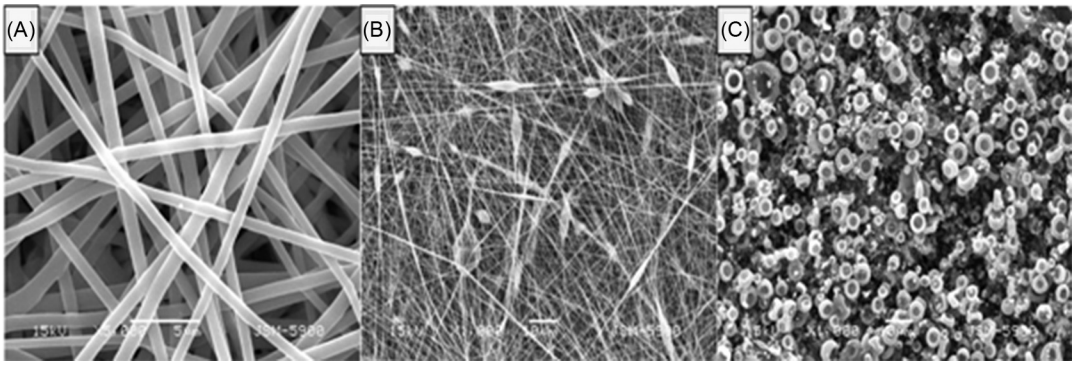

FIGURE 3.2

The morphology of nanofibers depends on a large set of parameters which will be discussed in the later part of this chapter. (Original SEM data showing the nanofiber morphology at different concentrations of cellulose acetate nanofibers: [A] 18 wt.%, [B] 10 wt.%, and [C] 8 wt.%).

high velocities (of 40 ms^{-1} or more) on the counter electrode [23]. In a closer observation, the electrospinning process seems to be a very complex process. The spinner jet follows a direct path toward the counter electrode for a certain distance, but then changes its appearance significantly to be moved laterally and forms a series of coils. Finally, it forms a cone opening toward the counter electrode. During such case, beads, rather than fibers, are formed during electrospinning; fibers with beaded dimensions on the fibers were formed as shown in Figure 3.2.

3.3.1 THEORETICAL BACKGROUND

Electrospinning process is a very complex process and is associated with the interaction of several physical instability processes. According to Reneker and Chun, the stable electrospinning jet is composed of four regions: the base, the jet, the splay, and the collection. In the base region, the jet emerges from the needle to form a cone known as the Taylor cone. The shape of the base depends upon the surface tension of the liquid and the force of the electric field. If the electric field is strong enough, the jets can be ejected from surfaces that are essentially flat. Solutions of higher conductivity being more conducive are easy for jet formation. Then the electric forces accelerate and stretch the polymer jet, causing the diameter to decrease as its length increases. Solvents with high vapor pressures may begin to evaporate, causing a decrease in jet diameter and velocity. The charge repulsions cause the jet to "splay" into many small fibers of approximately equal diameter and charge per unit length [25]. Rutledge et al. have reported high-speed photography with exposure times as low as 18 ns to demonstrate that the jet that appears to splay is actually a single, rapidly whipping jet. After traveling to a short distance in high electric fields, the jet becomes unstable, begins to whip with a high frequency, and undergoes bending and stretching [26]. Rutledge et al. examined the competition between these instabilities for various applied electric fields, flow rates, and determined the dominant mode. They constructed operating diagrams that outlined the conditions at which whipping could be expected; their predictions agreed well with experimental results [27].

3.4 EFFECTS OF PARAMETERS ON ELECTROSPINNING

In the electrospinning process, there are a large number of parameters which contribute toward the fiber morphology. Doshi and Reneker broadly classified the working parameters into three parts such as solution parameters, process parameters (controlled variables), and ambient parameters [28]. Each of these parameters can directly affect the fiber morphologies and we can fabricate electrospun fibers with desired morphologies and diameters by controlling these parameters carefully.

3.4.1 SOLUTION PARAMETERS

Viscosity, conductivity, surface tension, polymer molecular weight, dipole moment, and dielectric constant are the most important parameters that are considered as the solution properties. Varying one parameter can generally affect other solution properties, so it is difficult to isolate the effects of the solution properties independently (e.g., changing the conductivity can also vary the viscosity).

3.4.2 CONCENTRATION AND VISCOSITY

Controlled variables include flow rate, electric field strength, distance between tip and collector, needle tip design, collector composition, and geometry. Ambient parameters include temperature, humidity, and air velocity. In this section, studies that investigate the effects of each parameter on electrospun fiber morphologies and sizes are highlighted. Solution viscosity/concentration play an important role in determining the fiber size and morphology when spinning polymeric fibers. The relationship between the polymer viscosity and concentration are relative in nature, as viscosity is controlled by changing the polymer concentration. Based on the solutions viscosity from low to high, the fiber morphology may also change [29]. If the concentration is very low, polymeric micro (nano) particles will be obtained. At this time, electrospray occurs instead of electrospinning due to the low viscosity of the solution. If the concentration is little higher, a mixture of beads and fibers may be obtained. When the concentration is suitable, smooth nanofibers can be obtained. If the concentration is very high, not nanoscaled fibers, helix-shaped microribbons will be observed. The fiber morphologies are shown in Figure 3.3.

3.4.3 MOLECULAR WEIGHT

Molecular weight of the polymer also has an important effect on morphologies of electrospun fiber. If we lower the molecular weight of the polymer without changing the concentration for spinning, it will form beads rather than smooth fiber. Increasing the molecular weight to an optimum level will result in smooth fibers. It is also significant to note that high molecular weight favors the formation of microfibers. However, it is also important to point out that the molecular weight is not always essential for electrospinning if sufficient intermolecular interactions can be provided by oligomers.

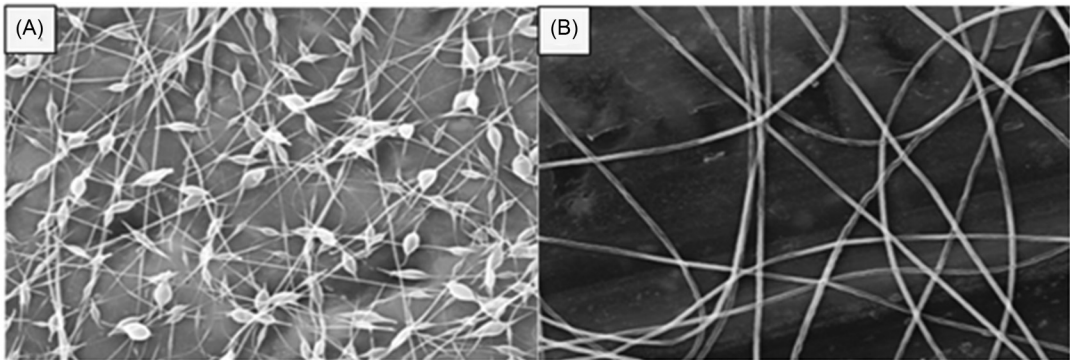

FIGURE 3.3

The morphology of beaded fibers versus solution viscosity.

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3.4.4 SURFACE TENSION

Surface tension, as the function of solvent compositions of the solution, is a main factor in electrospinning. The different solvents may contribute different surface tensions. Keeping the concentration fixed, reducing the surface tension of the solution, beaded fibers can be converted into smooth fibers. More importantly, the surface tension and solution viscosity can be adjusted by changing the mass ratio of solvents mix and fiber morphologies will be changed accordingly. Basically, surface tension determines the upper and lower boundaries of the electrospinning window if all other conditions are fixed.

3.4.5 CONDUCTIVITY OF THE SOLUTION

Solution conductivity is mainly determined by the polymer type, solvent, and the salt present. Natural polymers are generally polyelectrolytic in nature, in which the ions increase the charge carrying ability of the polymer jet. It may cause the poor fiber formation subjecting to higher tension under the electric field when compared to the synthetic counterpart [31]. The presence of ionic salts can result in nanofibers with small diameters. Sometimes, high solution conductivity can be also achieved by using organic acid as the solvent. In summary, the formation of thinner fibers was favored by the increase in the solution conductivity.

3.4.6 APPLIED VOLTAGE

Applied voltage is the crucial factor for the electrospinning process. Only the applied voltage higher than the threshold voltage can cause the charged jets ejected from Taylor cone to occur. At low applied voltages, the drop is typically suspended at the needle tip, as the voltage is increased and a jet will originate from the Taylor cone producing bead-free spinning. But the affection of the applied voltages on the diameter of electrospun fibers is always a controversial matter. It is mainly reported

that higher voltages facilitated the formation of large fiber diameter. Several groups suggested that higher voltages can increase the electrostatic repulsive force on the charged jet, favoring the narrowing of fiber diameter [32]. Researchers also demonstrated that higher voltage offers greater probability of bead formation. Thus, we can find that voltage does influence fiber diameter, but the level of significances varies with the polymer solution concentration and the distance between the tip and the collector [33].

3.4.7 FLOW RATE OF THE SOLUTION

The flow rate of the polymer solution within the syringe is another important process parameter. Usually, lower flow rate is more recommended as the polymer solution will get enough time for polarization. If the flow rate is very high, bead fibers with thick diameter will form rather than the smooth fiber with thin diameter owing to the short drying time prior to reaching the collector and low stretching forces.

3.4.8 TIP TO COLLECTOR DISTANCE

The distance variation between the tip and the collector has been applied as another approach to control the fiber diameters and morphology. It has been observed that a minimum distance is required to allow the fibers sufficient time to dry before reaching the collector [34]. It is well known that one important physical aspect of the electrospun fiber is the dryness from the solvent, so minimum distance is favorable.

3.4.9 COLLECTOR COMPOSITION AND GEOMETRY

Collectors usually act as the conductive substrate to collect the charged fibers during the electrospinning process. Aluminum foil is used as a collector in most cases but it is difficult to transfer the collected nanofibers to other substrates for various applications. Different kinds of collectors have been developed including wire mesh [35], pin [36], grids [37], parallel or gridded bar [38], rotating rods or wheel [38], liquid bath [39], etc., depending on the type of application. It was also found that the packing density was influenced by the conductivity of the collectors. When this charge was not dissipated when collected on nonconducting collectors, the fibers repelled one another, yielding a more porous structure.

3.4.10 AMBIENT PARAMETERS

Ambient parameters such as humidity, temperature can also affect the fiber diameters and morphologies. Usually, low humidity dry the solvent easily and may increase the velocity of the solvent evaporation. At the same time, high humidity will lead to the thick fiber diameter owing to the charges on the jet that can be neutralized and the stretching forces become small.

3.5 BIOMEDICAL APPLICATIONS OF ELECTROSPUN NANOFIBERS

Electrospun nanofibrous matrices are significant for tissue engineering, since they resemble the natural extracellular matrix (ECM). Nanofibers for tissue regeneration are highly adaptive mainly because of the wide range of biocompatible polymers available, and the flexibility in process optimization. Moreover, the electrospinning processes, such as the techniques mentioned at the beginning, can be used to further enhance nanofiber scaffold performance. Also, bioactive agents such as proteins can be added to the nanofiber scaffold as well, further enhancing the performance [40]. The ECM is the fibrous network in the body along which the cells naturally grow and spread, hence a body-mimicking structure that imitates the ECM that can support cell growth is of great beneficence. The size range of electrospun nanofibers and the very large surface area of the constructs formed are the two traits shared with natural ECM. The flexibility of the electrospinning process is another great benefit, as different cells have different needs for optimal growth and by using electrospinning, the morphology of both fibers and scaffolds can be easily varied and optimized. Also, a wide variety of materials can be electrospun and incorporation of particles and various agents, such as growth factors, is possible.

Nanofibers can also be used to deliver proteins to target tissues in a controlled manner. In fact, the use of nanofibers in encapsulating and delivering therapeutics is another area of focus in biomedical nanofibers. Nanofibers are attractive for two main reasons. First, nanofibers have a large surface area to volume ratio, which is even higher considering the pores that exist inside the fibers. Not only can the large surface area ensure a high therapeutics take-up, it can also reduce the constraint to drug diffusion leading to increases in the total fraction of drug that can be released. Second, relevant nanofiber properties, such as fiber diameter, porosity, and drug binding mechanisms, are highly customizable through process parameters and material choice, and the rate of drug release can be tailored for each application. The adaptability of nanofibrous drug carriers allows this technology to show potential in treating many types of diseases. In tissue regeneration studies, the performance of nanofiber drug carriers, in terms of total amount of drug released, is shown to be greater than microfibers and gel films. Despite having gained significant understanding in nanofiber drug delivery, there are still several aspects that are not well understood. The future work must focus on better understanding the drug release mechanism and drug carrier response in biological systems rather than test solutions.

There is a huge potential to use electrospun nanofibers in wound care applications. One of the main benefits is based on the possibilities with encapsulation of various agents (chemical substances like growth agents, etc.) in the nanofibers. If the material dissolves in the solvent, together with the polymer, nanofibers with distribution of the material similar to that in the solvent are feasible. Together with suitable degradation behavior of the biopolymer matrix, unique wound-healing applications can be designed. For wound healing, an ideal dressing should have certain characteristics such as hemostatic ability, absorption ability of excess exudates (wound-fluid/pus), efficiency as bacterial barrier, appropriate water vapor transmission rate, adequate gaseous exchange ability, ability to conform to the contour of the wound area, functional adhesion, i.e., adherent to healthy tissue but nonadherent to wound tissue, painless to patient and ease of removal, and finally low cost [41]. The present efforts for using polymer nanofibrous membranes as medical dressing are still in its infancy but electrospun materials meet most of the requirements outlined for wound-healing

polymer matrices because their microfibrous and nanofibrous structures provide the nonwoven textile with desirable properties and there are also reports of cytocompatibility and cell behavior of normal human keratinocytes and fibroblasts onto electrospun nanofibrous membranes [42].

Electrospun polymer nanofibers can also be utilized with or without various biomolecules as a cosmetic skin care mask for the treatment of various skin-related applications such as skin healing, skin cleansing, or other therapeutical and medical properties [43]. The electrospun nanofibrous skin mask has advantage of high surface area, which facilitates better utilization and also speeds up the transfer rate of the additives to the skin. The electrospun nanofibrous cosmetic skin mask can be introduced gently and painlessly and also directly to the targeted area of the skin to provide healing or care treatment to the skin [44]. For skin health and renewal, skin-revitalizing factors can be impregnated into nanofiber masks [45]. Due to very small pore size and high surface area to volume ratio, electrospun nanofibers have the potential to be used as skin masks for cosmetic purposes.

3.6 CONCLUSION

Electrospinning is a simple, versatile, and cost-effective technology which generates nanofibers with high surface area to volume ratio, porosity, and tunable porosity. Because of these properties, this process seems to be a promising candidate for various applications especially in nanomedicine field. The important solution parameters such as viscosity, molecular weight, concentration of the polymer, applied voltage, tip to collector distance, and conductivity, can seriously affect the fiber formation. The electrospun fibers were increasingly being used in a variety of applications such as tissue engineering scaffold, wound dressing material, drug delivery material, and cosmetic materials. Recently developed methods for the oriented deposition of electrospun fibers, for the fabrication and oriented deposition of single polymer fibers, and for the production of electrospun fibers with defined lengths will offer entirely new opportunities for the realization of new properties and applications. Several attempts were being made to improve the design and cellular migration through the electrospun fibers. In general, the electrospinning process shows excellent promise for tissue engineering and regenerative medicine which can be a breakthrough in nanomedicine field.

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