Polymer-Based Nanofibers: Preparation, Fabrication, and Applications

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Abstract

Polymer-based nanofibers as an important group of materials have attracted considerable attention of research and industrial areas. Polymer nanofibers with diameters in submicrometer (<1 μm) possess unique properties including large specific surface area per unit mass, which facilitated adding functionalities to surface for specific applications.

Typically, polymer nanofibers have been synthesized by electrospinning, spinneret-based tunable engineered parameters (STEP) or drawing techniques, template synthesis, phase separation/inversion, self-assembly, solution blowing (air jet spinning), forcespinning (centrifugal spinning), and interfacial polymerization of nanofibers. The most common method is electrospinning due to its feasibility, cost-effectiveness, ability to fabricate continuous fibers from various

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polymers, and mass production. However, pros and cons of synthesis methods will also be presented. Furthermore, characterization methods of polymer nanofibers and effective factors on nanofibers will be provided.

Polymer nanofibers are fabricated from both natural and synthetic polymers. Polymer blends are also used to improve biodegradability in medical applications and conductivity in sensors and neural tissue engineering.

This chapter will also present recent developments of polymer nanofiber applications as scaffolds for tissue engineering, wound dressing, drug delivery, filters, protective clothing, sensors, and reinforcement in composite materials.

Keywords
Polymer · Nanofibers · Preparation · Fabrication · Application

Introduction

Polymers are the most common materials used in the production of nanofibers. A large number of publications in the field of nanofibers have been dedicated on polymer nanofibers because of their unique properties and variability of applications [1–3]. Several approaches have been used for the processing of polymer nanofibers consisting of spinneret-based tunable engineered parameters (STEP) or drawing techniques, phase separation/inversion, template synthesis, self-assembly, solution blowing (air jet spinning), forcespinning (centrifugal spinning), interfacial polymerization of nanofibers, and electrospinning (e-spinning). Among them, electrospinning has been considered as the most famous technique to processing of polymer-based nanofibers because of its ability to use a wide range of polymers (versatility), reducing the fiber diameter in the scale of nanometer, and possibility of scale-up production [2, 4–7]. However, it has some limitations including safety problems, low production rate, and high polymer-dependent properties. Therefore, to improve production rate, other nonelectrospinning methods were presented. In the perspective of industrialization and scalability, air jet- and forcespinning like electrospinning have the most advantages. The comparison of various spinning methods including electro- and nonelectro spinning has been provided in Table 1.

Large surface area, scalable porosity, and versatility make the nanofibers a perfect candidate for different applications consisting of scaffolds for tissue engineering, wound dressing, drug and gene delivery, artificial organs, cosmetic facial mask, biosensors, filtration, protective clothing, energy production, stabilization of enzymes, affinity membrane, and dental [1, 2, 6, 7, 9].

Characteristics of polymer nanofibers including diameter, morphology, and their orientation in mesh nanofibers are controlled by various parameters such as parameters related to the polymer characteristics, processing system, and environmental parameters [11].

So far, it has been reported that more than 100 polymers have been spun into continuous fibers with a diameter in nanometer scale and a length from tens of meters and more. Typically, natural and synthetic polymers or the blends of them

Table 1 Comparison of nanofiber spinning techniques from the aspects of industrial production [8–10]

Methods	Electrospinning	Air jet spinning/ solution blowing	Centrifugal spinning	Template synthesis	Phase inversion freeze drying	STEP techniques
Nanofiber diameter range	40 nm to 2 μm	40 nm to several μm	25 nm to several μm	40 nm to few hundreds nanometers	50 nm to 1 μm	50 nm to several μm
Production rate (injection rate)	5 μL/min	20 μL/min	Up to 1 ml/min per nozzle			15–100 μL/min
Influencing parameters	Voltages Viscosity Solution feeding rate Distance	Nozzle geometry Viscosity Solution feeding rate Gas pressure	Viscosity Rotational speed Orifice diameter Evaporation rate Distance	Template shape Template pore size	Freezing rate Solvent properties Polymer concentration	Polymer type Molecular weight Solvent properties Substrate speed
Industrialization	YES	YES	YES	NO	NO	NO
Possibility of producing aligned nanofibers	YES	YES	YES	YES	YES	YES
Possibility for melt spinning	YES	YES	YES	YES	NO	NO
Possibility for spinning from highly concentrated polymer solutions	YES	YES	YES	NO	NO	YES
Voltage requirement	10–40 kV	NO	NO	~30 V (for electropolymerization)	NO	NO
Production of polymer/ ceramic composite fiber	YES	YES	YES	YES		YES
Production of core/shell nanofibers	YES	YES	YES	Hollow		NO
Possibility of producing 3D nanofibrous structures	YES	YES	YES	YES	YES	YES

have been used in the various applications [3, 7, 8, 12–14]. The most commonly used polymers consist of collagen, elastin, fibrinogen, alginate, polyesters, polyurethane, blends of them, etc. [3, 7, 15]. The biomedical fields including tissue engineering and drug delivery are the most important applications of polymer nanofibers. Since the nano-sized fibers are in the same scale of biological molecules, they are suitable for mimicking the biological environment including native ECM. Nanofibrous meshes due to the large surface area to volume ratio, the high porosity, and interconnectivity of porous compared to macromolecular matrices show the enhanced cellular behaviors such as the increased cell adhesion, proliferation, and differentiation. Furthermore, the biological molecules loading, the exchange of nutrients, and wastes through the pores is also possible [4, 16]. Drug delivery via nanofibrous scaffolds have also advantages such as enhancing the therapeutic efficacy and reducing the drug toxicity due to the controlled release of drug. In addition, the topical and the site-specific drug delivery by nanofibers are possible. The release profile of drugs and bioactive compounds incorporated in nanofibers can be controlled by changing in morphology, porosity, and combination of fibers [2]. A blend of natural and synthetic polymers can be used for the optimal scaffolding construction in both tissue engineering and drug delivery. Biodegradability and biocompatibility are two important characteristics of polymer nanofibers in the biomedical applications [7, 17], because they convert into the biodegradable and biocompatible metabolites in the body and also the need for the secondary surgery to remove the implants will be eliminated. Moreover, the immunological reactions which lead to the incidence of allergic reactions will not be stimulated.

In this chapter, various topics about polymer nanofibers focusing on the processing methods, parameters related to the synthesis affecting the size and morphology of polymer nanofibers, characterization methods, polymers used in spun nanofibers, their different applications, limitations of the technology, and ultimately the future prospective will be presented.

Processing Methods

In recent years, a number of processing techniques have been used for the formation of polymeric nanofibers, which will be discussed below [1, 5, 8, 18].

Electrospinning

Electrospinning is the process of spinning under electrostatic forces in which continuous nanofibers can be prepared from polymer solutions or melts. Therefore, high voltage supply is needed to create electrically charged solution to jet into nanofibers.

The interaction of forces (electrostatic and surface tension) on a charged surface of polymer droplet plays a critical role in nanofiber production. As soon as the electric forces overcome the surface tension, the jet from Taylor cone throws in the conductive grounded target and finally polymer nanofibers solidified on the collector to form a nonwoven mesh.

Electrospinning is the most famous method to synthesize fibrous structures in nanoscale. It has a wide variety of advantages such as cost-effectiveness and the ability to make nanofibers with a high surface area to volume ratio which increases the surface functionalization for various applications especially biomedical ones.

However, it has some limitations consisting of the slow production rate, safety problems, and the high voltage requirement. Nonelectrospinning techniques have been designed to resolve some limitations which are discussed in the next sections.

The Effective Parameters on the Electrospun Polymer Nanofibers

A brief description of the effective parameters on the electrospun polymer nanofibers has been shown in Table 2.

Polymer Solution-Related Parameters

Although electrospinning is affected by various factors, polymer solution plays a crucial role in the formation of nanofibers with a large variety of size and morphology which will be discussed in the following sections.

Concentration

The polymer concentration must be optimum for chain entanglement to occur, neither too low nor too high. The range of concentrations to get the continuous

Table 2 Affecting parameters on morphology of electrospun polymer nanofibers

Parameters	Effect on fiber morphology
Solution parameters	
↑ Molecular weight of polymer	↓ Beads and droplet formation Formation of irregular shape with larger pores
↑ Polymer concentration (viscosity)	↓ Bead formation ↑ Fiber diameter (within optimal range)
↑ Solution conductivity	↓ Uniform bead-free fibers Fiber diameter with broad diameter distribution
↑ Solvent volatility	Generation of pores on the surface fiber (microtexture)
Processing parameters	
↑ Applied voltage	↑↓ First fiber diameter, after that with bead formation
↑ Distance between tip and collector (working distance)	↓ Fiber diameter Bead formation occurs in too short or too far distance Minimum distance is required for uniform fibers generation
↓ Feed rate/flow rate	↓ Fiber diameter Bead formation with very high feed rate
Ambient parameters	
↑ Temperature	↓↓ Fiber diameter and viscosity
↑ Humidity	Generation of circular pores on the fibers
↑ Air velocity	↑ Fiber diameter

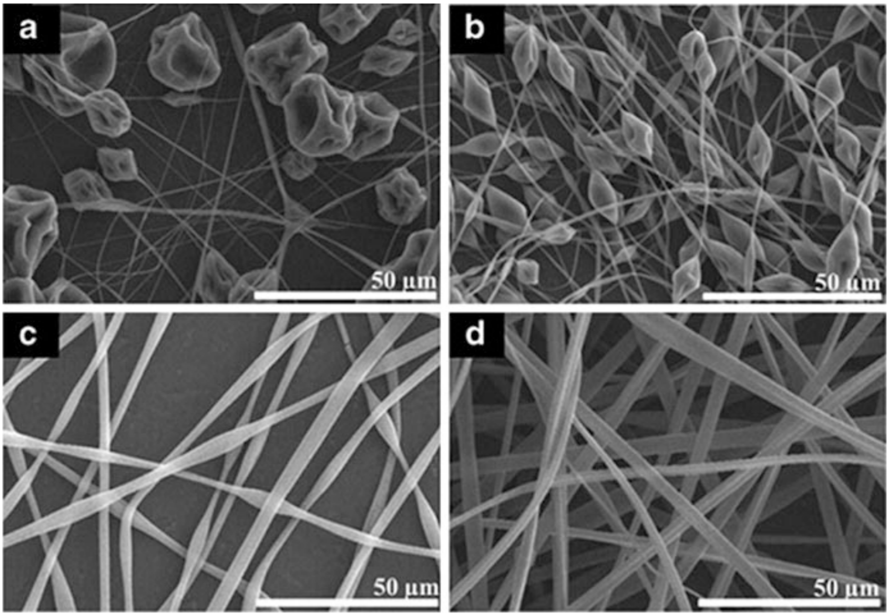


Fig. 1 (**a**–**d**) SEM images of the electrospun PMMA fibers obtained at polymer concentrations of (**a**) 12, (**b**) 15, (**c**) 18, and (**d**) 21 wt% and at a humidity of 25% (Reprinted by permission from Bae et al. [19]. Springer Nature. Copyright 2018)

fibers in electrospinning is determined by viscosity and surface tension. In solutions with low concentrations, the effects of surface tension lead to the formation of droplets during the electrospinning process; therefore, bead formation happens instead of fibers (Fig. 1). Moreover, when polymer in solution is very concentrated, it is stopped in the capillary tip because of viscosity in which rate of charged polymer flow through capillary is disturbed.

In this regard, investigating electrospinning of PEO/water solutions consisting of different concentrations of PEO have demonstrated that in viscosity of <800 centipoises, the droplets appeared while viscosity of >4000 centipoises is too tick to electrospun.

In another study, increasing the concentration of polystyrene in THF increased the fiber diameter while resulting in a narrower pore-size distribution. Taken together, in a range of optimum concentrations, increasing concentration caused an increase in fiber diameter [3, 4, 7, 12].

Solvent

Choosing an appropriate solvent to prepare polymer solution is an essential step in its spinnability, because polymer dissolution in solvent is the first step in the process of e-spinning. The used solvent should have characteristics such as good evaporation rate, vapor pressure, and boiling point while maintaining the integrity of polymer solution. In a binary polymer-solvent system, interactions between molecules including attraction or repulsion only depends on the type of solvent. As the polymer jet is traveling the distance between tip and collector, the solvent evaporation and phase separation occur before deposition of solid polymer fibers, a process which is strongly influenced by the evaporation rate of solvent [20]. In order for the solvent to evaporate from a jet during the distance, a volatile solvent should be selected. In the electrospinning process, fast solvent evaporation and phase separation take place due to the jet thinning. The solvent vapor pressure plays a critical role in determining the vapor rate and drying time. Since the solvent evaporation rate also affects the process of phase separation, it has a significant role in the formation of nanofibers [7].

Solvents such as chloroform, dichloromethane (DCM), ethanol, hexafluoroisopropanol (HFIP), and dimethylformamide (DMF) have been used for electrospinning of synthetic polymers, which demonstrated the physical properties depending on the solvent selection. Applied organic solvents not only are expensive but also not environmentally friendly. Moreover, the small amount of residual organic solvents in electrospun products is harmful for biological applications such as tissue engineering and wound dressing. So, there is a need for more washing or purification before application [4].

It has been proved that polymer solution characteristics such as viscosity and surface tension play a determining role in the morphology and size of electrospun nanofibers. Viscosity of solution results from the polymer concentration, but the surface tension value depends on both polymer and solvent. Different solvents may have various surface tensions. Renker and Doshi indicated that decreasing the surface tension of polymer solution leads to the production of bead free fibers. This experience should be carried on cautiously, because the surface tension is more a function of solvent composition than polymer concentration. Therefore, the low surface tension of solvent is not always suitable for electrospinning [7].

Solvent characteristics have a great effect on the fiber diameter. Several important characteristics of different solvents such as surface tension, dielectric constant, and boiling point which should be considered for selection of them in electrospinning process have been shown in Table 3.

The fiber diameter is influenced by the type of solvent (Fig. 2). Electrospun PVC fiber diameter obtained from dimethylformamide (DMF) solution or a mixture of tetrahydrofuran (THF)/DMF solution is less than those obtained from THF solution. Further, it has been found that the diameter of the electrospun polycaprolactone nanofibers depends on the solvent composition and the mixture of methylene chloride/dimethylformamide while having strong correlation with the solution dielectric constant [8].

The effects of different solvent concentrations have also been studied in electrospinning of chitosan solution in acetic acid. It has been demonstrated that by increasing the solvent concentration, the surface tension of solution gradually decreased leading to the production of thinner fibers.

Solvents used in electrospinning of polymers can also provide useful information about the solution conductivity. Dimethylformamide (DMF), a dipolar aprotic solvent (high polarity and low reactivity), with the high dielectric constant has been used as a solvent of polyacrylonitrile/polyurethane urea copolymer and poly

Table 3 Properties of the solvents used in electrospinning

Solvents	Surface tension (mN/m) at 20 °C	Dielectric constant Ɛ	Boiling point (°C)	Density (g/ml)	Conductivity (mS/Cm)	Viscosity η (mPa s) at 20 °C	Vapor pressure at 20 °C (mmHg)	Dipole moment μ (debye)
Chloroform (CHL)	26.5	4.8	61.6	1.498	1.0×10^{-4} (μS/Cm)	0.563	156	1.01
Dimethyl formamide (DMF)	37.1	38.3	153	0.994	1.09	0.82 (cP at 25 °C)	3.8	3.82
Hexafluoro isopropanol [1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP)]	16.1	16.7	58.2	1.596	–	1.65	120 (16 kPa at 20 °C)	–
Tetrahydrofuran (THF)	26.4	7.6	66	0.886	0.037	0.55 at 25 °C	133	1.75
Acetone	25.20	21	56.1	0.786	0.0202	0.304	231 (30.8 KPa)	2.7
Water	72.8	80	100	1.000	–	0.8905	–	1.84
Methanol	22.3	33	64.5	0.791	0.12	0.5445	–	1.6
Acetic acid	26.9	6.2	118.1	1.049	–	1.124	–	1.5
Formic acid	37	58	100	1.21	–	1.8	–	1.4
Dichloro methane (DCM)	27.2	9.1	40	1.326	4.3×10^{-5} μ	0.425	376	1.60
Ethanol (EtOH)	21.9	24.6	78.3	0.789	0.0554 1.35×10^{-13} μ	1.17	45.7	1.7
Trifluoro acetic acid (TFA)	13.5	42.1	72.4	1.525	–	0.81 mPaS	105 (14 KPa)	–
Isopropanol	18.3	19.9	82.3	0.781	0.0385	2.073		1.66
N,N′-dimethyl acetamide (DMAc)	34	37.8	166	0.945	–	0.92 (cP at 25 °C)	1	3.8
Dimethyl sulfoxide(DMSO)	43.7	46.6	189	1.101	–	2.0 (cP at 25 °C)	0.7	3.96

(*continued*)

Table 3 (continued)

Solvents	Surface tension (mN/m) at 20 °C	Dielectric constant Ɛ	Boiling point (°C)	Density (g/ml)	Conductivity (mS/Cm)	Viscosity η (mPa s) at 20 °C	Vapor pressure at 20 °C (mmHg)	Dipole moment μ (debye)
MEK: Methyl ethyl ketone (butanone)	23.42	18.5	79.60	0.79	4.41	0.38	–	2.76
Benzene	27.57	2.3	80.10	0.87	0.00	0.56	–	0.00
Carbon tetrachloride CCl_4	25.69	2.2	76.80	1.57	0.00	0.84	–	0.00
Chlorobenzene	32.34	–	131.70	1.10	0.00	0.69	–	1.69
Cyclohexane	24.07	15	80.70	0.77	0.00	0.84	–	0.61
1,2 Dichloroethane	31.55	–	83.50	1.24	0.34	0.72	–	2.94
Ethylacetate (EA)	22.68	6.02	77.10	0.89	0.29	0.40	76 (10.13 KPa)	1.78
Hexane	17.45	1.88	68.70	0.65	8.40	0.28	151.5 (20.2 KPa)	0.00
Nitrobenzene	42.66	34.8	210.80	1.19	3.31	1.73	–	4.22
Toluene	27.35	2.38	110.60	0.82	0.00	0.52	28.42 (3.79 KPa)	0.36

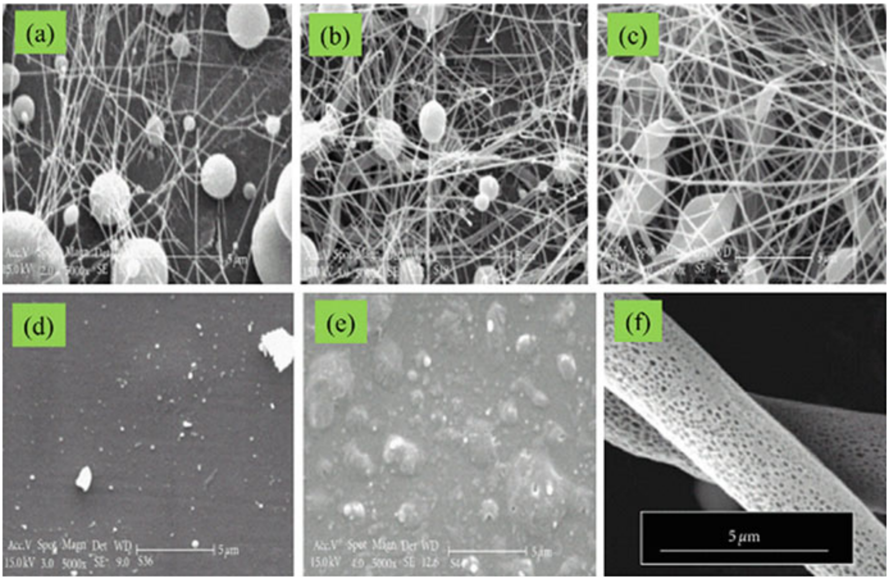


Fig. 2 SEM images of 5% PCL solutions dissolved in different solvents: (**a**) glacial acetic acid, (**b**) 90% acetic acid, (**c**) methylene chloride/DMF = 4/1, (**d**) glacial formic acid, (**e**) and formic acid/acetone, along with (**f**) SEM images of PVB nanofibers prepared from 10 wt% THF/DMSO (9/1 v/v) [20]

(p-dioxanone-co-L-lactide)-block poly (ethylene glycol) biodegradable copolymer during the process of electrospinning. It was reported that increasing the conductivity of solution leads to the formation of uniform bead-free fibers [7].

In addition, the solvent evaporation rate affects the morphology of fibers. The rapid solvent evaporation leads to the formation of flat fibers to usual round ones. Actually, flat fibers are formed when a portion of the solvent is trapped within the fibers, so the fiber collapses into a flat as the solvent evaporates [21].

Among the solvents, using the more volatile solvent is preferred; however, it depends on the processing conditions [3, 4, 7, 18, 22]. The effect of two different solvents isopropyl alcohol and dimethyl lactamide on poly (ethylene-co-vinyl alcohol), i.e., EVOH electrospinning, was examined by Lu et al. It was concluded that the presence of hydrogen bonds can influence the diameter and morphology of fibers. Furthermore, the effects of both ethanol and acetic acid solvents were investigated in another study. Because the surface tension of ethanol (22.4 dynes cm^{-1}) is lower than the surface tension of acetic acid (28 dynes cm^{-1}), ethanol evaporated faster than acetic acid. This high evaporation rate may lead to the formation of thicker fibers. It is also noteworthy that the dielectric constant of ethanol was 24.3 $C^2m^{-2}N^{-1}$ in 25 °C while the dielectric constant of acetic acid was 6.2 $C^2m^{-2}N^{-1}$ in 20 °C. In this regard, Lee et al. showed that the solvent electrolytic tendency could be the most important factor in the e-spinning process. The porous nanofibers containing nanopores in the range of 5.5–9.8 nm and different orientations have also been produced by using a variety of solvents and their mixtures. It causes changes in the surface roughness of fibers to improve the cellular adhesion, since the reaction of cells to nanotopography has been proved previously [18].

The type of solvent also affects the fiber porosity (Fig. 2). The structural characteristics of the electrospun polystyrene fibers from solutions containing different ratios of DMF and THF have been studied by Megelski et al. Electrospinning of solutions from 100% THF (more volatility) demonstrated a high density pores which increased the fiber surface area to more than 20–40% depending on the fiber diameter. However, the smooth fibers with approximately a complete elimination of microtexture have been formed by electrospinning of solutions from 100% DMF (lower volatility). Between these two extremes, decreased pore density was observed resulting from the enhanced pore size and reduced pore depth [7].

Electrical Conductivity

The electrical conductivity of the polymer solution is another effective factor in the nanofibers production by the electrospinning process. The polymer solution conductivity is mainly determined by the polymer type, solvent used, and the availability of ionizable salts [4]. Conductive solutions have a greater charge density compared to low conductivity solutions. Therefore, in the presence of an electric field, the fiber jet from high conductivity solutions compared to fiber jet from low conductivity ones will be exposed to greater tensile forces.

It was found that increasing the electrical conductivity of the solution during spinning leads to a significant reduction in the nanofiber diameter. However, with decreasing the conductivity, the electric field cannot create an enough jet elongation for producing uniform fibers, so the beads appear. Hayati et al. [7] showed that highly conductive solutions in the presence of the strong electric field are very unstable leading to a considerable bending instability and the wide diameter distribution. However, relatively stable fibers were formed by semiconducting and insulating solutions including paraffinic oil. It was also found that the fiber jet radius is inversely related to the cube root of the electrical conductivity of the solution. Natural polymers such as gelatin which inherently are poly-electrolyte have lower ability to form fibers compared to synthetic polymers. Because the carrying charges capacity is increased by ions, consequently, they incur more stress when they are in the electrospinning process subjected to an electric field.

The addition of salts leads to produce thinner and more uniform fibers, and the bead formation is also reduced [4, 7, 18, 20]. The reason for this phenomenon is the increased charge density which allows the more elongation and dielectric forces to act on the jet polymer; therefore, thinner fibers are fabricated [18].

Viscosity

According to most studies, viscosity is the main factor in determining the diameter and morphology of fibers. The increased viscosity due to the molecular weight or the high concentration of polymers leads to the formation of fibers with larger diameter, although the possibility of bead formation is decreased, and the more uniform fibers are produced. It was shown that with very low viscosity, any continuous fiber has not been formed due to the lack of chain entanglement and the fiber jet is broken into the droplets. On the other hand, with very high viscosity, there is a problem in throwing jet from polymer solution and polymer flow stops at the tip of the needle.

In addition, a study conducted in 1981 illustrated that the viscosity has also an important role in the melt electrospinning.

Three factors consisting of viscosity, polymer concentration, and molecular weight have correlated to each other. The viscosity of the polymer solution has strongly related to the polymer concentration. The relationship between these two factors and the morphology of the e-spin fibers has been reported by a number of studies investigating PLGA, PEO, PVA, PMMA, PLLA, gelatin, and dextran. Viscous polymer solutions show a longer stress relaxation time which can prevent throwing jets failure during electrospinning. Moreover, the larger and more uniform fibers are formed by increasing the viscosity or concentration of the solution. Viscosity has an important role in determining the range of concentrations in which continuous fibers can be achieved. In polymer solutions with low viscosity, surface tension is a dominant factor leading to the formation of beaded fibers. While above the optimum concentration, a continuous nanofibrous structure was obtained whose morphology has been affected by the concentration of the solution [1, 3, 4, 7].

Taken together, there is an optimum viscosity value for each polymer in electrospinning process, and this characteristic has a significant efficacy on the fiber morphology (Fig. 3).

Molecular Weight

Another important parameter related to the solution is the molecular weight which is also effective on the fiber morphology. Molecular weight has the significant impact on the rheological properties including viscosity, surface tension, and electrical properties such as conductivity and dielectric strength [23].

Therefore, to produce fiber usually high molecular weight polymers are used as they provide the desired viscosity. In addition, Casper and et al. found that increasing the molecular weight of the polymer leads to changes in the fiber morphology such as the reduced number of beads and irregular shape while the pores become larger. Thus, the possibility of constructing a mesh with the more uniform biophysical characteristics was achieved [4, 18].

Low molecular weight solutions tend to form beads instead of fibers. In other words, in solutions with low molecular weight instead of the electrospinning, electrospray is occurring. However, the high molecular weight results in the fibers with a larger average diameter [4].

Molecular weight is representative of the number of entanglement in the solution and consequently its viscosity. Chain entanglement has an important role in the electrospinning process, such as when HM-PLLA (high molecular weight poly-L-lactic acid) is used despite the low concentration of polymer. Because it can provide sufficient entanglement, sufficient viscosity is provided for uniform fiber formation. Moreover, the effects of the surface tension are prevented which has important role in the bead formation.

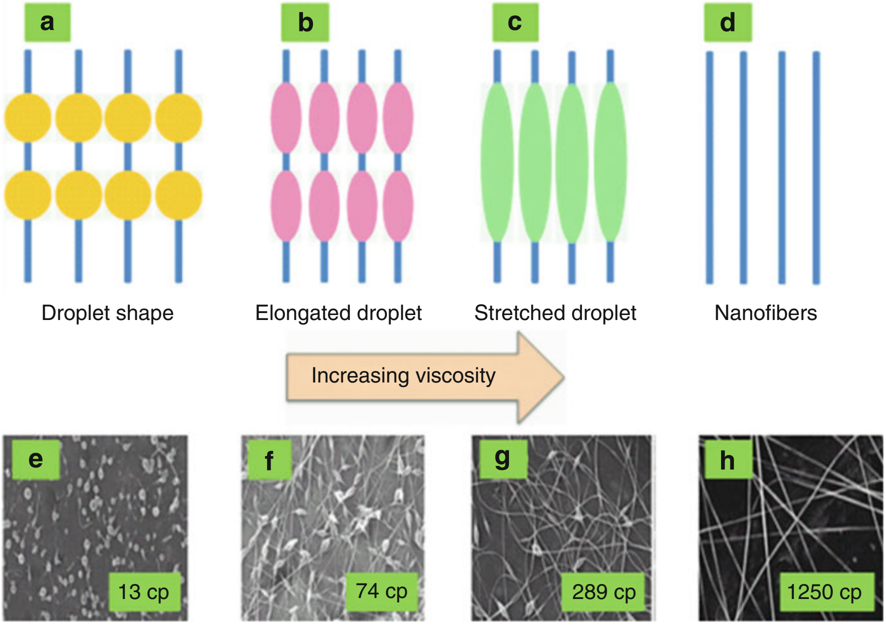


Fig. 3 Variation in morphology of electrospun nanofibers of PEO with viscosity: (**a**–**d**) schematic and (**e**–**h**) SEM micrographs [20] (Reprinted by permission from Zhang et al. [26]. Springer Nature. Copyright 2018)

In a study to investigate the effect of molecular weight, PMMA with different molecular weight ranging from 12.4 to 365.7 KDa was used. The researchers found that with increasing the molecular weight, the number of beads and droplets is reduced.

The ability to spin fibers is dependent on the entanglement initiating between polymer chains which happened on the molecular weight of 10,000 g/mol where a number of chain loops is formed [3].

It has been demonstrated that the high molecular weight is not always essential for producing uniform nanofibers, but the chain entanglement is more important. It is worth mentioning that if interactions between molecules are enough to consider as chain entanglement, nanofiber fabrication will be occurred. For example, electrospinning behavior of polymers with strong quadruple hydrogen-bonging ability was similar to nonfunctional polymers with the high molecular weight. Based on this principle, nonwoven membranes were produced by electrospinning of oligomer-sized phospholipids from lecithin solutions [7].

On the other hand, although the chain entanglement of polymer to form fibers is an important characteristic, the solution viscosity is a more general property because ceramic substrates, despite their low molecular weight, can also be electrospun [22].

Parameters Related to the Electrospinning Equipment

The Applied Voltage

There are some contradictions about the effects of voltage on the size and morphology of electrospun nanofibers. It has been indicated that the high voltage because of more exiting polymers lead to thicker fibers. However, some others claimed increasing voltage due to impose electrostatic repulsion forces on the jet polymers lead to production of thinner fibers. Actually, in most cases the stronger electric fields lead to the rapid evaporation of the solvent and the reduced fiber diameter which induced by the larger imposed columbic forces in the jet. So, the probability of bead formation is increased at the high voltages. A study conducted by Larrondo and Manley showed that by doubling the applied electric field, the fiber diameter is reduced almost by half. Which, the applied electric field in electrospinning is effective on the fiber diameter whose amount effect is changed by the polymer solution concentration and the distance between the tip and the collector [7].

Deitzel et al. by investigating polyethylene oxide (PEO)/water found that by increasing the voltage, shape of the surface is changed where Taylor cone and jet fiber formed (Fig. 4) [20].

Feed Rate/Flow Rate

The polymer flow rate within the syringe affects the jet intensity and the material delivery speed; so, it is also effective on the diameter and morphology of fibers.

The flow rate of the polymer solution in the electrospinning process is influenced by the electric field strength, gravity, and the possible use of the pump. The thinner fibers can be achieved by a slower flow rate while increasing the polymer solution feed rate caused the increased fiber diameter.

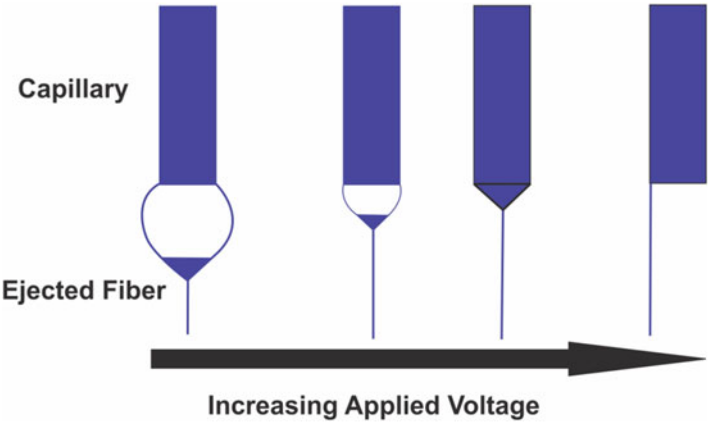


Fig. 4 Applied voltage effects on the Taylor cone formation. At low voltage, a pendant droplet (*white*) is formed at the capillary tip while Taylor cone (*dark blue*) is formed at the pendant droplet tip. By increasing voltage, Taylor cone is formed at the capillary tip and then, further voltage lead to ejection of fiber jet through the capillary [12]

A lower feed rate is more desirable because the solvent has enough time to evaporate. However, high flow rate leads to the formation of beaded fibers which are caused by insufficient time for evaporating solvent before reaching the collector plate. Similar results were also observed by Zuo et al. [3, 7]

Moreover, the flow rate can be effective on the porosity and the shape of fibers. Studying the effects of flow rate on the structure of electrospun fibers from polystyrene/tetrahydrofuran (THF) by Megelski et al. was shown that both fiber diameter and pore size increased with increasing the flow rate. Moreover, significant amounts of bead defects were observed at the high flow rates, which is induced by the inability of the fibers to completely dry before reaching the collector [18]. Incomplete drying of fibers also resulted in ribbon-like (or flat) fibers in contrast to fibers with a spherical cross section [20].

Distance Between Tip and Collector

The morphology and fiber diameter are also dependent on the distance between the spinneret and collector. A minimum distance is required to provide sufficient time for drying the fibers before they reach the collector. Otherwise, beads are observed in distances too close or too far. Actually, the distance can determine which eventually happened during electrospining or electrospray. Electrospinning of PVA, gelatin, chitosan, and poly (vinylidene chloride) has been shown that the effects of the distance between tip and collector are not as much as other parameters. It has also been reported that more flat fibers are formed at a closer distance while more round ones are achieved by increasing the distance [7].

According to Doshi and Renker, increasing distance from Taylor cone leads to the reduction of the fiber diameter. In addition, electrospun fiber diameter from polymer solution of PEO/water has been studied as a function of distance from the Taylor cone by Jaeger et al. It was reported that the fiber diameter was decreased from 19 to 9 μm, almost twice, by increasing the distance from 1 to 3.5cm [12].

Regardless of the polymer solution concentration, a flat or quasi-ribbon fiber and a beaded structure will be achieved at short distances [18]. It is attributed to inadequate drying of polymer fiber before reaching the collector [20].

Determining the optimal distance is affected by other parameters, including the nature of the solvent. So that, short distances were used for high volatility solvents while for low volatility solvents such as water, the longer distance is required for enough evaporation.

A minimum distance, approximately 8–15 cm, is necessary for the fibers to have enough time to dry before reaching the collector, and hence to form smooth and bead free fibers [4].

Environmental Parameters

In addition to device and substrate parameters, environmental conditions consisting of temperature, humidity and air flow velocity are also factors that play an important role in the quality of electrospun nanofibers.

Although electrospinning was usually done at room temperature, increasing the temperature from 25 °C to 60 °C resulted in decreased fiber diameter, which is caused by the reduced viscosity. Viscosity and temperature are inversely correlated.

Moreover, electrospining of polystyrene solutions in different humidity was studied (Fig. 5). It was demonstrated that by increasing the humidity the small spherical pores appeared on the surface and by further increasing the humidity the pores will be connected.

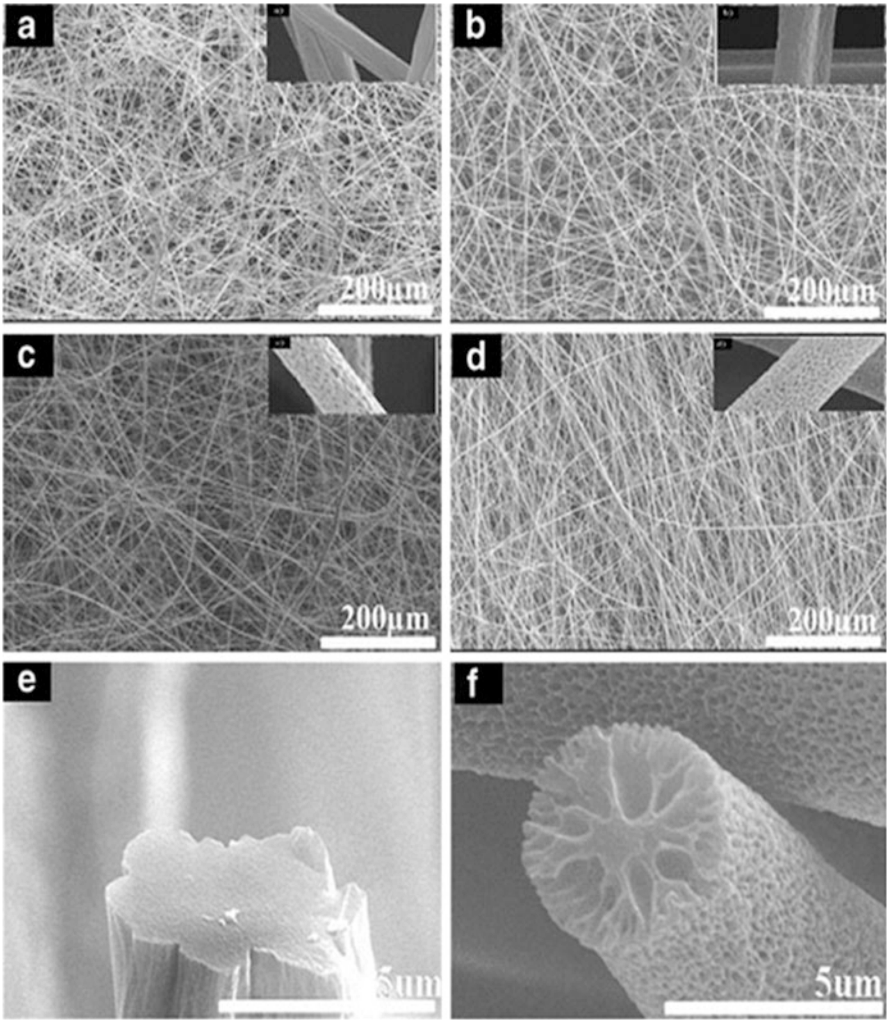


Fig. 5 (**a**–**f**) FE-SEM images of the electrospun PMMA fibers obtained under different humidity conditions: (**a**) 15–25%, (**b**) 26–40%, (**c**) 41–55%, (**d**) 56–70%, (**e**) cross-section of a nonporous fiber, and (**f**) cross-section of a porous fiber [19]

Very low humidity is also problematic because in low humidity, solvent evaporation rate is increased and the solvent dried very fast. It was also reported that high humidity can lead to the discharge of electrospun solution.

The air flow above the needle can also lead to increased evaporation rate through convection; as a result, a larger fiber diameter is achieved [4, 7, 18].

Polymers Used in Electrospinning

The most important property of electrospinning is the ability to apply a wide range of polymers for nanofibers production with different applications. Polymers can be divided into several categories, including natural polymers, synthetic polymers, or a mixture of them [7]. A list of polymers used in electrospinning process is shown in Table 4.

Natural and Synthetic Polymers

The electrospun nanofibers are generally composed of natural polymers since they mimic the physicochemical characteristics of the natural ECM. Natural polymers consist of proteins (e.g., collagen), nucleic acids (e.g., DNA), polysaccharides (e.g., hyaluronic acid), and lipids (e.g., lecithin). Natural polymers exhibited better biocompatibility and lower immunogenicity compared to synthetic polymers when used in medical fields.

The most important characteristics of natural polymers is their innate affinity or attachment to cells because of possessing a special protein sequence such as RGD (arginine, glycine, and aspartic acid) which makes them good candidates for tissue engineering applications. Natural polymers that commonly have been reported for electrospinning include collagen, gelatin, elastin, silk fibroin, casein, cellulose acetate, chitosan, fibrinogen, chitin, etc. Scaffolds based on natural polymers demonstrate the better clinical performance. However, according to various studies, the partial denaturation of natural polymers is worrying.

For the first time, it was reported that using solvents like fluoroalcohols including 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) or 2,2,2- trifluoroethanol (TFE) in the process of collagen electrospinning led to loss of main properties of collagen. Collagen is a natural polymer that is broadly used in tissue engineering because of its unique biological and physicochemical properties. Similar results have also been observed in the case of noncollagenous proteins [18].

However, in current studies, volatile fluoroalcohols such as HFP and TFE has been widely used as a solvent for pure collagen or collagen-poly (3-caprolacton) mixture.

Synthetic polymers have more benefits compared to natural polymers because of the mechanical properties (viscoelasticity and power) and the higher rate of degradation. Synthetic polymers commonly used in medical applications are often hydrophobic biodegradable polyesters, such as polyglycolide (PGA), polylactide (PLA), and poly (έ-caprolactone) (PCL). They have been electrospun to nanofibrous scaffolds for tissue engineering.

Moreover, biodegradable polymers such as poly caprolactone (PCL), poly (lactic acid) (PLA), poly (glycolic acid) (PGA), polyurethane (PU), copolymer poly

Table 4 Current polymers applied in electrospinning for biomedical applications [7, 8, 12, 20, 24]

Polymer	Solvent	Properties	Applications
Synthetic polymers			
Poly(L-lactic acid) (PLLA)	Dimethyl formamide, mixture of methylene chloride and dimethyl formamide, dichloromethane	Biodegradable (>24 months)	3D cell substrate, drug delivery system (DDS)
Poly(glycolic acid) (PGA)		Biodegradable (6–12 months)	Nonwoven tissue engineering (TE) scaffolds
Poly(lactic-co-glycolic acid) (PLGA)	Mixture of tetrahydrofuran and dimethylformamide	Biodegradable (1–12 months), controllable copolymer ratio	Biomedical applications, wound healing, DDS
Polycaprolactone (PCL)	Mixture of chloroform and methanol, toluene and methanol, dichloromethane and methanol DMF + methylene chloride	Biodegradable (>24 months), highly elastic	General TE, DDS
Poly(lactide-co-caprolactone) (PLCL)	HFP, acetone	Biodegradable (12–16 moths), highly elastic, controllable copolymer ratio	Vascular TE
Polyurethane (PU)	Dimethyl formamide, water	Good barrier properties, oxygen permeability	Nonwoven tissue template wound healing
Natural polymers			
Collagen	HFP	Most abundant protein in the body, good biodegradability and biocompatibility in physiological environments	General TE
Gelatin	2,2,2-trifluoroethanol (TFE)/HFP	Most abundant protein in the body, good biodegradability and biocompatibility in physiological environments	General TE Scaffold for wound healing
Chitin/chitosan	HFP/PBS HFP, TFA, acetic acid	Antibacterial activity, physicochemical properties	Skin TE, wound dressings

(*continued*)

Table 4 (continued)

Polymer	Solvent	Properties	Applications
Silk fibroin	Formic acid	Obtained from silkworms and spiders, good biocompatibility, minimal inflammatory reaction	Nanofibrous scaffolds for wound healing
Hyaluronic acid	DMF/water	Main component of ECM of connective tissue	Medical implant
Polymer blends			
Poly(glycolic acid) and chitin	HFP	–	General TE
Collagen and poly (ethylene oxide)	10 mM HCl (pH 2.0)	–	General TE
Poly(D,L-lactide-co-glycolide), collagen, and elastin	HFP	–	Vascular TE
Poly(L-lactide-co-e-caprolactone) and collagen	HFP	–	Vascular TE
Poly (e-caprolactone) and collagen	HFP	–	Neural TE
Poly(L-lactic acid) and hydroxylapatite	DCM and 1,4-dioxane	–	Bone TE
(a) Poly (e-caprolactone) and poly(ethylene glycol) (shell) (b) dextran (core)	(a) Chloroform and DMF (b) water	–	DDS: Drug delivery systems; (BSA)
Poly(D,L-lactic-co-glycolic acid), PEG-b-PLA, and PLA	DMF	–	DDS (Mefoxin, cefoxitin sodium)
Poly(L-lactide-co-glycolide) and PEG-PLLA	Chloroform	–	DDS (BCNU)

(lactic-co-glycolide) (PLGA), and copolymer of poly (L-lactide-co-έ-caprolactone) [PLLA-CL)] have been applied for bone tissue engineering, heart grafts, wound dressing, and engineering to replace heart vessels [7].

Composite Polymers/Copolymers

By mixing the natural and synthetic polymers in electrospinning process, it is possible to take the benefits of both natural polymers (cellular affinity) and synthetic polymers (mechanical properties). For example, PCL coated with gelatin (Fig. 6), PCL-PLLA coated with collagen, silk/PEO blend, collagen/PCL-PLLA blend, starch/PCL blend, hyaluronan and PCL, chitosan-PEO, PHBV with PDLLA blend,

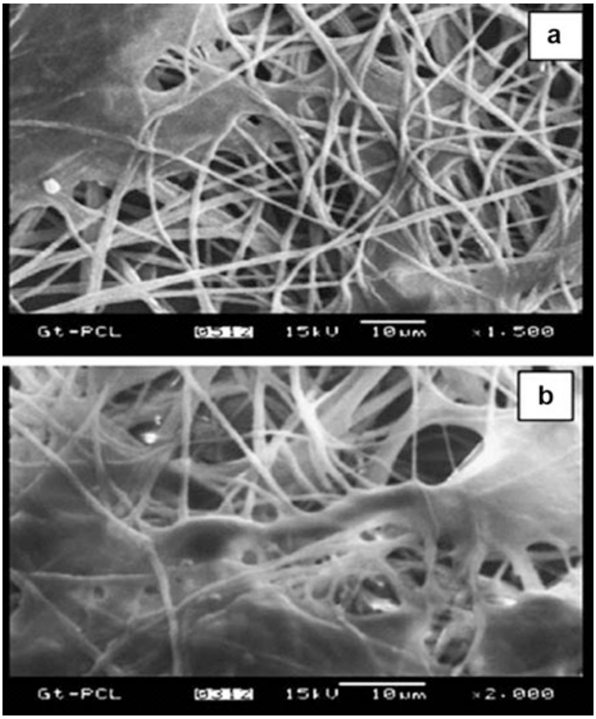


Fig. 6 Interaction of bone marrow stromal cells with [12] gelatin/PCL composite scaffolds after 7 days of cell culture: (**a**) cell ingrowth, and (**b**) layered cells (Reprinted by permission from Stojanovska et al. [9]. Royal Society of Chemistry. Copyright 2018)

PLLA or PLGA, or a mixture of natural polymers such as collagen and chondroitin sulphate, collagen and elastin, collagen and chitosan, collagen and PHBV, and gelatin with PHBV have been reported [18].

Furthermore, the cellular affinity, mechanical properties, morphology, structure, size and distribution of pores, biodegradability, and other physical characteristics can be adjusted using copolymers in electrospinning. For example, elastic poly (ethylene-co-vinyl alcohol) (PEVA) nanofibrous mat became stronger after the addition of poly (glycolide) (PGA) to the spinning blend. A three-block copolymer containing PLA, p-dioxanone, and PEG (PLA-b-DX-b-PEG) indicated a good balance between decomposition speed and hydrophilicity. Moreover, using methacrylic acid (MAA) in the copolymerization of methyl methacrylate (MMA) led to its thermal stability because the glass transition temperature of poly (methacrylic acid) (PMAA) is higher than PMMA and it also showed higher degradation temperature due to anhydride formation in high temperature. A new block copolymer including poly (p-dioxanone-co-L-lactide) -block-poly (ethylene glycol) (PPDO/PLLA-b-PEG) was e-spun for tissue engineering and drug release by Bhattarai et al. and it was demonstrated that the random deposition of PPDO and PLLA components and integration of PEG have significantly improved the biodegradability and hydrophilicity of scaffolds. Therefore, using copolymers is an important strategy to increase the properties of polymers for various applications [7].

Blending of poly (ethylene oxide) and PCL polymers was allowed the development of nanofibrous scaffolds with appropriate porosity for growth and infiltration of cells on the scaffold. Since PEO is a polymer with high degradation rate while PCL slowly degrades, it has an important role in the creation of larger pores [18].

Combination of natural polymers such as chitosan, collagen, and gelatin with synthetic polymers was widely used for the scaffolds production. Composite nanofibers from natural and synthetic polymers have also been studied in vivo. For example, electrospun composite collagen/PCL nanofibers have been investigated for vascular tissue engineering [22].

Polymer Composite with Bioactive Inorganic Nanoparticles

Electrospun blends of synthetic polymers and various bioactive inorganic materials such as hydroxyapatite (HA) and calcium phosphate have mainly been utilized as nanofibrous scaffolds for bone tissue engineering. Since bone possess a unique texture composed of organic fibrous matrix and inorganic apatite crystals, different studies have indicated that using polymer composites leads to increased attachment, proliferation, and differentiation of bone cells in vitro and bone tissue regeneration in vivo.

Investigating the electrospun poly (L-lactic acid) (PLLA)/HA composite nanofibers demonstrated that incorporating of HA not only changed the general morphology of fibers but also indicated smooth interconnected nanofibers with high porosity. PLLA/HA composite nanofibers could present appropriate structure for osteoblasts seeding in targeted bone tissue regeneration due to the combination of mechanical strength advantages of HA with nanofibrous structure. Furthermore, it was found that HA/PLGA composite adjusts behavior of human mesenchymal stem cells (hMSC). The results showed that HA disperse homogeneously and the enhanced roughness depends on the amount of HA. HA integration leads to increased alkaline phosphatase activity, expression of osteocalcin, bone sialoprotein, and calcium mineralization in hMSC.

A composite of synthetic polymers and demineralized bone powder (DBP) including PLA/DBP has also been reported to be effective for bone tissue regeneration. The osteoconductive effects of these electrospun composite nanofibers have been demonstrated in both in vitro and in vivo studies [22].

Electrospun Conductive Polymers

Electrical stimulation has a crucial role in regulating cell behaviors such as attachment, proliferation, and differentiation. The effects of electrical stimulation in bone, cartilage, skin, and nervous tissue regeneration have been reported by several studies [25]. Conductive polymer nanofibrous scaffolds composed of polypyrrole (PPy), polythiophene, or polyaniline (PANi) not only act as a template for cell growth and tissue regeneration, but also can locally conduct physiological electrical signals to the site of damaged tissue.

The experience of using conductive polymers in nerve tissue engineering demonstrated that electrical stimulation of PC12 cells through PPy conductive film led to significant neurite outgrowth.

In addition, attachment and proliferation of heart myoblasts and neurite outgrowth in vitro were also indicated by using PANi. Despite the mentioned advantages, it is noteworthy that electrically conducting polymers are not biodegradable, so their remnants can result in the immunogenicity and chronic inflammation in the body which required secondary surgery. To overcome this limitation, a mixture of minimum amount of conductive polymers with synthetic polymers (PANi and PLCL) has been used to maintain electrical conductivity while minimizing the toxicity.

These composite nanofibers display the significant increase in the number and length of myotubes, the expression of myogenic genes including myogenin, troponin T, and myosin heavy chain. Thus, the composite PLCL/PANi nanofibers can be used in muscle tissue engineering and investigating the electrical stimulation role in muscle cell differentiation.

Growth and differentiation of PC12 cells on electrically conducting nanofibers have also been observed by the deposition of PPy on PLGA electrospun nanofibers indicating the potential of electrically conducting nanofibers in nerve tissue engineering [22].

Applications

Tissue Engineering and Scaffolds

An important field of electrospun polymer nanofiber applications is scaffolds for tissue engineering of various tissues including nerve, blood vessels, skin, muscle, bone, and cartilage, which in recent years has been much discussed (Figs. 7 and 8). The main goal of tissue engineering is to repair damaged tissues. Nanofibrous structures of biodegradable polymers due to the similar fibrous structure with the native ECM act as a support for the adhesion, proliferation, and differentiation of various cells, so they will have a huge potential in the scaffolds for tissue regeneration [8].

Keratin, elastin, and collagen fibers derived from the extracellular matrix (ECM) are the most widely used materials since they naturally have a fibrous nature and can be easily made into fibrous scaffolds.

Proteins, polysaccharides, and other biological materials have also been investigated for scaffolds fabrication because of their unique features such as water solubility, water absorption, biodegradability, hydrophilicity/hydrophobicity, and biocompatibility.

Furthermore, cellulose, dextran, amylose, chitin, hyaluronic acid, chondroitin sulfate, heparin, and glycosaminoglycan have been extensively applied as compounds for scaffolds. On the other hand, synthetic materials including poly lactic acid (PLA), poly glycolic acid (PGA), poly lactic co glycolic acid (PLGA), polyhydroxyalkanoates (PHA), polyvinyl alcohol (PVA), poly caprolactone (PCL), and bioactive ceramics also play a promising role in scaffolds production [27]. Although preliminary work with electrospun fibers has shown promise in the reconstruction of the certain types of tissues, more modifications of chemical, biological, and mechanical characteristics will allow them to further progress [24]. Therefore, the design of

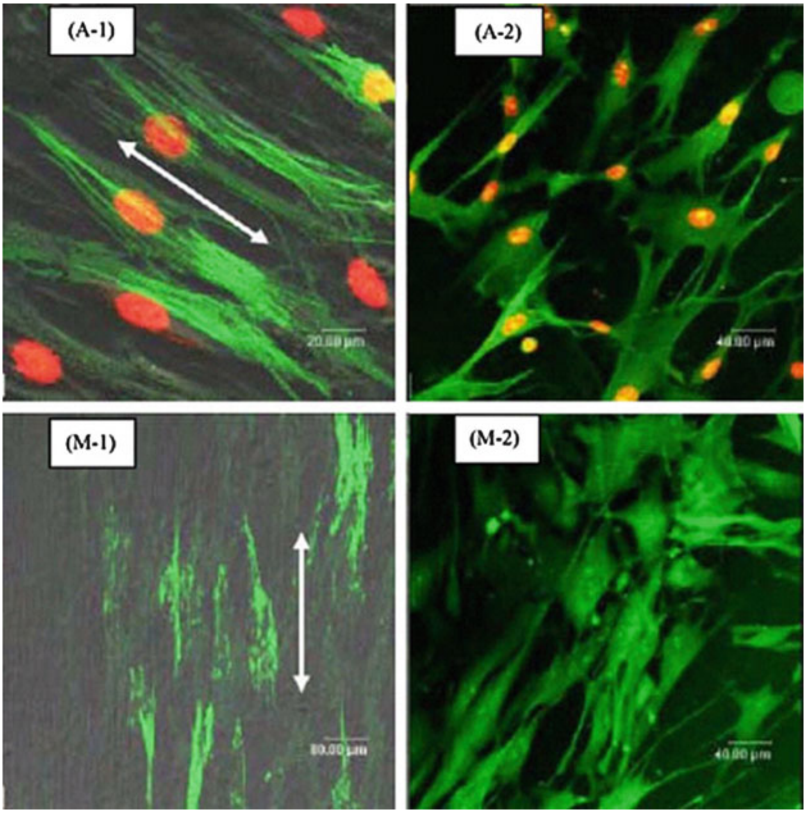


Fig. 7 Laser scanning confocal microscope images of immunostained α-actin filaments (A-1, A-2) and myosin filaments (M-1, M-2) in smooth muscle cells on aligned nanofibrous scaffold (A-1, M-1) and tissue culture polystyrene (A-2, M-2) after 1 day of cell culture. Potential aligned poly(L-lactid-co-e-caprolactone) [P(LLA-CL)] (75:25) copolymer nanofibrous scaffold for blood vessel engineering [26] (Reprinted with permission from Behrens et al. [44]. Copyright (2014) American Chemical Society)

an ideal scaffold that mimics the structure and biofunctions of native ECM remains as a great challenge, and it should be considered as a critical remark in the design of TE scaffolds [3].

Wound Healing Dressing

For wound healing, the high porosity of electrospun nanofibers can provide more structural space to accommodate the transplanted cells, facilitate the cell proliferation and migration, and improve the oxygen exchange, nutrients delivery, and waste outflow. On the other hand, the small pore size of nanofibrous scaffolds is able to limit the wound infection and dehydration during the wound healing. Moreover, the adjustable mechanical characteristics of electrospun nanofibers can retain the

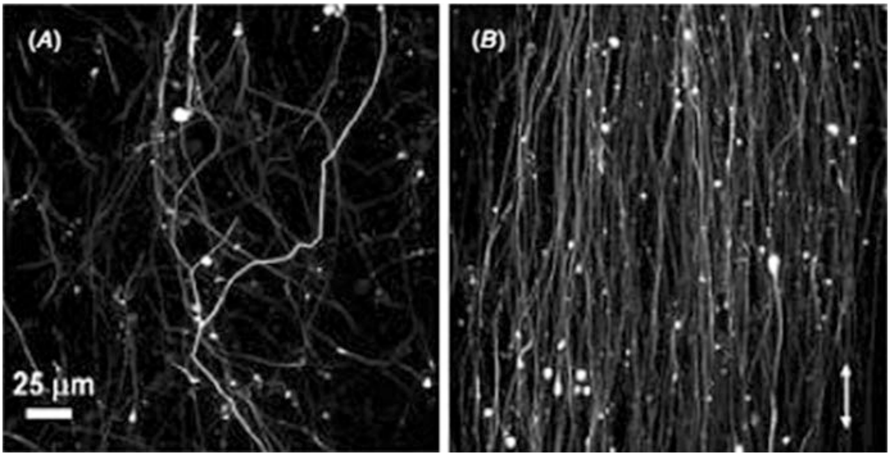


Fig. 8 (**a**) and (**b**) High-magnification confocal microscopy images of neurite morphology on (**a**) random and (**b**) aligned surface modified PLLA nanofibers with bFGF. Neurites oriented in the direction of aligned nanofibers while more neurite branching on random nanofibers was seen [10] (Reprinted with permission from Taghavi and Larson [45]. Copyright (2018) by the American Physical Society)

mechanical consistency between the TE grafts and the host tissue and also prevent the shrinkage and wrinkling of the wound during the implantation.

Several natural and synthetic polymers have been electrospun into nanofibrous scaffolds for skin TE. Natural polymers, such as collagen, gelatin, silk, chitosan, and fibrinogen have been fabricated to the nanofibers for wound healing. Among them, collagen type 1 with two α1 chains and an α2 chain is an excellent specific candidate for the skin TE scaffolds. Since collagen is the main component of human skin ECM, it forms a fibrillar 3D network structure (diameter of fiber 50–500 nm) to regulate the attachment, proliferation, and differentiation in the skin texture. Electrospun cellulose acetate/gelatin nanofibers have been developed to mimic the ECM composition of the skin (a complex combination of proteins and polysaccharides). It was demonstrated that 25/75 cellulose acetate/gelatin nanofibers showed the specific adhesion properties and the increased fibroblast proliferation of human skin. However, both the low resistance to enzymatic degradation and the poor mechanical properties are considered as main problems of tissue engineering by natural polymers. On the other hand, a number of biodegradable synthetic polymers consisting PGA, PLA, PCL, and other copolymers are usually utilized for skin TE and others due to its favorable mechanical and biodegradable properties. For example, by PLGA electrospining with (85:15, 75:25) lactide/glycolide molar ratios can be achieved the desirable biodegradable scaffolds to replace the damaged skin. However, the hydrophobic surface and the lack of cell-detection signals limit the use of synthetic polymers. Lately, the composite nanofibrous scaffolds with both physical characteristics of synthetic polymers and the bioactivity of natural polymers have attracted much attention. In this regard, it is found that PLCL/collagen electrospun nanofibers in comparison with the net PLCL nanofibers not only increase the proliferation rate of MSCs, but also increase the differentiation of epidermal stem cells. Similarly, some biodegradable composite nanofibers such as PLGA/dextran, PCL/gelatin, PLCL/gelatin, and PLCL/fibrinogen have also been developed to skin tissue engineering, which obtained the promising results.

Since prevention of infection during wound healing is essential for skin regeneration, a wide range of antibacterial nanofibers included with antibacterial factors (metal, organic, and inorganic) have increasingly emerged, which are effective treatments for both Gram-positive and Gram-negative bacteria during wound healing. Silver is the most commonly used metal antibacterial agent that illustrates a wide variety of biocidal activity with reduced bacterial resistance. In wound healing, silver demonstrates the capability to decrease surface inflammation, to enhance surface calcium, and to stimulate the production of epithelium. It has been indicated that the antibacterial activity of PLCL electrospun nanofibers against *Staphylococcus aureus* and *Salmonella enterica* can be enhanced by increasing the incorporated silver nanoparticles concentration. Moreover, PLA, PLGA, PVA, polysulfone, beta-cyclodextrin, and polyurethane (PU) were also electrospun into nanofibers and mixed or covered with silver nanoparticles to stimulate the antibacterial properties. Insertion of other inorganic materials such as titanium into the electrospun polymer nanofibers has also been demonstrated to show antimicrobial properties against the growth of several bacteria. PU/TiO2 nanofibers showed antibacterial efficacy against *Pseudomonas aeruginosa* and *S. aureus*. In addition, the electrospun silk fibroin/TiO2 nanofibers showed not only good blood and cell compatibility, but also demonstrated good antibacterial activity against *Escherichia coli* under UV irradiation.

It has been indicated that carbon nanotubes are very toxic to bacteria and kill germs on contact. Accordingly, Schiffman found that even at low concentrations (0.1–1 wt%) of single-walled carbon nanotubes embedded into electrospun polysulfone nanofibers, destroying of bacteria (*E. coli*) was observed. Inspired by nature, some natural antibacterial agents such as shikonin, alkannin, fusidic acid, chitosan, lysostaphin, and cinnamaldehyde have also been developed and merged into the electrospun nanofibers to provide the biocidal activity for wound healing [3].

Drug Delivery

Different delivery systems including liposomes, polymer micelles, and nanofibers have been investigated to improve the therapeutic efficacy and reduce the toxicity of conventional dosage forms [28–31]. Electrospinning, due to the significant characteristics such as flexibility in the choice of materials and medicines, increasing loading capacity and encapsulation efficiency, simultaneous delivery of therapeutic agents, and the cost-effectiveness, provides an attractive candidate in drug delivery applications especially for wound covering materials and the topical chemotherapy after surgery [32].

Moreover, a localized and controlled release drug delivery system can be achieved by electrospun nanofibers because of their well-interconnected open porous structure and large surface area. Therefore, many attempts have been made to chemically or physically integrate bioactive molecules into the scaffolds after electrospinning. Entrapment of biomolecules into electrospun nanofibers is performed by dip-coating method as the simplest procedure. So, biomolecules in the form of pure solutions or emulsions are physically absorbed into nanofibers through electrostatic forces. Alternatively, in a blend electrospinning, bioactive molecules are mixed with polymer solutions to produce composite nanofibers. Because blend electrospinning encapsulates biomolecules into nanofibers better than simple dipping, more controlled release profile was observed [24].

Methods like blending, surface modification, and co-axial electrospinning have been applied for drug loading into nanofibers. However, some critical characteristics such as biocompatibility and biodegradability, effective control of drug release, and the sufficient mechanical performance should be considered for drug-eluting scaffolds. Biodegradability, drug release kinetics, and mechanical characteristics can be adjusted through accurate choice of polymers and electrospining parameters while biocompatibility property can be achieved via surface modifications. Biodegradability of drug-eluting nanofibers ensures effective drug release and avoidance of surgical removal after the drug delivery. Using nanofibers in drug delivery systems allows improved therapeutic index, the possibility of localized delivery, and reduced toxicity of drugs. Drug release from electrospun nanofibrous mats can occur through different routes, mainly diffusion, desorption, and destruction of scaffold. Release may be adjusted through precise control of fiber characteristics (diameter, pore size, porosity, etc.); moreover, blending of different modes of scaffold construction such as emulsion and co-axial electrospinning is also used to optimize the kinetics of release. Such systems have been used for rhodamine B 237 loaded PCL electrospun nanofibers including chitosan nanoparticles and for controlled release of other multiple hydrophobic and hydrophilic drugs.

The drug loaded electrospun nanofibrous mats can be directly implanted into the tumor, which leads to higher drug bioavailability. In addition, the drug eluting nanofibers give special benefits such as the increased drug solubility, stability, and targeting. On the other hand, the drug eluting electrospun nanofibers constructed by mixing hydrophilic/hydrophobic polymers can be used to overcome the explosion effect [2].

While the classic drug delivery systems lead to delivery of drugs such as anticancer and antibiotics, electrospun nanofibers enable the integration of genes (DNA), RNA, cells, and different growth factors. Mainly, the carrier polymers were achieved by PLA, PLGA, and PCL while adjusting the biodegradability and the hydrophilic nature of fibers, and then setting behavior of release were obtained by adding other synthetic or natural polymers. The local chemotherapy field for the electrospun nanofiber mats is known only recently. Actually, the advantages of this treatment in comparison with the other dosage forms include the reduced system toxicity and the enhanced local drug concentration. Local cancer chemotherapy is a good choice for the treatment of unresectable tumor or prevention of recurrence after surgery [32].

Sensors and Biosensors

In response to the urgent needs for the cheaper, faster, simpler, and more reliable detections, significant progress has been made in the development of highly sensitive chemical and biological sensors. In this regard, the process of electrospinning to produce polymer nanofibers has been used for sensing applications. For example, it was recently shown that certain optical sensors based on electrospun fluorescent polymer nanofibers indicated sensitivity up to three times magnitude more than it was obtained from film sensors to detect nitro compounds, ferric, and mercury ions. Moreover, the high surface area to volume ratio and the excellent electrical properties make electrospun conductive polymer nanofibers such as polyaniline (PANI) electrospun nanowires interesting candidate particularly for sensing applications [33].

Nanofibrous systems with very thin diameter of less than 20 nm show several amazing features including a large surface area, high porosity, and superior mechanical performance, which makes them optimized candidates for applications in ultrasensitive sensors and ultra-thin filters [34].

Moreover, nylon polymer due to the chemical resistance, desirable mechanical performance, durability, and biocompatibility has a wide variety of applications in biosensors, which should be modified physically or chemically before using.

A miracle of nanofibers in sensing applications is where nylon nanofibers despite its polymer films, without any treatment show unique capacities including increased loading, sensitivity, stability, long life time, effective immobilization, and high reproducibility.

Recently synthesized glucose biosensors from electrodes modified with composite nanofibers of CP PBIBA (conductive polymer) showed excellent properties of stabilizing matrix through increasing covalent bonding between GOx and the surface of composite nanofibers. It can also be applied for the development of various electrochemical biosensors [35].

Nowadays, the importance of environmental pollution leads to the development of gas sensor technology, which is influenced by gas sensing structures to detect target gases based on various sensing methods. So far, different electrospun nanofibrous materials including polymers as the sensing interfaces have been used to detect a wide variety of gases with a better limit of detection.

H2 sensing test results achieved by the electrode modified with poly (vinylpyrrolidone) (PVP) /LiTaO3 electrospun composite nanofibers showed higher sensitivity and faster response to target gas compared to a flat film-based sensor [34, 36].

It has been shown that the dynamic response of opto-chemical sensors was considerably intensified by detecting the actual sensing layers in the form of highly porous 3D membrane including the electrospun polymer nanofibers instead of a compacted layer while performance parameters such as accuracy, optical characteristics, and long-term stability of optical conventional sensors was simultaneously maintained [37].

PEDOT nanofiber-based biosensor shows significant improvement on sensitivity, detection limit, and longevity compared to PEDOT film counterpart in the heparin diagnosis. The technique can be used for various applications in food science, homeland security, and biomedical fields [38].

Air filtration

Solving the problem of air pollution, especially fine particles in the air, has become a necessity for our daily life and industrial applications. Moreover, microorganisms and volatile organic gases (VOCs) in the air can also cause great damage to human life [39]. Electrospun nanofibers to capture the volatile organic compounds (VOC) in the air were presented by various authors. So that more rapid adsorption and desorption of VOC through electrospun nanofibrous membranes (ENMs) was reported compared to usual activated carbon.

In traditional HEPA filters, based on filtration theory, the nonslip flow mechanism is dominant; as the nanofibrous layer is coated on a conventional filter (Figs. 9 and 10), the sliding mechanism is overcome resulting from capability of smaller size of fiber to disturb the airflow [41].

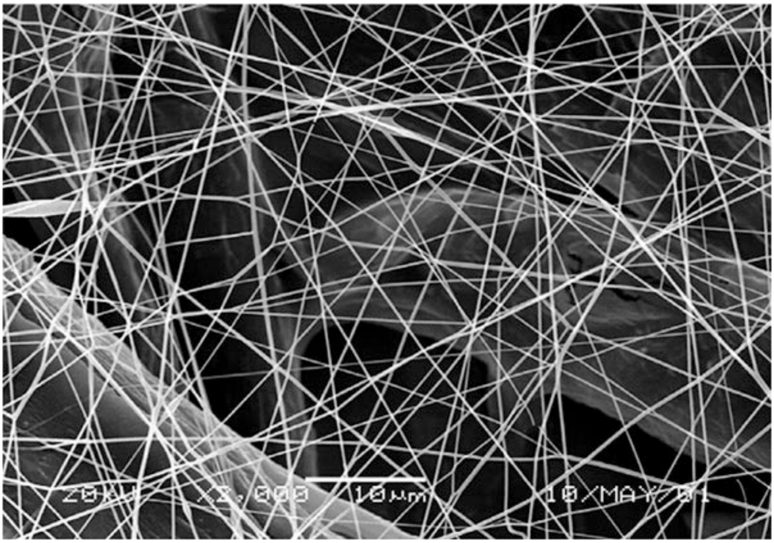


Fig. 9 Nanofibers on a cellulose filter media substrate [40]

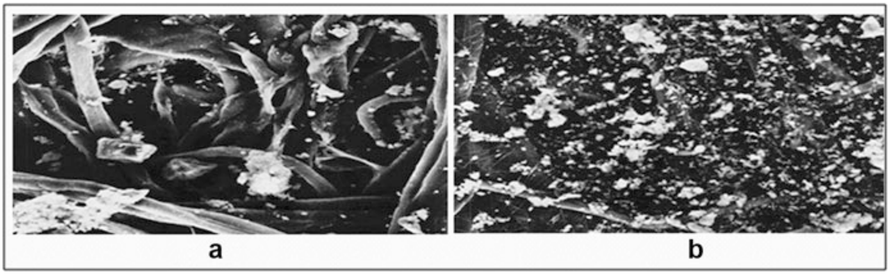


Fig. 10 ISO Fine dust loading on (**a**) cellulose and (**b**) cellulose/nanofiber composite [40] (Reprinted with permission from Cheng et al. [47]. Copyright (2008) American Chemical Society)

Structural parameters of electrospun fibrous membranes such as fiber diameter and diameter distribution, surface area and pore size distribution, basis weight fiber, and density play important role in the filtration process which has significant effects on the performance of filter membranes. B. Maze et al. noted that fibers with smaller diameter will increase the available surface area, resulting in lower pressure drop. As a result, a suitable electrospun nanofibers diameter is critical to optimize the filtration performance. Moreover, Hung et al. reported that more basis weights resulted in improved filtration efficiency but not QF (Quality factor) of filters due to the pressure drop enhancement during the filtering process. It was demonstrated that stacking several layers of electrospun fiber membranes with a lower basis weight is more effective than a single layer of electrospun fibrous membrane with high basis weight. In a study by Kim et al., it was shown that a proper electrospun nanofibrous film thickness contributes to the air filtration media efficiency, but very thick films will decrease the air filtration performance resulting from the increased pressure drop through the filtration media.

Besides these structural features, some environmental parameters and test conditions like face velocity, particle size, temperature, and humidity also significantly affect the filtration performance [39].

Recently, the electrospun nanofibrous membranes for air filtration have attracted great interest in both research and industry due to the outstanding surface characteristics of electrospun nanofibers, such as the excellent surface adhesion, high porosity, large specific surface area, and the low basis weight with the uniform fiber size, which result in the high performance filter media.

Surprisingly, the filtration efficiency of some electrospun filtration membranes can be 99.9998% with117.5 Pa pressure drop for 300–500 nm fine particles.

It is worth mentioning that a library of polymers including PAN, PVA, polyethylene terephthalate (PET), polyamide (nylon 66, nylon 6), polyurethane (PU), PEO, polysulfone (PSU), chitosan, cellulose acetate, and lignin has been used in high-performance electrospun nanofibrous membranes [39]. Furthermore, many efforts have also been allocated to prepare antibacterial membranes by incorporating different ingredients like inorganic compounds: Ag, Cu, CNTs, and TiO2, and some natural plant extracts (*Melaleuca alternifolia* extracts, *Sophora flavescens* extracts, eucalyptus extracts, and greensoy protein) [39, 41].

So far, different types of electrospun nanofibrous air filters such as composite, multilevel structured, thermal stability, antibacterial, reusable and self-cleaning air filter membranes have been developed.

Although we have observed numerous advantages for electrospinning technique application in HEPA filters over the past decade, there are some challenges like enhancing the mechanical strength of nanofibers at industrial applications to prevent breaking or crack of filters and development of making process without use of the harmful organic solvents. Despite the challenges, we are very convinced that the air filtration media is mainly influenced by the electrospinning technique which paves the way for producing safe and clean environment with the air filtration systems [39].

Protective Clothing

Currently, polymer nanofibers as a protective obstacle on textile fabrics have attracted great interest in different fields including wound dressing, air filtration, tissue scaffolds, sensors, and fire-retardant fabrics.

Many attempts have been made to integrate nanoparticles into spun fibers to improve features of fire-retardant and anti-microbial activity; polymers, for instance, polyamide (PA), polyvinyl alcohol (PVA), polyurethane (PU), polypropylene (PPy), and their composite are modified to increase flame retardant. On the other hand, PA or nylon 6 has been treated with nanoparticles of MgO, SiO2, TiO2, ZnO, and ZrO2 to enhance the physical, mechanical, and thermal characteristics. Similarly, nano-metal oxides integrated in the polymer matrix as an additive were used for the multipurpose applications including anti-flammability, UV protection, and anti-microbial activities.

Furthermore, the biodegradable polyelectrolytic nylon 6 resulting from other modifications has also been largely used in the textile industry because of its mechanical, antimicrobial, thermal, and physical properties.

It is also worth mentioning that MgO/nylon 6 hybrid nanofibers coated cotton textiles led to increased flame resistance, antimicrobial activity, and finally proper physical features which provided a good candidate for protective clothing for soldiers [42].

It was found that water vapor transmission characteristics of ENMs are comparable with textile materials and thus they can be used in protective clothing applications. Reactive organic compounds ((3-carboxy-4-iodosobenzyl) oxy-b-cyclodextrin) and nanoparticles were integrated into nanofibers by mixing with polymer solutions followed by simple electrospinning and tested for decontamination of chemical warfare agents (CWA). The disinfection efficacy of such ENMs was found to be much higher than conventional activated charcoal.

Facini et al. examined nylon nanofibers as the potential candidates for filtering of nanoparticles in protective suits [41].

Energy Devices

Regarding depletion of fossil fuels and the enhanced energy demands, development of renewable energy supplies is required for maintaining the economic growth.

It is found that nanofibers due to their unique characteristics of large aspect ratio, low density, and high porosity have more benefits than common materials in devices for energy harvesting, conversion, and storage. In fact, these 1D nanostructures provide the excellent materials for applications in energy devices like solar cells (SCs), nanogenerator, and lithium-ion batteries (LIBs). For example, nanofibers in solar cells have demonstrated the large photoelectric conversion efficiency based on the effective charge transmission and separation, and the maximum light absorption which was primarily attributed to the large porosity and the high specific surface area. Moreover, the unique properties of nanofibers (NFs) affected by the large surface area to volume ratio (SVR) and the small diameter lead to the high specific capacity and better cycling stability in NFs-based electrodes in SCs.

On the other hand, the hydrogen production was improved resulting from the photocatalytic activity of electrospun nanofibers as a photocatalysts in water splitting.

Furthermore, it is worth mentioning that LIBs for their unique properties such as high energy density and long life cycle have become a milestone for the advancement of energy storage technologies, which have been used in many fields. However, nanofibers with good electrochemical function, high mechanical strength, and large specific surface area can be used as amazing materials in LIBs [43].

Melt Electrospinning

In melt electrospinning, molten polymers are used instead of polymer solutions, which should be done in vacuum [18]. Melt electrospinning has its own advantages including no requirement to organic solvent, environmental safety, higher productivity without any reduction in the volume induced by the solvent evaporation, and the production of submicron fibers from polymers which have no suitable solvents at room temperature [8]. Although the melt electrospinning has many cons, it has been still in the early stages, because of the limitations including high viscosity, high processing temperatures, and their inability to obtain nanoscale fibers [7, 8, 20]. A list of some polymers which can be spun in molten form along with necessary temperatures has been shown in Table 5.

Solution Blowing or Air Jet Spinning

Solution blowing is the most feasible techniques to spun nanofibers from solution polymers using high-velocity gas flow as a fiber-forming driving force. In a well-known model, the system consists of concentric nozzle system where solution polymer is injected into inner nozzle while simultaneously a high pressure gas from outer nozzle is surrounding the polymer solution jet. The polymer solution jet into collector as multiple strands affected by stretching forces resulted from high speed gas. Evaporation of solvent occurs within jet process induced by shear forces at gas/solution interfaces, and finally polymer nanofibers solidified on the collector to form a no-woven mesh. Formation of spun nanofibers is affected by several

Table 5 Molten polymers used in electrospinning [7]

Polymer	Processing temperature (°C)
Polypropylene	220–240
Poly(ethylene terephthalate)	270
Poly-(ethylene glycol-block- ε-caprolactone	58.2
Polyethylene	200–220
Poly(methyl methacrylate)	130–157
Polyamides (nylon)	220
Polystyrene	240

Table 6 Parameters for the solution blowing process [9, 15]

Solution parameters	Viscosity	Explained in "Viscosity" section
	Polymer concentration	The most influencial on the fiber diameter
		Strongly correlated with the fiber diameter
		Polymer concentrations >15 wt% → ↑ fiber diameter
		Low polymer concentration not enable adequate chain entanglement → beads formation unless to be sufficient molecular weight to maintain the solution viscosity
	Molecular weight	Explained in "Molecular Weight" section
	Surface tension	
	Vapor pressure	
Process parameters	Air pressure	The greatest effect on the web uniformity and defect density
		↓ air pressures→ polymer droplets
		Not linearly influence on nanofiber diameter
	Nozzle collector distance	The optimal working distance: 30 cm; at lower and greater distance (5 cm and 50 cm) the nanofiber formation limited, formation of films occur because of solvent evaporation and insufficient drawing of fibers
	Solution flow-rate	↑ flow rate→ fibers with larger diameters and a greater amount of droplets
System parameters	Nozzle diameter Nozzle geometry	
Ambient	Temperature Humidity Atmospheric pressure	Explained in "Environmental Parameters" section

parameters that have been briefly described in the Table 6. A schematic of the solution blowing is also indicated in Fig. 11.

Solution Blown Nanofiber Applications

Air jet spinning has numerous applications from energy to biomedical applications which are summarized in the Scheme 1. This technique due to the properties which is free of electrostatic restrictions and the solvent constraints caused by dielectric constant is applicable for voltage-sensitive polymers. An example of these nanofibers for biomedical applications has been demonstrated in Fig. 12.

Forcespinning or Centrifugal Spinning

Forcespinning is another alternative approach to fabricate nanofibers from polymer solution or melt. It takes advantages of high speed, low cost, production safety, and large scale production. Centrifugal spinning has been designed to overcome

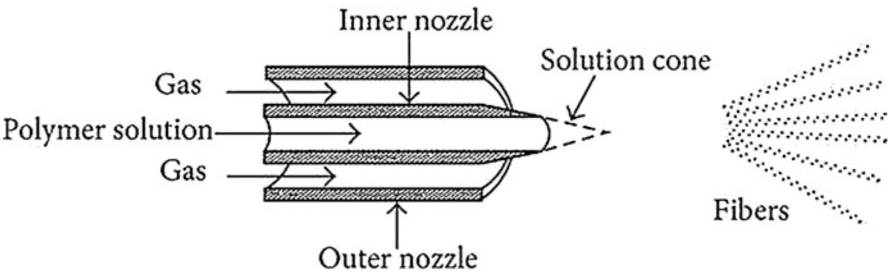
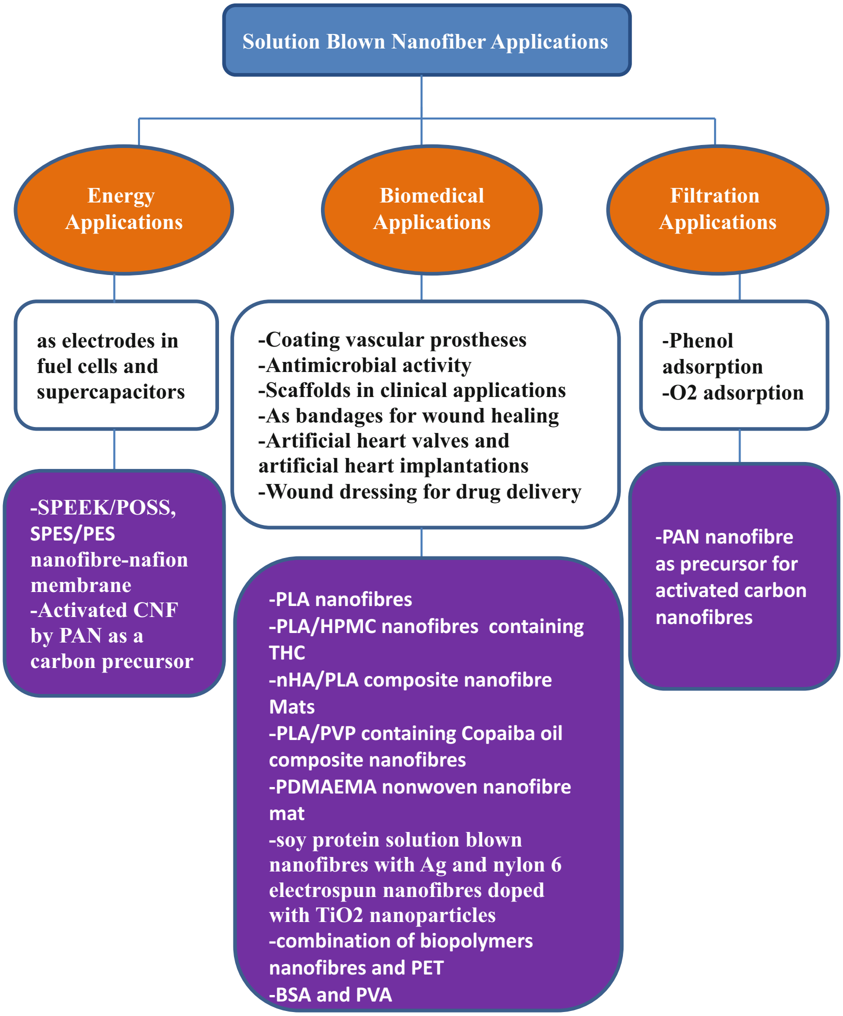


Fig. 11 Schematic presentation of solution blowing system [16]



Scheme 1 Applications of solution blown nanofibres [9, 44]

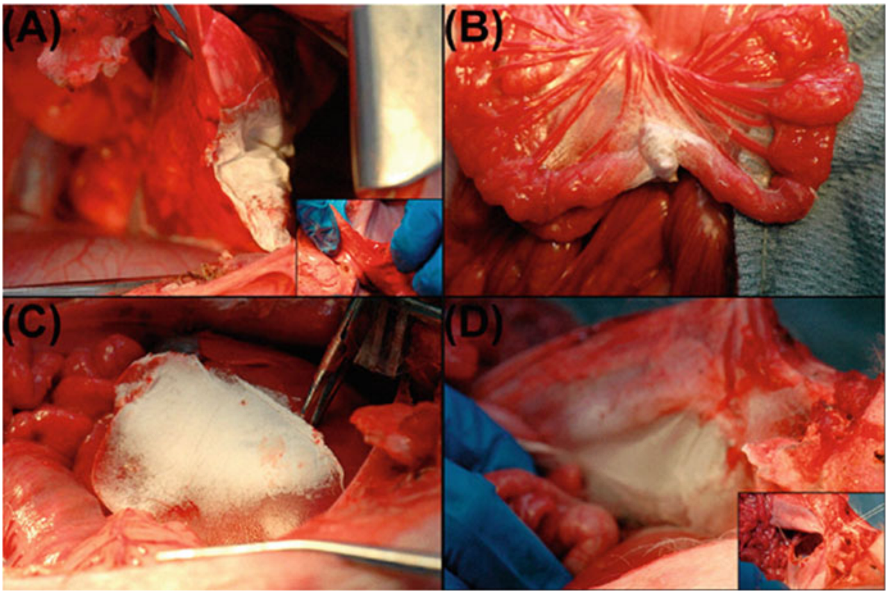
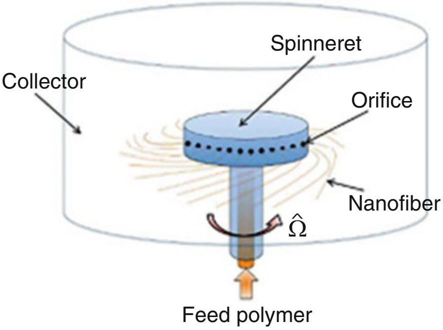


Fig. 12 Direct deposition of conformal PLGA nanofiber mats on piglet organs: (**a**) Lung resection; (**b**) Intestinal anastomosis; (**c**) Liver injury; (**d**) Diaphragmatic hernia. In all cases, nanofibrous mats fabricated over the defect in less than 1 min which ceased the liver bleeding and air leakage from the lung after segmentectomy [44] (Reproduced from Stojanovska et al. [9] with permission of The Royal Society of Chemistry. Copyright 2018)

Fig. 13 Schematic of centrifugal spinning device [45]



constraints of electrospinning consisting of low production rate and requirement to high voltage. Simple structure of forcespinning consists of a spinneret containing polymer solution or melt imbedded into rotating chamber with two or more pores which presented its schematic design in Fig. 13. Centrifugal force acts as a driving force to expel nanofibers out of the pores, when it exceeds the polymer surface tension. Determinant parameters in centrifugal spinning process have been summarized in Table 7.

Table 7 Parameters on centrifugal spinning process [9, 14, 45]

Process parameters	Centrifugal forces	More increasing → breaking jet and bead formation
	Angular velocity of chamber	Low angular velocity → bead formation
	Orifice radius	↓orifice diameter → ↓ diameter fibers and ↓beads
	Distance of orifice to collector	
	Evaporation rate for solution applications	Low evaporation rate → the solvent cannot evaporate completely and the fibers get collected as a thin film on the collector
		High evaporation rate→ Suppression of jet elongation, increased fiber diameter
	Temperature for melt-spun applications	↑Temperature → corrupted or burned polymer
		↓Temperature→ ↑ fiber diameter or the jet cannot be formed
Solution parameters	Viscoelasticity	↓Viscosity → bead formation ↑Viscosity →not jet formation
	Concentration of solution	Related to viscosity has to exceed the critical value for obtaining adequate chain entanglement
	Surface tension	

Applications of Centrifugally Spun Nanofibers

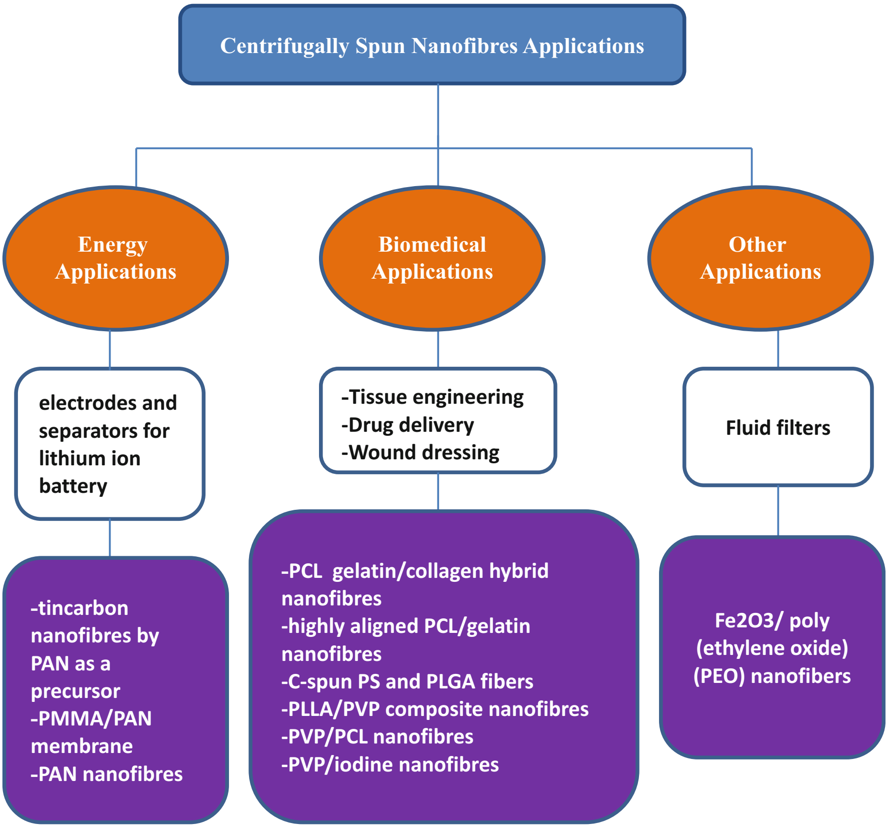
Several applications of centrifugally spun nanofibers have been summarized in Scheme 2. It can also be used commercially for various polymers (Fig. 14).

Drawing or Spinneret-Based Tunable Engineered Parameters (STEP) Method

A process like dry spinning in the fiber industry produces very long individual nanofibers separately. In the basic production process, a sharp probe tip such as micropipette is dipped into the edge of droplet that is previously deposited on the glass slide; then, the micropipette by a micromanipulator is withdrawn from polymer solution with a constant rate of 100 μm/S. Ultimately, the pulled nanofibers were deposited on the surface by touching the micropipette end. Drawing techniques with well-controlled fiber diameter, precise spacing, and orientation of fibrils has the ability to form 3D structures for biomedical applications such as scaffolds which mimic the native ECM.

Several solution parameters such as polymer type and its molecular weight, solvent characteristics, and polymer concentration control the fiber dimensions and beads formation.

It is also worth mentioning that, just a viscoelastic material which can undergo a strong deformation while maintaining its integration and tolerating the increased stress during the pulling-off is converted to nanofibers by drawing [1, 8, 18, 46].



Scheme 2 Centrifugally spun nanofibers applications

Template Synthesis

Template synthesis is another common method. As the name offers, it utilizes a nanoporous membrane as a template to produce solid (fibrils) or hollow (tubules) nanofibers. Using this method, a variety of materials such as electricity conducting polymers, metals, semiconductors, and carbons could be converted to the tubules and the fibrils in nanoscale diameter which can be used in electronics, optoelectronics, chemical or gas sensors, and batteries. However, there is no possibility to produce continuous nanofibers by this technique [8, 18, 47]. A shematic design of template synthesis has been shown in Fig. 15.

Phase Separation

Phase separation method includes five stages: polymer dissolution in a solvent to achieve a homogenized mixture, gelatinization, extraction by a different solvent,

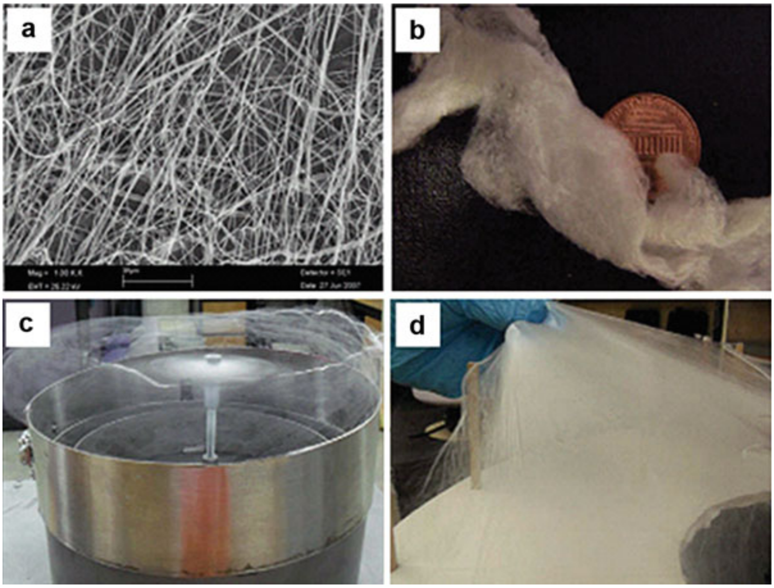


Fig. 14 (**a**) PEO Nanofibers (Solution) and (**b**) PS Mat (Melt) produced by the Forcespinning™ Method, (**c**) nanofiber webs and (**d**) free standing nonwoven mats are also produced by the presented method [14]

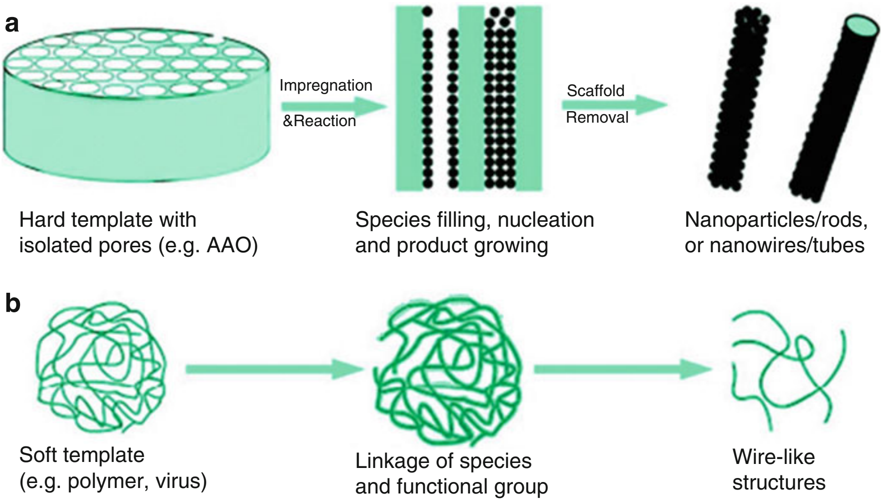


Fig. 15 Schematic description of (**a**) hard and (**b**) soft template synthesis of nanofibrous structures [47]

freezing, and freeze drying, which ultimately fabricated porous nanofibrous foam. Unfortunately, making a porous structure through this method is a time-consuming process [8, 18, 24].

Parameters such as solvents, polymer concentration, and phase separation temperature affect the nanofibers. For example, increased polymer concentration prevents the aggregation of large ice crystals, which allows the formation of porous nanofibers. Moreover, adjusting the freezing rate led to the adjusting fibers alignment which can be obtained by gradually freezing the polymer solution at constant rate or extruding the solution on a frozen rotating drum.

Achieved porous nanofibrous mats can be utilized in drug delivery systems, as precursors for carbon nanofibers with high porosity, or as templates for synthesis of inorganic fibers.

Self-Assembly

Self-assembly is a process in which amphiphile compounds consisting of custom-designed peptide-like amphiphiles, amphiphile peptides with balanced hydrophilic/hydrophobic amino acid domains, and di-block or tri-block copolymers under physiological conditions spontaneously organize to nanofiberous structures and patterns. The mechanism underlying the spontaneous phenomenon is intermolecular forces which brings together the smaller units. In this method, designing peptide sequences, optimizing, and stabilizing of their structures also take a long time [1, 8, 18, 24].

Characterization

The polymer characterization usually includes physical, mechanical, and chemical characteristics. In order to determine the structural and morphological characteristics of nanofibers as a function of process parameters, various studies have been done and demonstrated in Table 8.

Physical Characterization

Physical or geometric characteristics include structural features and the sample morphology; therefore, the structure of nanofibers determines their physical and mechanical characteristics. Fiber diameter, diameter distribution, fiber orientation, and morphology of fiber such as the shape of cross section and surface roughness were considered as geometric characteristics of nanofibers. SEM, FESEM, TEM, and AFM will be applied as the common techniques for characterization of geometry.

SEM technique has been used as the most common technique to determine the diameter and morphology of nanofibers. However, it has some limitations including

Table 8 Characterization of nanofibers and nanofiber mats [8]

Fiber or mat	Properties	Details	Instruments and techniques
Nanofiber	Physical and chemical	Molecular structure, molecular orientation, cross-linking, crystallinity	FTIR, NMR, optical birefringence, FTIR, WAXD, SAXC, DSC
	Geometric surface	Diameter, diameter distribution, orientation	SEM, TEM, AFM
		Chemistry	XPS, FTIR-ATR, water contact angle measurement
		Roughness	AFM
	Tensile	Young's modulus, tensile strength, elongation at break, tenacity	Cantilever technique
Nanofiber mat	Porosity	Pore size and size distribution	Mercury porosimeter, capillary flow porometer
	Permeability	Water vapor and gas diffusion	Dynamic moisture vapor permeation cell
	Tensile	Young's modulus, tensile strength, elongation at break	Tensile tester
	Biological	Biodegradability in vitro and in vivo	Mass loss, strength loss, surface morphology change
		Cell attachment and proliferation	Optical microscopy, confocal microscopy, Biological assays

low resolution at maximum zoom and the samples should be conductive, so a coating of gold or titanium is used for the most polymers that may alter indicated diameter in higher magnification. However, SEM is a quick way to check the nanofibers but the studied sample sizes should be very small.

Moreover, TEM is also a suitable technique to determine the fibers with very small diameter (<300 nm). Another alternative to determine the fiber diameter is atomic force microscopy (AFM), but the accurate measurement is more difficult due to the complexity of the tip. However, AFM is the best technique for the characterization of fiber surface. To measure the diameter accurately, usually two fibers which cross each other will be selected on the surface; the horizontal tangent higher of lower fiber is considered as a reference. In fact, the above height of reference is the exact diameter of the above nanofiber [7, 8].

But in most cases, nanofiber surface is not smooth; because, based on the parameters and the various production methods, its morphology is different. If the nanofiber surface is smooth, the surface area and the ratio of surface area to volume can be easily obtained from diameter. But in most cases, nanofiber surface is not smooth, because of the parameters and the various production methods its morphology is different. On the walls of poly-L-lactic electrospun nanofibers has been observed the internal pores and it may require special tools to measure the surface area of this nanofibers.

To obtain information about sample's crystallinity, other types of characterization methods must be used. Polarized light microscopy is probably the easiest method and based on the generated birefringence, the sample's crystallinity will be determined. This method is very affordable and rapid test that can be performed on the collected fibers. Other methods that can be used to determine sample's crystallinity include X-ray diffraction, both wide angle and small angle (WAXS and SAXS) and differential scanning calorimetry (DSC). In these methods, a reference with a clear crystallinity is required to determine the required fiber crystallinity by comparison [8].

Porosity is another geometric parameter. Porosity and pore size of nanofibrous membrane were considered as very important factors for its various applications such as filtration, tissue engineering, wound dressing, etc. Capillary flow porometer and mercury porosimetry techniques can be used to measure the pore size. Based on these methods, several studies described porosity features of electrospun nanofibrous scaffolds with highly porous structure containing 91.63% porosity, 9.69 mL/g total pore volume, 23.54 m^2/g total pore area, and 2–465 μm distribution of pore size [7].

Mechanical Properties

Precise measurement of the mechanical properties of the nanofiber matrix is essential, especially for biomedical applications such as scaffolds, because scaffold should be able to tolerate imposed forces by growing tissue or applied forces during related physiological and biomechanical activities, for example, tolerating pulse blood flow.

Mechanical characterization was achieved by applying tensile loading test to prepared specimens from very thin nonwoven fibrous mats. During the mechanical characterization of individual nanofibers adequate care should be taken in mounting and establishing the sample to prevent the severe damage or manipulating samples.

Various methods for mechanical characterization of nanofibers and nanowires have been used, including nanoindentation, bending tests, measuring resonant frequency, and microscale tensile tests.

Many researchers reported when nanofibrous membranes were deposited on a static plate collector, there is no anisotropy in in-plane tensile behavior. However, Lee et al. found that when the membranes obtained from rotating drum, electrospun nonwoven mats had different characteristics in different directions, because the fiber orientation depends on the linear velocity of the drum surface and other electrospining parameters.

Young's modulus, tensile strength, and strain at failure are also determined through tensile test with individual polymer fibers. A nano-tensile testing of trading system (Nano Bionix System, MTS, TN, USA) to study the mechanical properties of very thin individual fibers from polycaprolactone (PLC) has been used to perform tensile tests. In addition, tensile tests for single electrospun nanofibers of poly (L-lactic acid) (PLLA) collected from a rotating disk at different speeds have also been applied [7]. A list of the polymer tensile strength has been shown in the Table 9.

Table 9 Mechanical strength of some electrospun polymers [7]

Polymers	Ultimate strength
Collagen II	3.3 ± 0.3 MPa
Poly(ε-caprolactone)	40 ± 10 MPa
Gelatin	4.79 MPa
Cross-linked gelatin	12.62 ± 1.28 MPa
Silk fibroin	7.25 MPa
Poly(vinylchloride)/polyurethane (25/75)	6.30 MPa
Polyethylene oxide	10 ± 0.2 MPa

Tensile tests to determine the mechanical strength of nanofiber easily follow the macroscale standards and to extract material properties are involved the minimal assumptions. For fibers with a diameter close to 1 μm, this method is useful which lead to the fiber testing until the breaking time [7].

Indirect measurement of tenacity of individual electrospun polyacrylonitrile nanofibers was performed through cantilever method by Warner et al. A cantilever consisting of a microscope slide, a glass fiber with a diameter of 30 μm attached to one of its end, and a nylon fiber with a diameter of 15 μm attached to the free end of glass fiber was prepared. The polyacrylonitrile fiber sample is attached to the free end of the nylon fiber with epoxy resin. As the fiber sample is drawn with a computer-controlled tensile tester, bending of the cantilever is measured by an optical microscopy. A graph was used to convert the curvature of the cantilever to real numbers of the fiber tenacity, and elongation to breaking of fibers was estimated by a caliper. Average tenacity and average elongation to fiber failure was 2.9 g/d and 190%, respectively [8].

Another method to determine the elastic characteristics of spun membranes consists of using AFM including a cantilever and tip which is used to scan the page. By measuring the bending of cantilever induced by the repulsiveness of contacting atomic shells of tip, the atomic resolution of samples could be obtained with very little contact. AFM imaging is an extension of the tapping mode which leads to detection of changes in the composition and tenacity. By micromechanical bending tests using AFM, deflection modulus and shear modulus of individual electrospun collagen fibers as both purified and cross-linked by glutaraldehyde were determined.

Contact-resonance AFM for measuring of elastic modulus of nanofibers has been used by Cuenot et al. In this test, the nanofibers must be attached to the tip of cantilevers. AFM-based nanoindentation method has been applied for measuring the elastic modulus of one-dimensional nanostructures including nanowires and nanofibers. Although this technique has been successfully used for the mechanical characterization, there are some certain limitations such as the uncertainty caused by the tip nanoindentor, the relative position of the fiber tip, the effect of roughness and deflection of the fiber surface, and the adhesive force between the sample and the indentor. Various research groups also applied a three-point bending test of nanoscale by an AFM tip to determine the elastic modulus of nanofibers. It is found that the elastic modulus increased by reducing the fiber diameter. This size-dependent behavior was mainly because of shearing of fibrils within nanofibers to overall deflection of the nanofibers and changes of mechanical properties due to the orientation of polymer molecules within the nanofibers caused by strong strain forces in polymer jets [7].

Chemical Characterization

The molecular structure of nanofibers can be characterized by Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) techniques. If two materials for making nanofibers are mixed together, not only the structures of two compounds are detectable, but also intermolecular interactions can be investigated. In relation to applied collagen and polyethylene oxide mixture for nanofibers, NMR spectrum showed a new structure which is induced by the formation of hydrogen bonds between ether oxygen of polyethylene oxide and protons of amine and hydroxyl groups in the collagen [8]. The presence of regular secondary structure of 3_{10} –helix for dissolved fibroin in TFIP has been confirmed by using ^{13}C–NMR and circular dichroism (CD). In fact, supramolecular structure is representative of locating way of macromolecules in nanofibers that can be characterized by optical birefringence, wide-angle X-ray diffraction (WAXD), small-angle X-ray scattering (SAXC), and differential scanning calorimetry (DSC).

Birefringence of three block copolymer styrene-butadiene-styrene nanofibers with a diameter about 100 nm under an optical microscopy was studied by Fong, Chun, and Renker. Birefringence phenomenon is indicative of molecular orientation [7].

The surface chemistry features can be measured by analyzing water contact angle measurement. Other methods of surface chemistry characterization include X-ray photoelectron spectroscopy (XPS) and FTIR-ATR. The atomic percent of fluorine in electrospun nanofibers made of PMMA-r-TAN (polymethyl methacrylate with varying tetrahydroperfluorooctyl acrylate) has been measured by Deitzel et al. It was reported that the percentage of fluorine atom in the region near the surface of the polymer nanofibers is almost double compared with the bulk polymer [8]. Raman spectroscopy and FTIR have been used for investigating changes that might occur at the molecular level [7].

Conclusion and Future Perspective

A wide variety of polymers can be electrospun into very thin fibers in the range of nanoscale by control of diameter, length, orientation, and topology of the surface. Factors related to the solution and the processing, including viscosity, polymer concentration, molecular weight, used electrical field strength, conductivity, distance between tip to collector, and so on, considerably affect the fiber morphology; by changing these factors, the desired properties for specific applications can be achieved [7].

Various innovations consisting of coaxial electrospining, mixing and multiple electrospining, core-shell electrospining, blow assisted electrospining, etc., can be used to improve the applicability of nanofibers [2, 6, 48, 49]. By coaxial electrospinning technique, the polymers whose processing is difficult can be simultaneously electrospun and the core-shell structure can be obtained. This technology through a combination of polymer materials showed the new characteristics and functionalities which has attracted considerable interest. For example, by this technique the problem of explosive drug release can be controlled, because the polymers' shell acts as a barrier for the release of drugs. Furthermore, the core-shell nanofibers along with growth factors can present the growth factors in controlled and programmed manner and thus increase the regeneration of damaged tissue. By development of electrospinning technique including co- and multi-electrospinning, co-axial electrospinning, and emulsion electrospinning, a wide range of natural and synthetic polymers and composites of them can be electrospun into nanometric fibers with controllable morphology and diameter [20].

For spinning the high molecular weight polymers, which is not possible spining in the solution form, the blow-assisted electrospinning can also be used. Nanofibrous scaffolds of various polymers can be used for the engineering of various soft and hard tissues including bone, skin, and the wound dressing. This scaffolds due to the mimicking ECM and creating a three-dimensional (3D) environment for cells increases the various cell behaviors consisting of adhesion, proliferation, and differentiation. Despite the various advantages, there are also some limitations such as small pore size and reduced cellular infiltration into fibers which has been improved by multilayering technique consisting of blending polymers with different degradation behaviors, and cell migration [7]. Copolymerization, polymer blends or using organic nanoparticles along with polymers during the electrospining process, and different stages of post-modification lead to achieving optimum physical and biological characteristics of the nanofibrous mesh [24, 50]. Embedding nanofibers into the hydrogels "hydrogel nanocomposites" by making a complex structure of fiber/gel similar to native ECM can also improve the mechanical characteristics of the system. Moreover, a number of new hydrogel polymers such as temperature-sensitive polymers, pH-sensitive polymers, chemical cross-linked hydrogels, and supramolecular polymers have been synthesized and indicated a great potential for construction of biodegradable hydrogel nanofibers for various biomedical applications [4].

Furthermore, the e-spinning limitations such as high voltage requirements, low production rate, high dependency on polymer properties, and safety problems lead to development of several nonelectrospinning techniques. Solution blowing is the most promising alternative method to improve the production rate.

Force spinning is also another intriguing alternative technique with industrial applications induced by high production capability.

Other nonelectrospinning methods like phase separation, drawing, self-assembly, and template synthesis have also been applied in the specific applications such as electronic, optoelectronic, sensor, and battery applications. Although these alternative techniques have lower production capacity, their 3D structures present promising candidates for biomedical applications including tissue engineering, reinforcing materials, smart textiles, actuators, or sensors.

Physicochemical and mechanical characteristics of polymer nanofibers have been also defined. Structure, morphology, porosity, geometry, and tensile properties of nanofibrous mats can be characterized by common techniques and instruments. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), nuclear magnetic resonance (NMR), etc., are generally used for the characterization of the nanofibers [7, 8].

Presently, most applications of polymer nanofibers are limited to laboratories, so more attempts will be required before releasing them into market. So far, most of the biomedical studies have been carried out in vitro [6, 20]; therefore, wide in vivo studies before clinical transferring or commercialization are necessary. In the future, it will be proved that polymer spun nanofibers will be an optimal candidate for a wide variety of applications, especially biomedical field in which more researches should be carried out to study issues like mechanical properties, rate of degradation, and biocompatibility of polymer nanofibers for using them in clinical applications.

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