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The Place of Electrospinning in Separation Science and Biomedical Engineering

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Abstract

Electrospunnanofibers have found myriad of applications from separation science to clinical translation. Electrospunnanofiber scaffolds have the benefits of unique properties such as high surface area to volume ratio, interfibrous pore sizes, strong penetrability, great deal of active sites for adsorption, excellent stability, better targeting, minimum toxicity, high drug-loading capacity, exceptional mechanical properties, flexibility in surface functionality, ease of encapsulation of drugs and bioactive compounds, suitability for thermos-liable drugs, enhanced cellular interactions, and protein absorption to facilitate binding sites for cell receptors. In the field of separation science, electrospunnanofiber scaffolds have extensively served as sorbent material for solid phase extraction techniques mainly due to the need to improve sorptive capacity and analyte selectivity. Given that almost all of the human tissues and organs are deposited in nanofibrous forms or structures, electrospunnanofibers/ nanocomposites are currently being investigated for potential clinical applications. It is noteworthy that the nanofiber fabrication technique and the material integrity are key components to obtaining clinically relevant nanofibers. Owing to the significance of fiber arrangement to nanofiber performance, electrospinning has a leading edge over other nanofiber fabrication techniques due to the ease of controlling fiber orientation, despite the inherent advantages of other conventional nanofiber fabrication techniques. The current review highlights the superb qualities of electrospunnanofibers, their various methods of fabrication, and their various applications especially in separation science and clinically. We further provided an overview of the electrospinning principles, types of electrospinning, parameters that affect the nanofibers fabrication via electrospinning, challenges, and the future directions. The advent of robotics-assisted electrospinning technique offers new opportunities for the traditional biofabrication in higher accuracy and controllability and hence will certainly drive nanotechnology from laboratory/industry toward patient care in the near future.

Keywords: electrospinning, separation science, biomedicine, nanoscience



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1. Introduction

The emergence of nanotechnology and the unique properties of nanoscale materials have rekindled a renewed interest in the scientific community. The advent of nanotechnology has birthed various functional materials with highly ordered hierarchical structures and superb attributes that can successfully mimic the sophisticated biological processes. An important and exciting direction of research in nanomedicine would be to gain an in-depth understanding and exploit the cellular response to nanostructures. For example, electrospunnanofibers have diameter in the nanometer range, are arbitrarily long, and possess larger surface area (to volume ratio), interfibrous pore sizes, strong penetrability, great deal of active sites for adsorption, and better interaction with other compounds as compared to their microfibers counterpart [1, 2]. They have excellent stability, better targeting, minimum toxicity, high drug-loading capacity, exceptional mechanical properties, flexibility in surface functionality, and encapsulation of drugs and bioactive compounds and are suitable for thermos-liable drugs [1–4]. Endowed with both topographical and biochemical signals such electrospun nanofibrous scaffolds may provide an optimal microenvironment for the seeded cells. As such, electrospunnanofiber scaffolds have found promising applications in various clinical fields. Some notable applications include tissue engineering, regenerative engineering, separation science, biosensors, filtration, wound dressings, drug delivery, and enzyme immobilization, among others [5–7]. Almost all of the human tissues and organs are deposited in nanofibrous forms or structures, such as skin, bone, dentin, collagen, and cartilage to mention but a few. Until recently (5-10 years), electrospinning did not elicit widespread interest as a potential polymer-processing technique for applications in tissue engineering and drug delivery despite the 30 years long history of tissue engineering [8, 9]. This renewed interest was instigated by the aforementioned properties that afford the opportunity to engineer scaffolds with micro- to nanoscale topography and high porosity similar to the natural extracellular matrix (ECM). Electrospinning also makes it possible to incorporate the benefits of nanoparticles in nanofibrous form thus addressing some or all of their limitations [9, 10]. The fibrous and continuous nature of electrospunnanofibers as opposed to nanoparticle expands the possibilities for use in separation science and analytical and clinical applications. The generated fibers have a high surface area to volume ratio; the fibrous mats are highly porous and display excellent mechanical properties when compared to other materials of the same scale. Interestingly, the characteristic high surface area to volume ratio of electrospunnanofiber scaffolds does enhance cell attachment, drug loading, and mass transfer properties [1, 2, 8–10]. Consequently, business opportunities for nanostructured materials in biomedical applications were estimated as on 2006 by Ramakrishna et al. and Teo et al. to be of the order of 180 billion US dollars in 2015 [11, 12].

1.1. Fabrication of electrospunnanofibers

The synthesized nanofibers can be tailored for specific purposes. Several techniques based on different physical principles have been reported in the fabrication of nanofibrous scaffolds with unique properties [13, 14]. The most common ones include drawing [15], template synthesis [16], self-assembly [17, 18], phase separation [13, 18], melt blowing [19–22], and electrospinning [12]. More so, in an attempt to construct nanostructured materials with remarkable biomimetic properties, four bioinspired strategies have emerged from the natural biomineralization process: biostructure mimicking, biofunction anchoring, biotemplating, and bioassembling [23].

1.1.1. Drawing

The tip of an atomic force microscope (AFM) or a micropipette is dipped into a droplet of a viscoelastic solution near the contact line using a micromanipulator. Pulled nanofibers are formed by slowly withdrawing the micropipette or AFM tip at a speed of approximately 1×10^{-4} ms⁻¹ and are deposited on the surface by touching it with the end of the micropipette. The micropipette or the AFM tip is smoothly withdrawn slowly from the solution (**Figure 1**). The viscosity of the material at the edge of the droplet is usually increased with evaporation. Hence, drawing a fiber requires a viscoelastic material that can undergo strong deformations while being cohesive enough to support the stresses developed during pulling. If the viscoelastic solution is too light, the drawn fiber will break due to Rayleigh instability. Alternatively, if the solution is concentrated at the edge of the droplet, the drawn fiber will break in a cohesive manner.

The drawing method had been successfully employed in fabricating sodium citrate nanofibers using chloroauric acid as the solvent [16]. With this method, it is possible to fabricate fibers with fiber diameters between 2 and 100 nm and fiber length of 10 microns to mms. The drawing process gives a good level of repeatability, convenient to process with minimum equipment requirement but control of fiber dimensions is limited. It is a discontinuous process that cannot be scaled up, and thus it is only suitable for laboratory production of nanofibers. The drawing process can be considered as dry spinning at a molecular level.

1.1.2. Template synthesis

Template synthesis implies the use of a template or mold to obtain a desired material or structure (see **Figure 2**). The template refers to a metal oxide membrane with through thickness pores of nanoscale diameter and for the creation of nanofibers with specified diameter the polymer solution is extruded through a template of an appropriate diameter [17]. The



Figure 1. Drawing process in which the micropipette that was in contact with a polymer droplet (step B) is drawn away to generate nanofibers (step C).



Figure 2. A typical process of obtaining nanofibers by template synthesis.

principle requires that water pressure be applied on one end while the porous end is restrained as this results in extrusion of the polymer melt/solution. Nanofibers are formed once the polymer extrusion is exposed to the solidifying solution and their diameters are determined by the pore sizes [17]. Feng and his coworkers successfully fabricated polyacrylonitrile (PAN) nanofibers of 100 nm fiber diameter and 10 micron fiber length in dimethylformamide (DMF) solvent employing this method [17]. A major advantage of this method is that fibers of different diameters can be easily achieved by using different templates.

1.1.3. Phase separation

In phase separation, a polymer solution is allowed to form a gel and then the solvent is extracted leaving behind the residual porous solid phase (Figure 3). The main mechanism



Figure 3. A phase separation process in which the successful gelation (step C) of a polymer solution (step A) and extracting the solvent result in the formation of nanofibers (step D).

in this process is-as the name suggests-the separation of phases due to physical incompatibility. One of the phase-which is that of the solvent-is then extracted, leaving behind the other remaining phase. In 1999, Ma and Zhang [24] had successfully produced 50–500 nm size nanofibrous poly (L-lactic) acid (PLLA) in tetrahydrofuran (THF) in five major steps: (i) polymer dissolution, (ii) gelation, (iii) solvent extraction, (iv) freezing, and (v) freeze-drying (**Figure 3**) [24].

Similar to drawing, this method has a minimal equipment requirement, batch-to-batch consistency is achieved easily, and the mechanical properties of the matrix can be tailored by adjusting polymer concentration [14]. Nevertheless, it is limited to a few polymer types and thus cannot be scaled up and there is only little or no control over the diameters/dimensions of fibers formed.

1.1.4. Self-assembly

In self-assembly, smaller molecules are used as building blocks to create nanofibers [14]. The main mechanism for a generic self-assembly is the intermolecular forces that bring the smaller units together and the shape of the smaller units of molecules that determine the overall shape of the macromolecular nanofiber. The method has been used extensively in synthesis of genetic materials such as DNA [18, 19] and many other copolymers [19]. According to Hartgerink and his colleagues, during the synthesis of nanofibers based on this method, an individual, preexisting molecule (**Figure 4** left) is systematically arranged such that intermolecular forces can bind the concentrically arranged smaller units together (**Figure 4** middle). Thus, the small molecules organize themselves into the preferred pattern and function that results in the formation of macromolecular nanofiber mesh (**Figure 4** right) [19].

Researchers have extensively explored this method in producing fibers of diameters between 7 and 100 nm and fiber lengths between 1 and 20 micron using PCEMA core-PS shell in THF, $PAA/y-Fe_2O_3$ in THF, PS core-P4VP corona in chloroform and peptide-amphiphile in chloroform [18, 19]. Self-assembly requires no machinery to move or orient components. Self-assembly can be used to produce atomically precise nanosystems, meaning it is good for obtaining smaller nanofibers. It is simple, has easy processability, and is used to make one by one continuous nanofiber with uniform shape. However, it is a very complex process that cannot be scaled up, fiber dimensions cannot be controlled, its loading efficiency is poor, maintaining its porosity for longer duration poses serious challenge, and for every product, the structure of the parts must encode the structure of the whole [14].



Figure 4. A typical representation of the self-assembly electrospinning process.

1.1.5. Melt blowing

Melt blowing involves the use of high-velocity air to produce fibers directly from polymers. It is a single-step process that converts polymer raw material directly into nanofibers. The polymer is melted in an extruder and then pumped through die holes into a high-speed, hot air chamber where the fibers formed are collected on a rotating collector (**Figure 5**) [20, 21]. The process has been widely used to generate nanofibers from polymers such as polypropylene, polyethylene, polybutylene terephthalate, Nylon 6, and polystyrene, and it has a high productivity [20, 21].

1.1.6. Electrospinning

The structure, morphology, and geometry of nanofibers and the porosity and tensile properties of nanofiber mats can be investigated through conventional techniques and instruments. Among these methods, electrospinning has been used to convert a large variety of polymers into nanofibers and has proven to be a process that has the potential for mass production. In simple terms, electrospinning involves the drawing of fluid, in the form of either molten polymer or polymer solution using electric field. In electrospinning, the needle attached to the syringe (containing the polymer solution/melt) is connected to high-voltage power source in order to create a high electric field between the polymer melt/solution and metallic fiber–collecting plate (**Figure 6**). The generation of sufficiently high electric field that can surmount the surface tension of the polymer solution results in the formation of droplets that travel toward the collector plate as a Taylor cone. Before the jet is collected on the aluminum foil plate as nanofiber mesh, the solvents dry off while the fiber jet is still traveling. The images in **Figure 6** show that the major electrospinning components are high-voltage power source, delivery channel for the viscoelastic polymer melt or solution, and collecting plates (be it flat or rotating plates) [12–14].

Whereas an external mechanical force drives the polymer solution/melt via a die in drawing method, electrospinning principle makes use of the high potential gradient generated from the power source connected to the needle to propel the droplet jet toward the collector. Upon



Figure 5. A typical melt blowing setup (Adapted from Ref. 21).



Figure 6. Schematic diagram to show polymer nanofibers by electrospinning (A) and the photograph of a typical electrospinning setup (B).

application of high voltage to the needle tip, surface charges accumulate and they lead to the deformation of the spherical droplet to a Taylor cone; beyond this point, a jet of polymer solution will therefore erupt from a polymer solution droplet. As the jet travels toward the collector, tensile forces brought about by surface charge repulsion lead to a bending motion. According to Taylor's theory, it is the instability induced on the surface of the electrically charged droplet that causes the nanofiber formation [25, 26]. Taylor hypothesized that a spherical droplet of polymer forms at the capillary tip and elongates as the applied voltage increases. The elongated droplet assumes a cone-like shape and a narrow jet of liquid ejects from this point [25, 26]. It is the change in shape of the droplet into conical shape that defines the onset of the fiber formation. The polymer chain entanglements within the solution will prevent the electrospinning jet from breaking up. The pendant electrically charged Taylor cone does not explode because of the chain entanglement in the concentrated polymeric solution. The surface area of the Taylor cone also increases to accommodate the charge buildup and this leads to stretching out of the cone and fiber formation [27].

Coupled with the ability of scaling up the electrospunnanofibers, one other unique advantage of electrospinning is that it is able to easily control the orientation of the nanofibers, which is important because fiber arrangement has a significant effect on the performance of the subsequent SPE sorbent devices [10–14]. Electrospinning technology is a useful, economical, and easily setup means of fabricating of 3D, highly porous, nanofibrous scaffolds tailored for a wide range of applications. Interestingly, several electrospun nanofibrous scaffolds have been revealed to support cellular activities and tissue formation [12–14]. The inherently high surface to volume ratio of electrospun scaffolds can enhance cell attachment, drug loading, and mass transfer properties. In addition to their high surface area to volume ratio, tunable porosity, and ability to manipulate nanofiber composition for desired properties, the nonwoven nanofibrous mats produced by electrospinning mimic extracellular matrix components much closely as compared to the conventional techniques [10–14]. Hence, the emergence of

electrospinning/nanotechnology comes with a high potential for clinical applications. Until recently (5–10 years), electrospinning was not extensively employed as potential polymer-processing technique for applications in tissue engineering and drug delivery despite the long history of tissue engineering (about 30 years) [28]. The renewed interest can be ascribed to the aforementioned advantages of electrospinning over other conventional methods [28].

In electrospinning principle, the viscoelastic solution before transforming into nanofibers undergoes a number of processes. In 2006, Reneker and Fong divided the electrospinning process into four stages and they include launching the jet, jet elongation, whipping instability, and solidification [29].

1.1.6.1. Launching the jet

As the first stage of electrospinning process, the jet launching stage comprises droplet generation and Taylor cone formation. In the absence of an applied electric field, a viscoelastic solution pumped through a capillary will form normal droplets and fall off under the influence of gravity without forming fiber. It is the instability induced on the surface of the electrically charged droplet that causes the nanofiber formation [25, 26]. According to Deitzel et al., [30], the jet initiation occurs from the surface layers of the cone.

1.1.6.2. Jet elongation

In 2001, Buer revealed that the velocity of the jet increases as it travels toward the collector. It is believed that the potential difference between the collector and the point of release (needle tip) plays a major role in this process. As a result of solvent evaporation and polymer stretching, the jet diameter decreases rapidly. Resultantly, when a voltage (Ve) exceeding the strength of surface tension of the polymer solution is applied, jet elongation is expected to occur [29].

1.1.6.3. Whipping instability

As the straight fiber jet travels toward the collector plate, it tends to bend and displays undulating movements due to the competition between different forces/fields acting on the charged jet (axis symmetric, bending, and whipping and Raleigh instabilities). It is the interplay of all these forces that determines the diameter of the jet. However, whipping instability is the main mechanism responsible for reducing nanofiber dimensions because the predominant mode of instability exhibited is usually dependent on the applied electric field, and stronger fields favor whipping instability [31–33]. Whipping instability can be suppressed using a secondary electric field or a short gap distance (between the tip of the needle and the collector), but this does not affect the average fiber diameter significantly [33]. Due to the contribution of all these forces, there is not yet a mathematical model that has singly explained the entire electrospinning process.

1.1.6.4. Jet solidification

The solvent employed during electrospinning plays a major role in the solidification, morphology, mechanical integrity, and the microstructure of the electrospunnanofibers because the volatility characteristics of a chosen solvent is essential in the process and equally determines the time available to the jet to undergo whipping [34]. It has been pointed out that with appropriate selection of solvents and process parameters, extremely fine nanofibers can be electrospun [35].

1.1.6.5. Types of electrospinning

Attempts to improve the productivity of the electrospinning process have led to the development of three groups of improved and more efficient versions of electrospinning. Highlighted below are mononozzle, multinozzle, and needleless electrospinning.

1.1.6.5.1. Mononozzle electrospinning

The mononozzle is the simplest, cheapest, and most popular type of electrospinning setup in which only one nozzle/needle discharges the polymer solution with low productivity though (**Figure 7**).

1.1.6.5.2. Multinozzle electrospinning

Here, the polymer solution is fed into an array of nozzles or needles that allows for the deposition of multicomponent structures if different polymer solutions are electrospun concurrently, thereby increasing productivity of electrospinning by increasing the number of nozzles [36]. While the static type of needles remains immobile, the moving-type array of needles is programmed to move in unison (**Figure 8**). Fluctuations in electric field between the nozzles and the collector can influence the fiber diameters.

1.1.6.5.3. Needleless electrospinning

The needles are replaced with holes from where the nanofibers extrude with the application of optimal electrical charges induced on the viscoelastic solution by an electrode inside the porous tube. The needleless electrospinning comprise a porous polyethylene tube placed inside a coaxial cylindrical drum, and internal air pressure helps to push the polymer solution through the pores of the porous polyethylene tube (**Figure 9**). Although this is the most efficient electrospinning method, reproducibility is usually low due to the difficulty



Figure 7. Schematic representation of a mononozzle electrospinning setup.



Figure 8. Schematic diagram of a multinozzle electrospinning setup.





in maintaining an even distribution of polymer solution and air pressure over the different holes in the porous drum [37].

1.1.6.6. Processing parameters of electrospinning

The parameters affecting electrospinning and the fibers may be broadly classified into polymer solution parameters, processing conditions (applied voltage, temperature, and effect of collector), and ambient conditions. Understanding these parameters makes possible the fabrication of fibrous structures of various forms, morphology, and arrangements.

The processing conditions are important parameters that affect electrospinning process, and these are various external factors (applied voltage, the feed-rate, temperature of the solution, type of collector, diameter of needle, and distance between the needle tip and collector) acting on the electrospinning jet. Although processing conditions have significant influence on the fiber morphology, they are less significant than the solution parameters discussed earlier [10–14].

1.1.6.6.1. Applied voltage

A high voltage will induce the necessary charges on a solution and, together with the external electric field, will initiate the electrospinning process when the electrostatic force in the solution overcomes the surface tension of the solution. In most cases, a higher voltage will lead to greater stretching of the viscoelastic solution due to the greater columbic forces in the jet as well as the stronger electric field. These have the effect of reducing the diameter of the fibers [38, 39] and also encourage faster solvent evaporation to yield drier fibers [1, 2, 40]. However, researchers had correlated an increase in beads' density to increased voltage and suggested it may be the result of increased instability of the jet as the Taylor cone recedes into the syringe needle [30, 40]. This is because the greater amount of charges generated will cause the jet to accelerate faster and hence more volume of solution will be drawn from the tip of the needle without a corresponding increase from the source of supply. This may result in a smaller and less stable Taylor cone [41] or the Taylor cone may recede into the needle [30, 40]. Given the changes in the shape of beads from spindle-like to spherical-like with increasing voltage [41], Krishnappa et al. [42] reported that increasing voltage will increase the beads' density, which, at an even higher voltage, the beads will join to form a thicker diameter fiber.

On the contrary, when the voltage is low, the duo of weak electric field and reduced jet acceleration may surge the jet flight time, thereby resulting in finer fibers [43]. Based on this theoretical premise, finer fibers can be obtained using a near-critical voltage for electrospinning [43]. Generally, both high negative and positive voltage of more than 6 kV are able to cause the solution drop at the tip of the needle to distort into the shape of a Taylor cone during jet initiation [26].

In addition to affecting fiber physical appearance, the application of high voltage during electrospinning will likely increase the order of polymer molecules, resulting in higher polymer fiber crystallinity [1, 2, 10–14]. Nevertheless, polymer fiber crystallinity is reduced beyond a certain voltage [1, 2, 10–14].

1.1.6.6.2. Feed-rate of polymer solution

Feed rate is the quantity of polymer solution pumped into the tip per unit time. For a steady state and continuous formation of fibers, the feed rate of the solution must correspond to the rate of its removal from the tip. When the feed rate is increased, there is a corresponding increase in the stretching of the solution and fiber diameter since there is a greater volume of solution that is drawn away from the needle tip [44]. The large volume of solution drawn from the needle tip affords the solvents in the deposited fibers limited time to evaporate given the same flight time. The residual solvents may cause the fibers to fuse together where they make contact forming webs. Moreover, at higher feed rates, larger fiber diameters and beads often result [36]. A lower feed rate is highly desirable to give the solvent more time for evaporation [10–14]; however, the Taylor cone often gets depleted and the electrospinning process may only be intermittent or even stop completely.

1.1.6.6.3. Temperature of polymer solution

Having said that increased temperature decreases viscosity and surface tension, with a lower viscosity, the Columbic forces are able to exert a greater stretching force on the solution thus

resulting in fibers of smaller and more uniform diameter [45]. Increased polymer molecule mobility due to increased temperature equally allows the Columbic force to stretch the solution further. Nevertheless, the use of high temperature in the electrospinning of biological composites (enzymes and proteins in polymer solution) is not advisable as it may cause the substance to lose its sensitive functionality.

1.1.6.6.4. Effect of collector

It is the electric field potential that is generated between the source (needle tip) and collector that initiates the release and deposition of fiber jets. The simplest and most commonly used collector is a stationary metal plate or an aluminum foil placed at a fixed distance from the needle tip. The collector plate is mostly made out of conductors that are electrically grounded so that there is a stable potential difference between the source and the collector to allow for a rapid discharge of the residual charges on the fibers.

In the case when a nonconductor is used as a collector, charges on the electrospinning jet will quickly accumulate on the collector, which will result in the deposit of fewer fibers with lower packing density (due to repulsive forces of accumulated charges) [14]. The material, nature, and geometry of the collector play a major role in defining the morphology of the fibers [13]. Several different shapes of collectors such as flat plate; rotating drum, mandrel, rotating disc, rectangular, triangular, or wire cylinder frame; electrode pair arrangements; ring and mesh electrode; and cones have been reported [1, 2, 10–14, 26]. It has also been demonstrated that some of the common solvents such as water [46] and methanol [46] could be better collectors than their solid counterparts. A liquid collector may equally be used to precipitate the nanofibers when nonvolatile solvents are used. Srinivasan and Reneker demonstrated this by electrospinning poly (p-phenylene terephthalamide) nanofibers from sulfuric acid solution into a grounded water bath to precipitate the polymer [47].

The nature of the collector (static or moving) significantly affects the electrospinning process. While rotating collector has been used to collect well-aligned fibers, it was found to assist in yielding fibers that are dry [48]. Hence, it is very useful for certain solvents like dimethylformamide (DMF), which is good for electrospinning but has a high boiling point that may result in the fibers being wet when they are collected. A rotating collector will give the solvent more time to evaporate [48] and also increase the rate of evaporation of the solvents on the fibers. This will certainly improve the morphology of the fiber especially where distinct fibers are required.

Studies have shown that the porosity of the collector plate affects the packing density of the deposited fibers [10–14]. Fiber meshes of lower packing density were collected on porous collectors (paper and metal mesh) as compared to the smooth surfaces such as metal foils [10–14]. Responsible for this observation were higher evaporation rate and faster diffusion of the remaining solvents on the fibers collected on the paper and metal mesh (due to higher surface area) as compared to the smooth surfaces that may cause an accumulation of solvents around the fibers due to slower evaporation rate [10–14]. The residual solvents on these fibers pull them together to give a more densely packed structure unlike the dried fibers on the porous collector where the residual charges remaining on the fiber repel subsequent fibers [10–14]. Nevertheless, on a smooth surface, the residual solvents will encourage the residual charges to be conducted away from the collector.

1.1.6.6.5. Distance between tip and collector

This is the distance extending from the capillary tip to the surface of the collector. The gap distance has a direct influence on both the flight time (available for solvent evaporation) and the electric field strength [1, 2, 13]. For independent fibers to form, the electrospinning jet must be allowed time for most of the solvents to evaporate; otherwise, shortening the gap distance implies that the excess solvent may cause the fibers to merge where they contact to form junctions resulting in inter- and intralayer bonding of interconnected fiber mesh, which may provide additional strength to the resultant scaffold [13]. Depending on the solution property, the effect of varying the distance may or may not have a significant effect on the fiber morphology. In some cases, changing the distance has no significant effect on the fiber diameter, but Megelski and his coworkers observed bead formation when distance was too low and it was attributed to increased field strength (high voltage) [39]. Having said that the field strength is too high, the increased instability of the jet may encourage bead formation [40], and increasing the distance results in a decrease in the average fiber diameter because the longer distance means that there is a longer flight time for the solution to be stretched before it is deposited on the collector [29, 43]. However, Zhao et al. [43] reported a case where no fibers were deposited on the collector due to very large distance and Lee et al. [49] revealed at a longer distance, and the fiber diameter increased due to the decrease in the electrostatic field strength resulting in less stretching of the fibers Lee et al. [49]. Hence, it suggests that there is an optimal electrostatic field strength below which the stretching of the solution will decrease resulting in increased fiber diameters [13, 14].

1.1.6.6.6. Diameter of pipette orifice/needle

Conducting materials such as metal needles as well as nonconducting materials such as glass and plastics have been used as the capillary tip in solution electrospinning [50], and their internal diameter or pipette orifice has a significant effect on the electrospinning process. A smaller internal diameter was found to reduce the fiber diameter, clogging, as well as the amount of beads on the electrospun fibers [43]. When the size of the droplet at the tip of the orifice is decreased, surface tension of the droplet increases, a greater columbic force is therefore required to cause jet initiation for the same voltage applied [43]. Consequently, the acceleration of the jet decreases and this allows more time for the solution to be stretched and elongated before it is collected. Also, the reduction in clogging could be due to less exposure of the solution to the atmosphere during electrospinning. However, if the diameter of the orifice is too small, it may not be possible to extrude a droplet of solution at the tip of the orifice [43].

Although most studies have reported the use of a simple and static capillary tip, a number of innovations have explored the use of movable tips. Kidoaki et al. used a movable tip to obtain an even deposition of nanofibers on a drum collector, and the moving tip helps to align the fibers evenly [36]. Li also used a tip made of a nonconducting fiber inserted in the lumen of a conducting capillary tip [51]. Ultimately, this modified tip allowed the electric field to be used solely to accelerate the jet and therefore reduced the potential needed to be applied [51].

1.1.6.6.7. Polymer solution parameters

The surface tension and viscosity of polymer solutions or melt significantly affect the morphology of fibers obtained from electrospinning. While surface tension contributes to the formation of beads, viscosity and electrical potential largely determine the extent of elongation and diameter of the electrospun fibers [14].

1.1.6.6.8. Molecular weight and solution viscosity

Viscosity is a measure of the resistance of a material to flow. Viscosity is a prerequisite for a successful electrospinning because the polymer solution or melt must be viscoelastic in order to stretch the electrically driven fiber jet from the needle tip toward the collector plate without breaking up. It is the entanglement of the molecule chains that is often determined by the length of polymer chain that prevents the fiber jet from breaking up, thus maintaining a continuous solution jet. Consequently, monomeric polymer solution does not form fibers when electrospun [13, 14].

It is worth noting that the viscosity of a polymer solution is directly affected by its molecular weight (length of polymer chain) since the polymer length determines the extent of entanglement of the polymer chains in a given solvent. Hence, employing polymers with high molecular weight increases viscosity just as increasing the polymer concentration equally increases viscosity. When viscosity is too low, surface tension overrides and hence electrospraying occurs or beaded fibers are formed, whereas with increased viscosity, the diameter of the fiber also increases probably due to the greater resistance of the solution to be stretched by the charges on the [39, 40, 48].

1.1.6.6.9. Surface tension and temperature

Surface tension is that force that is acting on the surface of a solution to hold it in place. It is the main force of attraction that opposes the coulomb repulsion in electrospinning. When a very small drop of water falls through the air, the droplet generally takes up a spherical shape due to its surface tension. Surface tension usually decreases the surface area per unit mass of a fluid. The initiation of electrospinning requires the charged solution to overcome its surface tension. However, as the jet travels toward the collection plate, the charged solution is stretched, while the surface tension may cause the formation of beads along the jet or breakup of solutions into droplets [13, 14]. To encourage the formation of smooth fibers, surface tension (ethanol) [13, 14].

At molecular level, liquid molecules at high temperature gain kinetic energy that increases their collision speed during their Brownian movement. Consequently, the molecules in cooler liquid bind more strongly than the loosely bound rapid-moving molecules [12–14]. Hence, surface tension drops when temperature is increased owing to decrease in bonding energy between the molecules [12–14].

1.1.6.6.10. Conductivity of solution and electric charge (voltage)

To initiate the electrospinning process, the repulsive forces within the solution must surmount the solution surface tension. The repulsive forces are as a result of the sufficient charges acquired by the solution molecules. These charges that the solution carries often play crucial role in the subsequent stretching or drawing of the electrospinning jet. Having said that electrospinning involves the stretching of solution caused by repulsion of the charges at its surface, an increase in the conductivity means more charges can be carried by the electrospinning jet. Since the presence of ions increases the conductivity of the solution, the critical voltage for electrospinning to occur will equally reduce [12–14]. The increased charges also result in a greater bending instability. As a result, the deposition area of the fibers is increased [12–14]. This will also favor the formation of finer fibers since the jet path is now increased.

To increase the conductivity of the solution at the same time reducing the surface tension, ionic surfactant such as triethyl benzyl ammonium chloride is added although it often reduces the fiber diameter [12–14]. However, there is a limit to the reduction in the fiber diameter because in some cases, the addition of ionic salt may cause an increase in the viscosity of the solution improving conductivity; thus, the viscoelastic force is stronger than the columbic forces of the charges resulting in an increased fiber diameter instead [45]. Carboxylic acids, mineral acids, some complexes of acids with amine, mineral salts, some tetraalkylammonium salts, and stannous chloride, among others can also increase solvent conductivity when introduced [13]. For example, the addition of a small amount of water to organic acid solvents will greatly increase their conductivity. Mixing of chemically noninteracting components will increase conductivity as well [13, 14].

1.1.6.6.11. Dielectric effect of solvent

The dielectric constant (E) is a measure of how effectively a material placed in electric field can concentrate the electrostatic lines of flux, that is, the solvent's ability to hold electrical charges. It has been widely reported that solvents or solutions with high dielectric properties such as N,N-dimethylformamide (DMF) enhance fiber morphology by reducing fiber diameter and bead formation [1, 2, 48, 52]. This is feasible because solutions with higher dielectric constants tend to disperse the surface charge density on the jet more evenly and this leads to the production of fibers with uniform morphologies and smaller diameters [48].

In a study by Min and his coworkers, they compared the morphologies of nanofibers electrospun from 15 wt% poly (lactide-co-glycolide) solutions in chloroform and in hexafluoropropylene (HFP) [53]. Results showed that different fiber morphologies were obtained with the two solvents and the average fiber diameter obtained from HFP (having a higher £ of about 16.7) was lower than those obtained from chloroform (having a lower value £ of about 4.81). Son et al. corroborated this fact when they spun polyethylene oxide (PEO) in different solvents where the solvents with higher £ resulted in smaller average diameters [52]. The interaction between an electrospinning solution and any solvent that increases the solution's dielectric constant will equally affect fiber morphology. This implies that only the high dielectric constant of the solvent introduced into a polymer solution is not the only factor that impacts the fiber morphology: the interaction between the mixtures also impacts the resulting fiber morphology. Bead formation was reported despite introducing DMF (high dielectric constant solvent) into polystyrene solution to improve electrospinnability and fiber morphology [48]. The investigators posit that the poor interaction between the polystyrene solution and DMF could possibly explain the beaded fibers formed in place of finer fibers [48] (**Table 1**).

Solvent	Chemical structure	Conductivity (S.m ⁻¹)	Viscosity (mPa.S)	Surface tension (mN.m ⁻¹)	Dielectric constant (F/ms or cP)
Hexafluoroisopropanol (HFIP)		-	1.25	16.1	16.7
Formic acid (FA)		6.4 × 10 ⁻⁷	1.96	37	58
Dichloroethane		3.0 × 10 ⁻⁸	0.84	32.23	10.45
2-Propanol	ОН	6.0×10^{-6}	2.4	23.3	18.6
Acetic acid	н₃с́он	6 × 10 ⁻⁹	1.12	26.9	6.15
Acetone		2×10^{-7}	0.32	24	20.7
Acetonitrile	- н с≡р н	7×10^{-6}	0.352	29.29	36
Chloroform		<10 ⁻¹⁰	0.56	27.14	4.8-4.9
Dichloromethane		4.3 × 10 ⁻¹¹	0.42	28.1	9.1
Dimethylformamide		6 × 10 ⁻⁸	0.8	35.2	36.71
Ethyl acetate		2 × 10 ⁻⁷	0.46	23.2	6.0
Ethanol	_	1.3×10^{-7}	1.04	22.39	24.55
m-Cresol	OH CH ₃	_	0.45	41.7	11.8
Methanol	∕_он	3.0×10^{-7}	0.544	22.07	32.6

Solvent	Chemical structure	Conductivity (S.m ⁻¹)	Viscosity (mPa.S)	Surface tension (mN.m ⁻¹)	Dielectric constant (F/ms or cP)
Pyridine		-	0.974	38	12.3
Tetrahydrofuran	$\langle \rangle$	1.5 × 10 ⁻¹¹	0.48	28.4	7.6
Toluene	СH ₃	4.0×10^{-10}	0.59	27.6	2.438
Trifluoroethanol	F OH	_	1.64	19.4	27
Water	$\overset{\delta^+}{\overset{O}{\overset{\delta^+}}}\overset{\delta^+}{\overset{B^+}{\overset{H}}}$	5.5×10^{-6}	0.890	72.75	80.2

Table 1. Dielectric constant of common electrospinning solvents.

1.1.6.6.12. Ambient parameters

Since electrospinning is driven by external electric field, changes in its surrounding are expected to affect the process. While high humidity has been found to cause the formation of pores on the fiber surfaces, other environmental factors like pressure, temperature, and type of atmosphere have equally been investigated [1, 2].

1.1.6.6.13. Humidity

Humidity has been revealed to affect fiber morphology especially if it is spun from a volatile solvent [39] because at high humidity water condenses on the surface of fibers and affects the rate of evaporation of solvents. For example, Casper and colleagues showed that smooth fibers are formed from PSU dissolved in THF only when humidity is less than 50%; circular pores were formed on the fiber surfaces when humidity was higher than 50% with their pore depth and sizes increasing with increased humidity [54].

Low humidity aids volatile solvents to dry up faster. However, if the rate of solvent escape/ removal from needle tip is slower than evaporation rate of the solvent, there is a good chance of needle clogging during electrospinning. It has been hypothesized that high humidity can help the discharge of electrostatic charges on electrospun fiber [51], but with decreasing humidity, there was an increase in the amount of charge on the particle. This is evidenced by a study on glass particles transported in a grounded copper pipe, where no charges were found on the particles at higher relative humidity (>76%) [51].

1.1.6.6.14. Type of atmosphere

Different gases behave differently under high electrostatic field. While helium breaks down under high electrostatic field rendering electrospinning impossible, Freon®-12 with higher breakdown voltage yields fibers with twice the diameter of those electrospun in air given all other conditions equal. For example, using a positively charged capillary tip in an electron-rich gaseous environment will impede the process, and an environment of highly electronegative gases (such as CO₂ or Freons) discourages the loss of surface charges and improves nanofiber quality [55].

1.1.6.6.15. Pressure

It is only possible to investigate the effect of pressure on electrospinning jet under an enclosed condition. Electrospinning is not possible at very low pressures due to direct discharge of the electrical charges [14]. The fluidity of a polymer melt/solution is rapidly increased below atmospheric pressure as the melt/solution bubbles rapidly at the needle tip, often causing unstable jet initiation. However, at high pressure, air may be delivered coaxially to the needle tip to provide an additional drag force for jet extension. When this drag force is dominant over the electrostatic force in driving jet extension, the process is referred to as electroblowing [13, 14].

1.1.6.6.16. Temperature

Given that temperature reduces viscosity and determines the rate of evaporation of the solvents in fiber jet, it controls the final diameter of the nanofibers. Um et al. used a jacket of heated air (25–57°C) to decrease solution viscosity and increase the rate of drying of the fiber when electrospinning an aqueous solution of hyaluronic acid (HA) [56]. Subramanian et al. suggested the use of an external heating source such as a heat gun or a high wattage lamp as an alternative for drying fibers [57].

1.2. Some notable pharmaceutical and medical applications of electrospunnanofibers

Electrospunnanofibers have found promising applications in various biomedical areas. Almost all of the human tissues and organs are deposited in nanofibrous forms or structures, such as skin, bone, dentin, collagen, and cartilage to mention but a few. Consequently, business opportunities for nanostructured materials in biomedical applications are estimated to be of the order of 180 billion US dollars in 2015 [12–14]. A few applications of ENs are highlighted below.

1.2.1. Electrospun polymer nanofibers as a solid-phase extraction sorbent

The amazing properties of polymer nanofibers have rekindled their interest in several vital applications. They have larger surface area to volume ratio (can be 103 times of that of a microfiber), ease of surface functionalities, and better mechanical performance (e.g., stiffness and tensile strength) as compared to their microfiber counterpart or any other known form of the polymer. [1, 2, 10, 11].

It has been demonstrated that the fiber-packed SPE device offers a reduced pressure drop during the extraction and the desorption compared to a conventional particle-packed SPE cartridge [1, 2, 10, 11]. Electrospunnanofibers exhibit superb analytical potential as they can be miniaturized into nanoscale to simplify sample preparation, preconcentration owing to their effective interaction with samples, and the ease of incorporating different chemistries [1, 2]. These SPE sorbents with high miniaturization tendencies, fast extraction, less solvent, cost-effective, excellent analyte recoveries, good sorptive capacity, high selectivity, and good mechanical and chemical stability tend to satisfy all the current sample preparation requirement; hence, it is the choice sample preparation protocol for several studies [1, 2].

Their large surface area makes them equally applicable as wonderful sensing tools as applied in test strips and other colorimetric probes. Hence, significant effort has been made to increase the surface area of the sensing interface in chemical sensors [58].

1.2.2. Electrospunnanofibers composite in colorimetric probes (medical diagnostic tool)

As casualties from cancer mortality continues to grow due to the absence of state-of-theart health facilities, there have been increasing demands for simple, rapid, highly sensitive, inexpensive yet reliable method for the early detection of cancer susceptibility. To this end, equipment-free sensor systems such as colorimetric detection by naked eye would be among the best and most practically useful methods as this could easily be fabricated into a test strip. Colorimetric biosensing does not require expensive or sophisticated instrumentation and maybe applied to field analysis and point of care diagnosis since color changes can be read by naked eye [58].

Nanoparticles often have unexpected visible properties because they are small enough to confine their electrons and produce quantum confinement effect: Their high surface activity and freely moving electrons could bring about Raman-enhanced light scattering effect and agglomeration. The high surface area to volume ratio reduces their incipient melting temperature. They often possess high molar extinction values, which makes them far more sensitive and stable than other conventional colorimetric probes [58]. Surface plasmon resonance (SPR) is a conspicuous property of metal nanoparticles that results from the combined resonance oscillations of the free electrons of the conduction band of the metal [58]. A sharp and intense absorption band is observed in the visible range [58]. In addition, electrospunnanofibers offer high surface area and porous membrane structure that are applicable for sensitive and fast sensing, which have shown improved sensitivities over conventional materials for applications such as gas sensors, chemical sensors, optical sensors, and biosensors [58].

In the recent past, there has been great interest in the unique mechanical, electrical, chemical, and optical properties that can be achieved by combining the advantages of gold nanoparticles and polymer nanofibers [58]. During the formation of nanocomposites, there is a high aggregation tendencies in the polymer matrix since they are metastable compared to their bulk materials due to the positive excess interfacial free energy [58]. Owing to the fact that their spatial distribution is the key to their optical property, there is a burning desire by analytical and pharmaceutical chemists to attain good dispersion during synthesis. Hence, the stabilization of nanoparticles in polymer matrix is a fundamental prerequisite in nanoscience technology. For example, the *in situ* one-step fabrication of gold nanoparticle filled-polymer nanofiber for the colorimetric probe of the carcinogenic biomarker 1-hydroxypyrene was demonstrated [58]. The fibers were fabricated in the form of a test strip for the biological monitoring of carcinogenic PAH exposure [58].

1.2.3. Electrospunnanofibers in drug release control

Controlled release is an efficient process of delivering drugs in medical therapy. This process is able to balance the delivery kinetics, minimize toxicity and side effects, and improve patient convenience. In a controlled release system, the active substance is loaded into a carrier or device first and then released at a predictable rate in vivo when administered by an injected or noninjected route. As a potential drug delivery carrier, electrospunnanofibers have exhibited many advantages. The drug loading is very easy to implement via electrospinning process, and the high applies voltage used in the electrospinning process had little influence on the drug activity. The high specific surface area and short diffusion passage length give the nanofiber drug system a higher overall release rate than the bulk material (e.g., film), while the release profile can be finely controlled by modulation of nanofiber morphology, porosity, and composition. Coating of the nanofibers with a polymer shell could also be an effective way of controlling the drug release profile. The early burst release of drugs can be lowered by encapsulating water-soluble drugs into nanoparticles, followed by incorporating the drugloaded nanoparticles into nanofibers. Also, the rate of releasing a water-soluble drug could be slowed down when nanofiber matrices are cross-linked [59]. Nanofibers for drug release systems are mainly made by electrospinning of biodegradable polymers, such as polylactic acid (PLA), poly(D-lactide) (PDLA), poly(L-lactide) (PLLA), poly(lactic-co-glycolic acid (PLGA), and hydrophilic polymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), and polyethylene oxide. The release of macromolecules, such as DNA and bioactive proteins from nanofibers, has also been investigated [59]. The main factors influencing the release performance of drugs include the type of polymers used, hydrophilicity and hydrophobicity of drugs and polymers, solubility, drug-polymer comparability, additives, and the existence of enzymes in the buffer solution.

The need for the control release of water-soluble drugs usually associated with an early-stage burst cannot be overemphasized. Although for applications like preventing postsurgeryinduced adhesion, early-burst release will be an ideal profile because most infections occur within the first few hours after surgery, for a long-lasting release process, it would be crucial to maintain an even and stable release. This is usually achieved by encapsulating the drug within a nanofiber matrix.

Alternatively, for water-insoluble drugs, the drug release from hydrophobic nanofibers into buffer solution is often difficult. In order to release the drug at a constant rate, an enzyme capable of degrading nanofibers is often mixed with the buffer. For example, Kim and his coworkers showed that rifampicin encapsulated in PLA nanofibers did release any drug, while the same polymer/drug with potassium revealed a zero kinetics drug-release profile [59].

1.2.4. Environmental remediation

Environmental quality issues are complex, challenging, and ever expanding; hence, regulatory bodies are increasing the amount of environmental monitoring required to ensure public safety. The high porosity, interconnectivity, microscale interstitial space, and large surface-to-volume ratio of nonwoven electrospunnanofiber meshes make them an excellent size-exclusion membrane for particulate removal from wastewater and air. The electrospunnanofiber membranes can effectively and successfully remove particles $3-10 \ \mu m$ in size (>95% rejection) from aqueous solution without a significant drop in flux performance and airborne particles with diameters between 1 and 5 μm by both physical trapping and adsorption (~100% rejection). In the environmental industry, affinity membranes have found applications in organic waste removal and heavy metal removal in water treatment. Affinity membranes are a broad class of membranes that selectively capture specific target molecules (or ligates) by immobilizing a specific capturing agent (or ligand) onto the membrane surface [12]. The use of enzymes like laccase or tyrosinase for the degradation of water pollutants such as endocrine disruptors has equally been reported: enzymatic remediation of endocrine disruptors in water [60].

1.2.5. Application of electrospunnanofibers in tissue engineering and scaffolding material in cell culture

For the treatment of tissues or organs that malfunction in a human body, one of the challenges to the field of tissue engineering/biomaterials is the design of ideal scaffolds/synthetic matrices that can perfectly mimic the structure and biological functions of the natural extracellular matrix (ECM). Of particular interest in tissue engineering is the fabrication of nontoxic, reproducible, and biocompatible three-dimensional scaffolds with high porosity of evenly distributed pore sizes, high surface area, structural integrity, biodegradability with the degradation rate matching the rate of neotissue formation that can positively interact with human cells to promote cell adhesion, proliferation, migration, and differentiated cell function for various tissue repair and replacement procedures. Recently, scientists have started paying much attention to making such scaffolds with synthetic biopolymers and/or biodegradable electrospun polymer nanofibers as they are believed to possess all the aforementioned qualities and can mimic the human native ECMs [1, 2]. Having said that human cells can attach and organize well around fibers with diameters smaller than those of the cells, nanoscale fibrous scaffolds can provide an optimal template for cells to seed, migrate, and grow.

Although the mechanisms by which a nanofibrous scaffold acts as a selective substrate are not yet known, a number of researchers have shown that the enhanced adsorption of cell adhesion matrix molecules enhances cell adhesion [61, 62]. Nikolovski et al. [61] and Woo et al. [62] have reported that electrospun nanofibrous scaffolds exhibited enhanced adsorption of cell adhesion ECM molecules, which may therefore enhance cell adhesion. Although fibronectin and vitronectin preferentially adsorbed to the nanofibrous scaffold at a level that was 2–4 times higher than those adsorbed to the solid-walled scaffold [62], vitronectin, rather than fibronectin, was the predominant matrix protein adsorbed from serum-containing medium onto poly(glycolic acid) (PGA) and poly(lactic acid) (PLA) [61].

While cells synthesize, assemble, organize, and maintain ECM macromolecules, ECM in itself provides structural integrity to the resident cells and acts as a messenger regulating cellular activities [63]. It is therefore expected that a scaffold that serves as a functional, temporary ECM must involve optimal cell-matrix interactions, as well as cell-cell interactions. Li and his coworkers evaluated the influence of the structural properties of biomaterial scaffolds on the biological activities of chondrocytes cultured in microfiber- and nanofiber-based scaffolds [8, 64]. While chondrocytes seeded onto nanofibrous scaffolds maintain a chondrocyte-like morphology, chondrocytes seeded into microfibrous scaffolds display dedifferentiated, fibroblast-like morphology [8, 64]. Yang and colleagues also demonstrated that a greater percentage of neural stem cells cultured on nanofibrous scaffolds exhibit a neuron-like morphology with longer neurite outgrowth as compared to their microfibrous scaffold counterpart [65]. Nanoscale fibers are believed to be smaller than cells by two orders and provide 3D environment that better promotes cell-cell and cell-ECM interaction, unlike the microfibers [64].

Studies have equally shown that nanofibrous scaffolds support multidifferentiation of mesenchymal stem cells (MSCs) [64]. With the aid of gene expression analysis and immunohistochemical detection of lineage-specific marker molecules, Li's group confirmed the formation of nanofibrous constructs containing mesenchymal stem cell (MSC) differentiated along adipogenic, chondrogenic, or osteogenic lineages [64]. It has been reported that basement membrane matrix (feeder cell layers) of embryonic fibroblast provides chemical and physical cue on embryonic stem cells (ESCs) and regulate their ability to self-renew and differentiate [66]. Hence, ESCs had successfully been cultured on nanofibrous scaffold resembling a basement membrane matrix, yet their "stemness" properties were reportedly maintained [67]. Given that nanofibrous scaffolds act as synthetic ECM network, providing physical and chemical cues to cells via cell-ECM interaction, nanofibrous scaffolds promote in vivo–like 3D matrix adhesion and activate cell signaling pathway. For example, Schindler and coworkers have demonstrated that nanofibrous cultures promote in vivo–like cell morphology of both fibroblasts and kidney cells [68].

1.2.6. Electrospunnanofibers as wound dressing material

Nonwoven nanofibrous membrane mats for wound dressing generally possess highly porous, well-interconnected pore sizes ranging from 500 to 1 mm, small enough to protect the wound from bacterial penetration via aerosol particle capturing mechanisms while exuding fluid from the wound [1, 2, 12–14]. Their high surface areas of 5–100 m²/g are extremely efficient for fluid absorption and dermal delivery and generally assist the control of fluid drainage. Polymer nanofibers can also be used for the treatment of wounds or burns of a human skin, as well as designed for hemostatic devices with some unique characteristics. Through electrospraying or electrospinning, fine fibers of biodegradable polymers can be directly sprayed/spun onto the injured location of skin to form a fibrous mat dressing (**Figure 10**), which can let wounds heal by encouraging the formation of normal skin growth and eliminate the formation of scar tissue, which is usually a problem with traditional treatment [12–14]. Electrospinning also offers a simple way to add drugs into the nanofibers for possible medical treatment and antibacterial purposes [1, 2, 11]. For example, studies have shown that the successful incorporation of antibiotic agents into ENs prevents postsurgery abdominal adhesions and improves



Int

Figure 10. Nanofibers for wound dressing (www.electrosols.com).

the healing process [13, 14, 69]. Given their higher loading efficiency, superior mechanical performance (stiffness and tensile strength), controlled release ability, and excellent stability, ENs help in the delivery of plasmid DNA, large protein drugs, genetic materials, and autologous stem cell to the target site [69].

1.2.7. Electrospunnanofibers for immobilization of digestive enzymes

Chemical reactions using enzymes as catalysis have high selectivity and mild reaction conditions. For easy separation from the reaction solution, enzymes are normally immobilized with a carrier. The immobilization efficiently mainly depends on the porous structure and enzymematrix interaction. Nanostructured materials were recently used as enzyme carriers because of their large specific surface area and the high loading capacity. Many approaches have been used to immobilize enzymes on electrospunnanofibers including grafting enzymes on fiber surface, physical adsorption, and incorporating of enzyme into nanofiber via electrospinning followed by cross-linking reaction. To graft enzymes on nanofiber surface, the polymer used should possess reactive groups for chemical bonding. The immobilized enzymes normally showed a slightly reduced activity in aqueous environment compared with the unimmobilized native counterpart, although the activity in nonaqueous solution was much higher. For example, α -chymotrypsin was used as a model enzyme to bond chemically on the surface of electrospun PS nanofibers. The hydrolytic activity of the enzyme loaded was found to be 65% of the native enzyme, while the activity in nonaqueous solution was over 3 orders of magnitude higher than that of its native enzymes under the same conditions [70]. In another study that employed polyacrylonitrile nanofibers to immobilize lipase, the tensile strength of the nanofiber membrane was improved after lipase immobilization, and the immobilized lipase retained >90% of its initial reactivity. Also the immobilized lipase still retained 70% of its specific activity after 10 repeated reaction cycles with improved pH and thermal stabilities [71, 72].

When redoxases were immobilized, the incorporation of carbon nanotubes into nanofibers apparently increased the enzyme uptake and the activity of the immobilized enzyme was enhanced. The presence of carbon nanotubes also improved the stability of the redoxases immobilized. This improvement in catalysis performance was attributed to the fact that carbon nanotubes could behave as electron transferors to donate/accept electrons during enzyme catalysis or render the composite nanofibers higher biocompatibility. In certain studies, enzymes have been incorporated into nanofibers via electrospinning and subsequent cross-linking of the incorporated enzymes effectively prevented their leaching. For instance, in the presence of PEO or PVA, casein and lipase were electrospun into ultra-thin fibers, on cross-linking with 4,4-methylenebis (phenyl isocyanate), the fibers became insoluble, and the lipase encapsulated exhibited six times higher hydrolytic activity [73].

1.2.8. Electrospunnanofibers for catalyst carriers

In medicine, a carrier for catalyst is used to preserve high catalysis activity, increase the stability and life of the catalyst, and simplify reaction processes. Electrospunnanofiber mats are used as catalyst carrier, because their extremely large surface area could provide a huge number of active sites, thus enhancing the catalytic activity. The well-interconnected small pores in the nanofiber mat warrant effective interactions between the reactant and catalyst, which is valuable for continuous-flow chemical reactions or biological processes. Also, the catalyst can be grafted onto the electrospunnanofiber surface via surface coating or surface modification [74, 75]. For instance, Pd-loaded PAN-acrylic acid nanofibers were confirmed to have high activity and good recycling property for hydrogenation of an olefin at room temperature. The yield of hexene to hexane catalyzed by the palladium /PAN-AA nanofibers was 4.7 times higher than that of Pd/ γ -Al₂O₃ [74]. In addition to Pd nanoparticles, Ag nanoparticles were incorporated into silica nanofibers, and the hybrid Ag-silica nanofibers sowed catalytic activity to assist NaBH₄ to reduce decomposition of methylene blue [44]. Photocatalysts, such a titania (TiO₂) and TiO₂-SiO₂, were also electrospun into nanofibers, and the photocatalytic activity was evaluated. In comparison to other nanostructured TiO, materials, such as commercial TiO₂ nanoparticles and mesoporous TiO₂, the nanofibers exhibited higher photocatalytic activities toward the degradation of methylene blue and gaseous formaldehyde [76].

1.2.9. Electrospunnanofibers as chemical sensors for carcinogenic heavy metals in medical diagnosis

The challenge in the field of new approaches toward high sensitivity detection techniques remains a major challenge in the field of chemical sensing. Sensors have been widely used to detect chemicals for medical diagnosis. The sensitivity of a sensor that detects analytes by interacting with molecules on the surface will increase with increasing surface area per unit mass. Therefore, considerable effort has been made to increase the surface area of the sensing interface in chemical sensors [13, 58]. The characteristics possessed by electrospunnanofibers match well with these requirements. Therefore, a nanofibrous structure is a promising physical structure to form a highly sensitive and fast response sensor. Nanofibers with sensing capability have been fabricated by electrospinning polymeric sensing materials, coating/grafting the nanofiber surface with the sensing material, or incorporating the sensing material into nanofibers. For example, pyrene methanol as a sensing material was grafted with polyacrylic and employed for the detection of Fe³⁺ and Hg²⁺ and an explosive 2,4-dinitrotoluene in water [77, 78]. Due to the quenching effect of these chemicals to the pyrene moieties, the fluorescent intensity of nanofiber had a linear response to the concentration of quenchers, and the nanofibers showed high sensitivities [77, 78]. Investigators equally detected methyl viologen and cytochrome C in aqueous solution [77, 78] using a layer-by-layer electrostatically assembled fluorescence optical sensors, whereas trinitrotoluene vapor had been traced by employing a porphyrin-doped silica nanofibers [79]. These nanofibers exhibited fast response as well as high sensitivity. Besides fluorescent properties, conjugated polymer-embedded electrospunnanofibers were also reported to be able to sense volatile organic compounds such as organochlorines based on optical absorption properties [80].

1.2.10. Electrospunnanofibers as ultrafilters

It has been proven that electrospunnanofiber mats were extremely efficient at trapping airborne particles [1, 2, 14] and a very small layer of electrospunnanofiber sprayed onto a porous substrate was sufficient to eliminate the particle penetration. Also, electrospun layers present minimal impedance to moisture vapor diffusion, which is the basis on which they are used as protective clothing in decontamination applications. Electrospunnanofiber membranes are believed to provide significant increase in filtration efficiency at relatively small decreases in permeability. Kosmider and Scott proposed that when compared with conventional filter fibers at the same pressure drop, nanofibers exhibited superior efficiency owing to their ability to collect thinner, finer fibers as the slip flow round the nanofibers enhances the diffusion, interception, and inertia impaction efficiencies [81]. With the aid of 300 nm test particles, thin electrospun nylon-6 membrane (thickness 100 μ m, pore size 0.24 μ m) also displayed higher filtration efficiency than a commercial highly efficient particulate air (HEPA) filter (thickness 500 μ m, pore size 1.7 μ m) [82].

1.2.11. Electrospunnanofibers as affinity membranes

Affinity membrane deals with the purification of molecules on the basis of their physical/chemical properties or biological functions instead of their molecular weights/sizes. The principle involves selectively capturing molecules by immobilizing specific ligands onto the membrane surface as opposed to mere sieving. Electrospunnanofibers have a great potential to be functionalized via incorporation of functional materials into the fibers, or via surface chemistry and coating techniques. Interestingly, Affinity membrane combines the exceptional selectivity of the chromatography resins and the reduced pressure drops associated with filtration membranes [10, 11]; thus, it

materializes the advancement in both fixed-bed liquid chromatography and membrane filtration. This technology has the merits of lower mass transfer limitation, reduced pressure drops, and enhanced flow rate and productivities when compared to conventional particle-packed column chromatography. When Ma and coworkers surface functionalized electrospun cellulose nanofibers with a dye Cibacron Blue F3GA (CB), the functionalized nanofiber membrane exhibited a strong affinity to bovine serum albumin (BSA) and bilirubin, with a capture ability of 13 mg and 4 mg per gram nanofibers, respectively [83].

1.2.12. Electrospun nanofibrous scaffolds-engineered tissues

The sophisticated architecture of body tissues/organs with their various layers makes it difficult for current synthetic 3D matrices to simulate such processes. Hence, the advent of electrospinning had further simplified the fabrication of both natural and synthetic polymers into biomaterial scaffolds that more closely mimic the tissue matrices. For example, PCL, collagen type I, and collage type I-coated PCL nanofibers had been successfully electrospun to fabricate a substitute for skin regeneration. The results proved that PCL fibers are able to partially support the growth of skin fibroblasts, while the presence of collagen on the scaffolds greatly enhances the interactions between cells and nanofibers [84]. Silk fibroin nanofibers [53], PLGA, and chitin/PLGA nanofibrous scaffolds cultured with keratinocytes and fibroblasts have also shown great promise in skin tissue engineering [8].

Electrospunnanofibers have extensively been investigated in the fabrication of tissue engineered artery. By assembling two electrospun nanofibrous tubes composed of different collagen/elastin ratios with cultured dermal fibroblasts, aortic smooth muscle cells, and umbilical vein endothelial cells in the outer, middle, and inner layers of the scaffold, respectively, Boland et al. fabricated a vascular scaffold that successfully simulated the anatomical three layers of an artery [85]. One major drawback of the study was that the mechanical integrity of the scaffolds was compromised unlike the mammalian artery. In an attempt to compliment for the mechanical integrity, researchers blended PLGA with collagen and elastin to produce an electrospun tripolymeric fibrous scaffold, therefore increasing the strength of the original collagen/elastin scaffold and rendering it mechanically comparable to a native artery [86].

The development of cartilage tissue engineering using the electrospinning technique had been reported [87]. In their study, the biological response of chondrocytes seeded onto 3D PCL nanofibrous scaffolds was compared to that of cells seeded as monolayers on standard tissue culture polystyrene (TCPS) [87]. Gene expression analysis revealed that the chondrocytes exhibited a round shape on the nanofibrous scaffolds, in contrast to a flat, well-spread morphology seen in monolayer cultures on TCPS. They concluded that the biological activities of chondrocytes are significantly dependent on the dimensionality of the extracellular scaffolds and that nanofibrous PCL may be a biologically preferred scaffold/substrate for proliferation and phenotype maintenance of chondrocytes [8, 87].

It is believed that the MSCs for bone tissue engineering must be seeded within electrospun nanofibrous scaffolds in order to promote osteogenic differentiation [8]. On seeding rat bone marrow MSCs in PCL nanofibrous scaffolds and culturing them in a rotatory oxygen-permeable bioreactor with an osteogenic medium, Yoshimoto et al. and Shin et al. demonstrated the osteogenic differentiation of MSCs in PCL nanofibrous scaffolds cultured *in vitro* and *in vivo* [88, 89].

It is worthy to note that a suitable tissue engineered muscle scaffold should be flexible in structure for cardiomyocyte contraction, sustain a reasonable tension for cell morphology maintenance, and have a good integrity for handling. In this line of thought, Shin et al. have successfully cultured primary cardiomyocytes from rat ventricles on PCL nanofiber suspended wire rings [90]. Their results suggested that the dimensionality of the extracellular scaffolds significantly influenced the biological activities of chondrocytes and that the PCL nanofibers served as the better biologically substrate for the cell proliferation and maintenance of the chondrocyte phenotype [90].

An investigation of the effects of fiber alignment on the ECM generation of human ligament fibroblasts (HLF) on polyurethane (PU) electrospunnanofibers revealed that cells cultured on aligned nanofibers were spindle shaped and oriented in the nanofiber direction, whereas cells on nonaligned nanofibers had no directionality [65, 91]. Taken together, the researchers concluded from the results that the biomimetic nature of aligned electrospunnanofibers provides an architectural environment similar to that which ligament fibroblasts normally encounter *in vivo*.

Finally, studies have equally investigated the potential of electrospun 3D scaffolds, both aligned and nonaligned, in neural/nerve tissue engineering employing a multipotent neural stem cell (NSC) line, C17–2, derived from a neonatal mouse cerebellum [8, 65]. Significant changes in the phenotype of cells based on directionality were reported and these results show a significant relationship of a decrease in fiber diameter increasing neurite outgrowth [8, 65]. Since successful nerve regeneration is dependent upon extensive growth of axonal processes, electrospinning presents a sophisticated technique to fabricate an ECM-like nerve tissue.

1.3. Challenges, prospects, and conclusion

It is no gainsaying that the advent of electrospinning has revolutionized the intrigues and applications of nanostructured materials. Several potential applications of electrospunnanofibers have been extensively investigated in separation science, tissue engineering, regenerative engineering, and other clinical fields. Despite the overwhelming benefits of electrospinning, there are still limitations in translating these fabricated electrospun nanomaterials from bench to bedside and/or fabricating human tissues using nanofibrous scaffolds. In the recent past, researchers have introduced a plethora of different new polymers for electrospinning, as well as various characterization techniques; nevertheless, there is limited progress in their biological evaluation. More recent studies are investigating cellular and molecular analyses of cell-cell and cell-nanofiber interactions based on the structural and functional resemblance of electrospunnanofiber scaffolds to native ECM. In addition to actively inducing favorable biological activities, emerging functional electrospun nanofibrous scaffolds are expected to provide structural and mechanical support for tissue regeneration/engineering. Hence, more extensive biological analyses as well as physical characterization are required to determine the biocompatibility of the fabricated nanofiber toward promoting of tissue growth. Owing to the fact that bioactive motifs, peptides, and growth factors are capable of eliciting cellular response, efforts should be channeled toward developing methodologies that can incorporate and optimize bioactive motifs or peptides or growth factors into the electrospun nanofibrous scaffold, thereby creating biologically active scaffolds [8]. Electrospinning is one such strategy that has been widely employed for the successful incorporation of the aforesaid bioactive compounds into nanofibrous scaffolds, as well as controlling the fiber orientation. Owing to the significance of fiber arrangement, electrospinning has a leading edge over other nanofiber fabrication techniques due to the fact that it is able to easily control the orientation of the nanofibers, despite the inherent advantages of conventional nanofiber fabrication techniques [1, 2, 8, 10-14]. It is important to note that the electrospinning process depends on several parameters, and the precise control of each parameter directly affects the morphology of the nanofibers [1, 2, 8, 10–14]. Given the expected complexity of in vivo nanofiber scaffolds, obtaining such biocompatibility, biodegradability, nontoxicity, and structural integrity scaffolds precisely using traditional electrospinning technique is challenging due to the unplanned randomly intertwined nanofibers [92]. To precisely control the fiber orientation and electrospinning diameter to produce thinner 3D fibers, an in-depth understanding of controlled fabrication, electrospinning parameters, properties, and functioning of electrospun materials is required to overcome the limitations. The current trend is the emerging robotics technology (3D printing, 3D bioplotting, nanoimprinting, etc.) that has immensely benefited the biofabrication process by improving the flexibility, accuracy, controllability, process parameters, nanofiber diameter, and the rate of nanofibers produced [92]. Currently, there is an overwhelming application of electrospunnanofiber scaffolds/sorbents in analytical field and separations science including cosmetics, as filter media, solid phase extraction (SPE) sorbent bed, purification devices, preconcentration devices, protective clothing, wound dressing, sensor devices, and healthcare systems [1, 2, 10, 11, 58, 93]. Conversely, there have been limited progress in the clinical translation of these nanofibers and the fabricating technique; thus, the future of electrospinning will tend toward drug delivery, cell delivery, gene delivery, DNA/plasmid delivery, tissue engineering, and regenerative engineering against important health challenges. Overall, the role of electrospinning in separation science and biomedical and clinical application cannot be overemphasized. In the near future, the advent of robotics-assisted electrospinning technique will certainly drive nanotechnology from laboratory/industry toward patient care/bedside.

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