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Electrospun Membrane Fabrication in Assisting Tissues Healing

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Abstract:
The arrangement of fibers into three-dimensional (3D) complex structure is constructing a sheet of membrane, depending on the fabrication technique. The fiber mats and scaffolds have been used in various applications including tissue engineering which involve the integration of cells and tissues within the pores between the fibers. There are several techniques that have been opted to produce specifically nanofibers as its efficacy in tissue healing is prominent compared to microfibers. Among the fabrication techniques (drawing, template synthesis, temperature-induced phase separation, molecular self-assembly, and electrospinning), electrospinning method has drawn attention due to their easy handling, inexpensive, and ability for membrane scale-up with the production of fibers ranging from few nanometers to several microns. Researchers have employed a variety of electrospinning methods, including blended/co-electrospinning, emulsion, coaxial, side-by-side, and triaxial electrospinning. In electrospinning smooth formation of nanofibers for tissue healing with less appearance of spray and beads, several parameters such as humidity, temperature, voltage, flow rate, viscosity, concentration, molecular weight, surface tension, conductivity, and solvent volatile need to be tailored. The morphology of nanofibers formation should support the size and structure of the surrounded cells and tissues. Besides, the types of degradable polymeric materials also play a role in the formation of stable nanofibers. This review paper aimed to provide information on the techniques to produce nanofibers, intended to the basic exploration of electrospinning.

Keywords: Electrospinning; Membrane; Nanofibers; Tissue healing

1. Introduction

Nanofibers are among the most intriguing and promising materials due to their special physicochemical characteristics, such as remarkable porosity with interconnection between pores in mats, mechanical flexibility and strength, large surface area, and high adaptability to construct composites with other materials [1, 2]. These features permitting its usage for a range of applications have generated enormous scientific and technical attention [1, 2]. The creation of nanofibers has thus far involved techniques including drawing [3], self-assembly [4], phase separation [5], and template synthesis [6]. They are time-consuming, expensive, and inefficient, which are some of their drawbacks. However, electrospinning-based designed electrospun membranes/nanofibers/scaffolds have distinctive features which make them quite appropriate for drug delivery system [7], tissue engineering scaffolds/membranes, and biomedical engineering [8].

Table 1 shows the comparison of advantages and disadvantages of different nanofiber techniques which includes drawing, template synthesis, temperature induced phase separation, molecular self-assembly [7, 9, 10]. These techniques have contained some main drawbacks which are time-consuming, expensive, and inefficient. Polymeric fibrous structures are identified as suitable candidates for drug-release systems and fibrous polymer structures. They have been prepared by a variety of methods such as electro-hydrodynamic (EHD) techniques **[**11]. In the EHD, electrostatic forces are employed to produce fibers or particles with an adjustable micro-structure [12]. As an outstanding cost-efficient method, electrospinning is categorized as one of the EHDs, that has been opted in vast applications in the industry and laboratory for fiber fabrication. In this method, pharmaceutical biomolecules or agents are directly encapsulated within the fibers, leading to their protection from environmental parameters and simultaneously, controlling the element release [13, 14]. Electrospinning is the famous technique which followed the working principle of EHD [11]. Electrospinning-based designed electrospun membranes/nanofibers/scaffolds have distinctive features which make them quite appropriate for drug delivery system, tissue engineering scaffolds/membranes and biomedical engineering. Electrospinning technique have covers unique characteristics which includes high porosity, tuneable pore size, high surface-to-volume ratio, and morphological correspondence with extracellular matrix (ECM) [10].

Table 1 - Comparison of different nanofiber techniques [7, 9].

Fabrication Technique	**Advantages**	**Disadvantages**
Drawing	Easy-to-handle equipment	Inconsistent process Not expandable Fiber diameters are not under the control
Template synthesis	Continuous process Fiber dimension can be varied using different template	Not scalable
Temperature-induced phase separation	Easy-to-handle equipment Easy processing Formation of fibers with good mechanical characteristics	Fabrication only involves polymer materials No scalable Unable to control fiber dimension
Molecular self-assembly	Only smaller nanofibers of few nm in diameter and few microns in length can be fabricated	Complicated process No scalable Unable to control fiber dimension
Electrospinning	Easy instrument handling Continual procedure Inexpensive Scalable Fabrication of fibers with sizes ranging from few nanometers to several microns	Instability in jet formation Certain harmful solvents Transportation, handling, and packaging

With the help of synthetic and natural polymers, it is simple to create antibacterial drug-loaded [7] and wound-healing nanofibers [15, 16] that are then electrospun [10]. Numerous antibacterial substances, including antibiotics, metallic nanoparticles, and proteins have been fabricated, to be contained within or on the surface of nanofibers [10, 17]. Previous research have demonstrated the potent antibacterial activity of electrospun membranes fabricated with natural and synthetic polymers such as gelatin [18], cellulose [19], chitosan [20], collagen [21], poly (methyl methacrylate) [10], polyvinylpyrrolidone (PVP) [22, 23], and polycaprolactone (PCL) [24] against a wide range of bacteria with strong biocompatibility for wound healing applications [10]. Therefore, this review paper aimed to

provide information on the techniques to produce nanofibers, intended to the basic exploration of electrospinning. The types of electrospinning specified parameters and dominant polymeric materials have been reviewed to provide an insight on its application towards tissue healing.

2. Electrospinning

Researchers have employed a variety of electrospinning methods, including blended/co-electrospinning (single fluid), emulsion electrospinning (single fluid), coaxial electrospinning (double fluid), side-by-side electrospinning (double fluid), and triaxial electrospinning (multi-fluid) as shown in Figure 1. Particularly to load-sensitive molecules or small water-soluble drugs, these strategies aid in controlling drug release from nanofibers, and support high surface area with improved morphological and biological properties in the required environment [10].

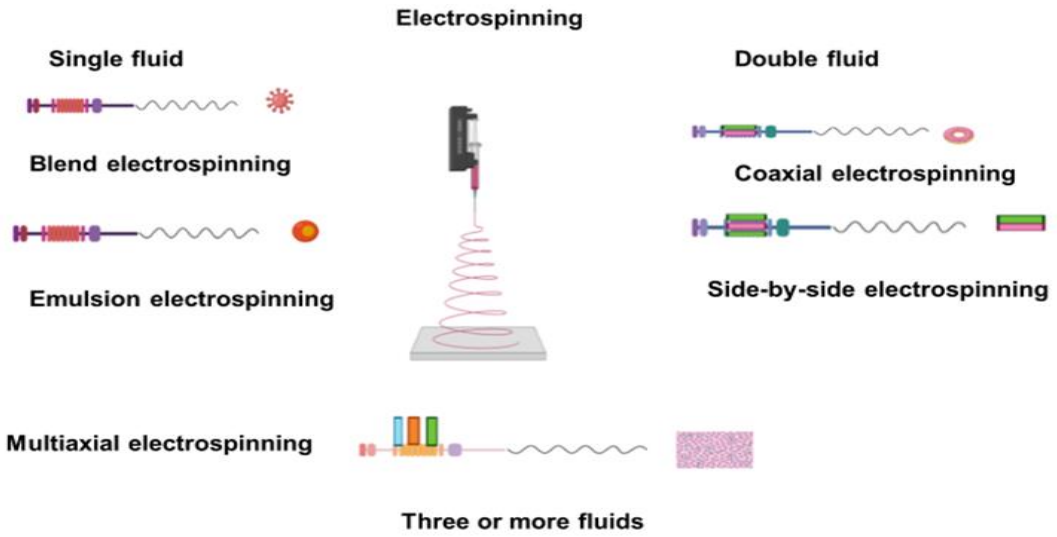

Figure 1 Illustration of different types of electrospinning methods

Co-electrospinning is a flexible and easy method for creating nanofibers of various polymers with the capacity to load a variety of molecules in these structures [25, 26]. Emulsion electrospinning is an easy and common technique for creating core-shell nanofibers, which are good for loading drugs [27]. The hydrophilic pharmaceuticals in emulsion electrospinning are typically dissolved in the water phase before being diffused into the oil phase, which contains surfactants/emulsifiers, in contrast to the blend electrospinning discussed above [28]. After electrospinning, the water/oil emulsion creates nanofibers with a core-shell structure, the core of which contains the drug [29]. As a result, it exhibits higher performance in the ability to encapsulate physiologically active molecules, such as proteins and medications [25].

The emulsion technique does not need a specific needle setup, but it does need a certain combination of solvent, polymers, and molecular characteristics. In the coaxial/multiaxial approach, the initial bioactivity of molecules is maintained by electrospinning without direct mixing the solution by utilizing core-shell nozzles [30]. The method of side-by-side electrospinning for creating Janus nanofibers was initially described by Gupta and Wilkes in 2003 [31]. The Janus structure is among the most fundamental ones. The two chambers of this construction are distinct from one another and in contact with the outside world, unlike the conventional core-sheath configuration. By figuring out the spinneret's structure and modifying the electrospinning settings, side-by-side electrospinning allows the fabrication of nanofibers with various characteristics [32].

By using a multi-layered nanofiber, each of which can perform a separate function while maintaining high mechanical stability. This double-layered approach can offer multifunctionality [33]. Hence in this context, it is concluded that coaxial emulsion, side-by-side, and multiaxial procedures are more difficult to be handled than blended electrospinning, and careful consideration of material choice, solvent combination, and particular volatility are required [10, 25]. Blended/co-electrospinning was adopted in this study to create polymer-based loaded leave extract and metallic nanoparticles electrospun membranes as it is a versatile and simple method.

Scientists have loaded plant extracts and bioactive ingredients within PCL by opting blended/co-electrospinning technique to produce various electrospun membranes with improved properties for wound healing applications. The recently reported works were PCL/chitosan/Aloevera [34], PCL/chitosan/curcumin [35], PCL/gelatin/ oregano oil [36], PCL/gelatin/clove essential oil [37], and PCL/gelatin/Utrica dioica/zinc oxide nanoparticles [38]. All membranes exhibited improved antibacterial and biocompatible properties for wound healing applications.

2.1 Electrospinning parameters

The structure and development of fibers produced by the simple technique of electrospinning are influenced by several factors. According to Table 2, the variables are broken down into three groups: ambient parameters, processing parameters, and solution parameters. All three groups should be adjusted to create smooth electrospun fibers.

Table 2 - Important parameters used during electrospinning.

Parameter	Effect	Parameter Value	Reference
Ambient Parameters			
Humidity	• High: Fiber diameter and pore size increased. • Low: Beads formation. • Smooth: Fibers formed 20 to 75%.	Between 50 - 60%	[39-42]
Temperature	• High: The rate of liquid evaporation increased, viscosity decreased, increase in temperature encouraged the formation of thin fibers. • Low: Chances of fiber creation trapped at the needle end	Room temperature (25 - 27˚C)	[42-45]
Processing Parameters			
Voltage	• High: Facilitated formation of large fiber diameter. • Low: Thin diameter. • Mixed: Affected fiber morphology due to polymer concentration, flow rate, the distance between needle and collector with applied voltage.	10 kV	[42, 46-48]
Flow rate	• Low: Preferrable for polymer polarization and thinner fiber formation. • High: Beads formation occurred, and fiber diameter became thicker.	1 mL/h	[40, 42, 49]
Solution Parameters			
Viscosity	• Depended on polymer concentration and molecular weight. • Low: No fiber formation, electrospraying • Slightly low: Formed beads and depended on surface tension. • Very high: Led to the hard solution being pushed out from the jet due to high surface tension. • High: Produced large fiber diameter.	15 wt% polymer solution	[41, 42, 48, 50]
Concentration	• Adjustable concentration is required to facilitate smooth fibers formation. • Low: No fiber formed. • High: Beads formation	Different polymer solution concentrations	[42]
Molecular weight	• Supported the entanglement of polymer chains in solution. • Low: Facilitated beads formation. • High: Produced smooth electrospun membranes	80 kDa	[41, 42, 47, 49]
Surface tension	• High: Inhibited electrospinning • Low: Allow electrospinning process, depended on the selected solvent and modification of the	-	[42, 46, 48, 50]

Parameter	Effect	Parameter Value	Reference
	ratios of solvents surface tension as well as viscosity		
Conductivity	• High conductivity is required to overcome surface tension and to produce bead less fibers. • Poor conductivity produced beads without the formation of fibers. Conductivity can be increased by adding salts, and drugs.	-	[41, 42, 47, 49, 51]
Solvent volatility	• A volatile solvent is recommended. • Prevent to use of extremely volatile solvents due to the fast evaporation rate and the solution may clog the needle. • Solvent evaporation is needed before reach to the collector otherwise it may merge and produce beads	Chloroform Methanol	[41, 51, 52]

2.2 Electrospinning Materials

Over natural polymers (biopolymers), synthetic polymers have several benefits, with the most significant benefit to modify the materials' chemical characteristics, molecular weight, copolymerization, crystallinity, and other characteristics to achieve better mechanical and degrading qualities [53, 54]. For wound dressing formulations, synthetic polymers that can be electrospun with natural polymers include poly(vinyl alcohol) (PVA), PLGA, polylactide (PLA), PCL, polyglycolic acid (PGA), polyurethane (PU), poly(ethylene oxide) (PEO)/poly(ethylene glycol) (PEG), poly(hydroxyethyl methacrylate) (PHEMA), and poly(vinyl pyrrolidone) (PVP) [52, 53, 55].

Additionally, the cross-linked dressings may have poor biological functions and ineffective tissue healing abilities, rendering them unsuitable for treating diabetic wounds. The encapsulation of bioactive compounds in these polymer-based dressings is a potential technique for tissue healing treatment, especially chronic wounds [56]. Antibiotics, growth factors, stem cells, plant extracts, antioxidants, anti-inflammatory medicines (e.g., curcumin, etc.), and vitamins are the examples of bioactive compounds which have been utilized in tissue healing applications. Wound dressings such as hydrogels, foams, membranes, films, nanofibers, transdermal patches, etc. are a few polymeric wound dressings that can hold bioactive compounds [57].

In a recent article by Ahmadian *et al*. [53], the authors notified the use and importance of synthetic polymers including PEG, PU, PVA, and PCL as well as natural polymers such as chitin, chitosan, and alginate. They further highlighted that the creation of innovative wound dressings is extremely important due to the drawbacks and shortcomings of gauzes and bandages as conventional wound dressings, including their inability to keep the wound moist, a requirement for frequent replacement, and painful separation [53]. The process of electrospinning is the one that is most frequently used to make wound dressings by using synthetic polymer [53, 58].

3. Conclusion

Electrospinning is one of the techniques to produce nanofibers that is widely explored for tissue healing application. There are several types of electrospinning variation to produce nanofiber membranes and scaffolds that require alteration in electrospinning parameters. A smooth projection of nanofibers that constructing 3D mat with interconnecting pores has capability to attract cells and tissue integration within the pores and between the nanofibers. More advanced and complex multi-fluid consist of natural and synthetic polymers electrospinning technology can be used in the future to create nanofibers with new shapes. Simultaneously, electrospun nanofibers can transport a range of active chemicals and can continually release medications, essential oils, plant extract, and nanoparticles, which are extremely advantageous for boosting the overall performance of tissue healing.

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Conflict of Interest

The authors declare no conflict of interest.

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