science, engineering and health studies

Review Article

Science, Engineering and Health Studies
https://lio1.tci-thaijo.org/index.php/sehs
ISSN (Online): 2630-0087

Electrospun nanofibers from natural polymers and their application

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***Received**: 14 December 2020*
***Revised**: 19 April 2021*
***Accepted**: 20 April 2021*
***Published**: 16 December 2021*

***Citation**: Chinatangkul, N., Limmatvapirat, C., and Limmatvapirat, S. (2021). Electrospun nanofibers from natural polymers and their application. Science, Engineering and Health Studies, 15, 21010005.*

ABSTRACT

Due to their small structure and large number of micropores, nanofibers can be employed effectively in a variety of applications, including drug delivery, wound dressing, tissue engineering, filtration, and in cosmetic products. Several fabrication techniques have recently been developed to produce nanofibers. Electrospinning has been widely used owing to its high-degree of flexibility in fabrication and its suitability for use in industrial-scale production. Both synthetic and natural polymers have been employed in the process of electrospinning nanofibers. Natural polymers appear to be particularly attractive materials for use in this process because their structures are similar to those found in extracellular matrices prevalent in the human body, resulting in a compatible interaction with this biological environment. This review summarizes the current development of nanofibers produced from natural polymers and their application in various fields. Fabrication limitations and future application are also considered.

Keywords: electrospinning; electrospun nanofiber; wound dressing; drug carrier; shellac

1. INTRODUCTION

Nanomaterials, which measure less than 100 nm in size, have been widely commercialized and increasingly utilized as commodities in various areas, such as healthcare, electronics, and cosmetics because of their unique physical and chemical characteristics.

Nanofibers, which feature a diameter range of 1-100 nm, have attracted considerable interest in several fields, such as wound healing, tissue engineering scaffold, sensor, air filtration, and drug delivery, because of their unique characteristics, including ultra-porous structure and large surface area-to-volume ratio. The number of studies on the development of electrospun nanofibers has dramatically increased in recent years because of the potential practicality and functionalization of these materials. In this review, an overall description of nanofibers, including enabling techniques, recent fabrication processes, unique properties, the polymers employed for preparing nanofibers, and the possible applications of electrospun nanofibers with notable properties, is provided. In particular, natural polymers have been considered for development in the future. The current trends in the production and application of nanofibers will also be presented.

2. FABRICATION OF NANOFIBERS

Nanofibers can currently be prepared using a variety of methods, which include drawing, phase separation, template synthesis, self-assembly, and electrospinning. The details of each methodology are described as follows.

2.1 Drawing

During this process, a micropipette measuring a few micrometers in diameter is plunged into a liquid close to the contact line and then rapidly pulled out of the droplet at a speed of approximately 1-10^{-4} m/s, resulting in a pulled nanofiber being deposited at the end of the micropipette. However, materials with viscoelastic properties are required for this process, and the process is discontinuous. The drawing of nanofibers can be repeated several times in this process . (Ramakrishna et al., 2005).

2.2 Template synthesis

Different nanoporous membranes are employed as templates to generate nanofibers of a fibril or a tube shape with the desired diameter. Various materials, such as electrically conducting polymers, carbons, semiconductors, and metals, are applied, but one-by-one continuous nanofibers cannot be obtained using this method (Huang et al., 2003). A metal oxide membrane with nanopores is used as a template to fabricate nanofibers. Water pressure is applied on one side, and then the extrusion of polymers through the porous membrane contacts with a solidifying solution, producing nanofibers (Ramakrishna et al., 2005).

2.3 Phase separation

Induced phase separation is conducted by introducing a non-solvent to the polymer solution or by using thermal energy (cooling of solution). In the process, a polymer is added to a solvent to prepare a polymer solution before undergoing gelation. After gelation, the solvent is removed from the gel by extraction with water. The gel is transferred into a freezer and then freeze-dried under vacuum, producing nanofibers with the same size as natural collagen of the extracellular matrix (ECM). The produced nanofibers can enhance cell adhesion, migration, and proliferation. However, phase separation is a laboratory-scale process that is restricted to the production of nanofiber scaffolds (Barot et al., 2014; Ramakrishna et al., 2005).

2.4 Self-assembly

Nanofibers are built using small molecules as basic building blocks. Intermolecular forces lead to the arrangement of small molecules in a concentric manner, and the extension in the plane's normal results in the longitudinal axis of a nanofiber. Biomaterials are introduced to mimic the human ECM. However, self-assembly has no potential for mass production similar to phase separation (Ramakrishna et al., 2005).

2.5 Electrospinning

Electrospinning is an extensively used method. It is highly flexible and could be further improved for mass production. During electrospinning, the polymer solution is filled in a syringe. High-voltage direct current is then supplied, producing an electric field between the collector and the metallic needle tip. When the surface charges are higher than the surface tension of the polymer solution, nanofibers form on the surface of the collector wrapped with an aluminum foil (Barot et al., 2014; Ramakrishna et al., 2005).

With electrospinning, submicron fibers with unique properties, including a microporous structure with excellent pore interconnection and a high surface area-to-volume ratio are obtained, and suitable for several advanced applications, such as wound healing, tissue engineering scaffold, sensor, filtration, energy storage, and drug delivery (Fang et al., 2008). Given their high porosity and extreme surface area, nanofibers have the following characteristics:

Hemostasis: the ultrafine pores and high effective surface area of nanofibers could promote hemostasis without using any hemostatic agents (Zahedi et al., 2009).

Absorbability: due to the large surface area-to-volume ratio, the water absorption of nanofiber dressings is 17.9%-213%, which is greater than that of typical film dressings (2.3%). Therefore, nanofibers made from hydrophilic polymers might be effectively used for highly exudative wounds (Zahedi et al., 2009).

Semi-permeability: nanofibers act as semi-permeable barriers that allow gas permeation while protecting the wound from bacterial infection and dehydration. The porous structure of nanofiber dressings reduces moisture transmission through the dressing from the wound surface to maintain moist wound conditions. The fine pore size can also prevent the wound penetration of bacteria (Zahedi et al., 2009).

Conformability: these aforementioned dressings are flexible and resilient due to the fineness of fibers. They have been proposed for use in would management because of their ability to align with the irregular shape of wounds, leading to excellent coverage and infection prevention (Zahedi et al., 2009).

Scar-free: electrospun nanofibers can be used for tissue repair. Given their similar structure to natural ECM in tissue and large surface area, nanofibers promote normal skin to develop prior to scar formation, promoting wound healing with minimal scarring. In addition, they have good cell conductivity and encourage other factors that improve wound healing and skin remodeling.

Functional ability: therapeutic compounds, including antiseptics, antifungals, cells (e.g., keratinocytes), growth factors (e.g., TGF, FGF, and EGF), and vasodilators (e.g., captopril), promote in-vascular permeability and increase the movement of leukocytes toward the site of affected tissue; such compounds are easily integrated into nanofiber dressings to produce multifunctional bioactive nanofiber dressings (Ambekar and Kandasubramanian, 2019; Zahedi et al., 2009). For example, encapsulation of the natural antimicrobial agent monolaurin (ML) into shellac fibers avoids possible infections (Chinatangkul et al., 2017).

Aside from their wide range of applications in wound dressing and tissue engineering, electrospun nanofibers can also provide the following properties suitable for use in other fields, such as air filtration and drug delivery.

Air filtration: Airborne dust particles and volatile organic compounds can be effectively captured on the nanofiber surface nanofibers due to their small diameters. Furthermore, electrospun nanofibers' filtration efficiency is enhanced by their large surface area and low airflow resistance (Sundarrajan et al., 2014). Previous research has indicated that airflow resistance across a nanofiber mask is significantly reduced, compared with that across a N95 mask, resulting in improved compliance but the same filtration efficacy (Skaria and Smaldone, 2014).

Drug encapsulation: the large encapsulation efficiency and high loading capacity of drugs are ascribed to the low weight and high surface area-to-volume ratio of electrospun nanofibers (Muthuraman and Kaur, 2017).

Dissolution profile: based on the large surface area-to-volume ratio and excessive porosity, electrospun nanofibers might exhibit a large area contacting the

biological environment, leading to a rapid rate and enhanced ability of dissolution (Braghirolli et al., 2014; Potrč et al., 2015). The release of drugs could be altered depending on the polymeric materials that are designed to be gradually degraded and/or be swollen in a surrounding environment (Kajdič et al., 2019).

3. TYPES OF ELECTROSPINNING

Two main types of electrospinning are currently available for the fabrication of nanofibers: needle-based electrospinning and needleless electrospinning.

3.1 Needle-based electrospinning

Various single-needle and multi-needle-based approaches have been developed to enhance the output of nanofibers.

3.1.1 Multi-axial electrospinning

3.1.1.1 Coaxial electrospinning

Coaxial electrospinning, a modification of the conventional system, has been generally used for drug encapsulation in the core structure of fibers. In addition, a large variety of materials, including electrospinnable and non-electrospinnable polymers, can be combined to form multiple core-sheath nanofibers in a single step, thus allowing them to be extensively utilized based on their multifunctional properties. Unlike the basis single-needle electrospinning, a coaxial spinneret comprises an inner and outer needle feeding the core and sheath fluids simultaneously as displayed in Figure 1. Under the high-voltage supply, a Taylor cone with a core-shell structure is formed, and the core-sheath nanofibers are respectively fabricated on the collector (Han and Steckl, 2019).

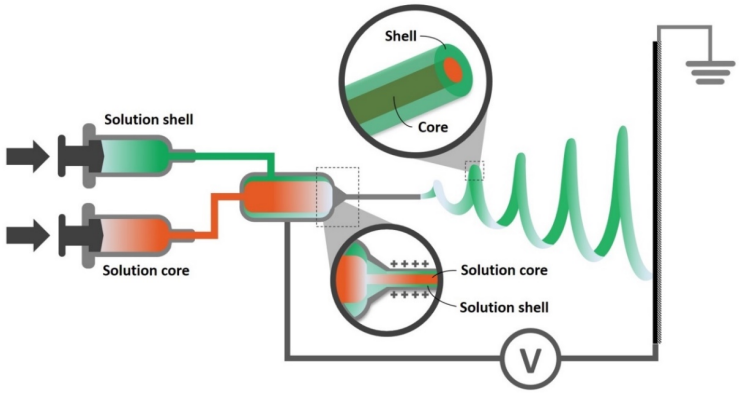

Figure 1. Schematic of coaxial electrospinning

3.1.1.2 Triaxial electrospinning

Three polymers could be carried out through a spinneret to form fibers with diverse properties during triaxial electrospinning. As shown in Figure 2, the multifunctional fiber consisting of three layers, which are core, intermediate and outer sheath, have been developed by using triaxial elctrospinning method in order to provide a multi-drug delivery carrier. In most cases, a burst release profile occurs from the outer shell. The core structure exhibits a sustained release action. Whereas, the intermediate layer might serve as a protective layer for preventing a rapid release of core (Han and Steckl, 2013).

3.1.2 Bicomponent electrospinning

A side-by-side bicomponent technique might equally exhibit the desired characteristics of each component on the surface of fibers differing from the core–shell or blended fibers. During the process, two polymer solutions are supplied through two separated compartments. A nozzle used for bicomponent electrospinning is composed of split outlets running side by side. A previous study synthesized 3D hydrogel hybrid fibrous scaffolds containing polyvinylpyrrolidone (PVP) on one side and polycaprolactone (PCL) on the other side by using a side-by-side bicomponent electrospinning device. When the prepared scaffolds were exposed to water, the side with PVP expanded and exhibited a hydrogel property, whereas that with the hydrophobic polymer PCL maintained the aligned structure of fibers. As a result, the increased pore volumes of scaffolds would allow the cellular penetration into its interior. In addition, the resultant scaffolds could be resistant to the cellular contractile tensions during implantation (Jin et al., 2014).

3.1.3 Multi-needle electrospinning

Large-scale fabrication is limited in single-nozzle electrospinning. To address this issue, multi-needle electrospinning as illustrated in Figure 3 has been developed to enhance the yield of nanofibers (He and Zhou, 2019). However, a repulsion force between the adjacent jets might occur which could result in difficulty in fiber collection (Kundu et al., 2013).

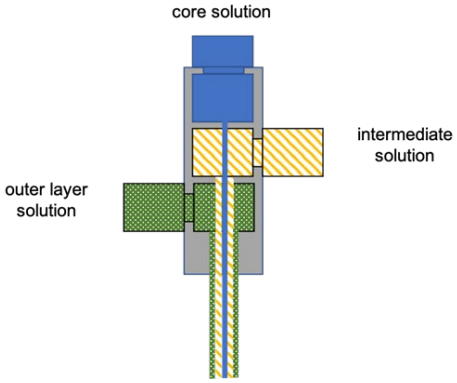

Figure 2. Schematic of triaxial electrospinning

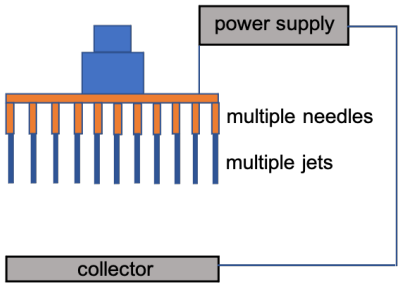

Figure 3. Schematic of multi-needle electrospinning

3.1.4 Conjugate electrospinning

Conjugate electrospinning has been recently exploited to prepare continuous fibers with well-aligned morphology. The schematic setup comprises two or three spinnerets coupled with high-voltage supplies with different polarities. Electrospun solutions are separately drawn from spinnerets in opposite positions. A previous study formulated electrospun nanofibers of poly(L-lactide)/nano-β-tricalcium phosphate (n-TCP) composite through conjugate electrospinning. The obtained yarns are likely to be oriented along the longitudinal axis, providing improved alignment (Xinsong et al., 2008).

3.1.5 Centrifugal electrospinning

Centrifugal electrospinning is another technique used to enhance fiber alignment and increase productivity. During the process, a centrifugal drawing force and an electrical force are employed to initiate the stretching of a polymer solution, contributing to the formation of nanofibers with an aligned structure. The required electrical power voltage is low with the addition of centrifugal force. Meanwhile, multiple nozzles attached around the axis of rotation are supposed to provide a high productivity. A previous study reported that the utilization of four nozzles can considerably increase fiber production within a short time (Kancheva et al., 2014).

3.2 Needleless electrospinning

Single-needle and multi-needle electrospinning have been recently modified and widely employed to magnify the production of nanofibers. However, needle-based electrospinning might result in some problems, such as clogging of the needle and has the disadvantage of requiring a complex configuration setup. Needleless spinning might eliminate these problems.

3.2.1 Bubble electrospinning

Bubble electrospinning, a potential electrospinning process that resembles spider spinning, has recently been used to fabricate continuous nanofibers with small diameters on a large scale. During the process, single or multiple bubbles are produced on the surface of aerated polymer solution. Under a strong applied electric field, the bubble surface is charged and then deformed into a conical shape. When the applied voltage exceeds the surface tension, a polymeric jet is emitted from the conical bubble. Multiple jets are required to increase the volume of fabrication. The number of multiple jets is associated with the applied voltage and the number and size of bubbles, which are affected by gas pressure, surface tension, and solution viscosity (He, 2012; Yang et al., 2009).

3.2.2 Blown bubble electrospinning

This approach is relatively similar to bubble electrospinning. Polymer bubbles can be produced and pulled upward by using a blowing hot air instead of a high electronic supply. The superfine fibers are collected on the receiver above (Dou and Liu, 2013).

3.2.3 Two-layer fluid electrospinning

Two-layer fluid electrospinning is performed according to the combination of electric and magnetic fields. Two-layer fluids are made up of a polymer solution on top and a ferromagnetic suspension on the bottom. Under the supplied magnetic field, several vertical spikes of magnetic fluid are formed in a steady pattern. The interlayer interface and the surface of upper polymer solution are disturbed by vertical spikes. In addition, an applied electrical field initiates the formation of multiple upward fluid jets. As a result, numerous nanofibers with submicron diameters are collected on the upper counter electrode (Yarin and Zussman, 2004).

3.2.4 Splashing electrospinning

Another needleless approach for large-scale production is splashing electrospinning. Polymer droplets from a solution distributor constructed with holes at its base and which is positioned above a spinneret, are splashed onto the superficial of a metal roller electrospinning spinneret to fabricate electrospun nanofibers. The droplet shape after hitting the spinneret surface changes from round to elliptical. Subsequently, the polymeric jets of solution droplets attaching on the surface of the roller spinneret are emitted and extended when the electrical voltage is applied, resulting in the formation of nanofibers (Tang et al., 2010).

3.2.5 Rotary cone electrospinning

A rotating cone is used as the spinneret in rotary cone electrospinning. During electrospinning, a droplet of polymer solution is fed to the cone surface and then positively charged. The electrical charged droplet is stretched and changed into an oval shape by mechanical rotation movement. Simultaneously, under a high electrical field, the elliptically shaped droplet is deformed and initially electrospun into nanofibers as the solution droplet reaches the rim of the rotary cone. A previous report found that the electrospinning throughput of the rotary cone technique is 1000 times greater than those of the basis needle system (Lu et al., 2010).

3.2.6 Edge electrospinning

Edge electrospinning has been considered for the high-throughput fabrication of nanofibers from a bowl edge, consisting of a polymer solution-filled vessel and a concentric cylindrical collector. Under a strong electrical field, multiple jets are spontaneously initiated and directly generated on the solution surface and further ejected to the edge around the bowl circumference to provide approximately equal-spaced spinning sites. The production rate of bowl electrospinning is 40 times higher than those of conventional needle electrospinning due to the simultaneous formation of numerous jets. Various polymers with different properties, including viscosity and solvent volatility, have been used in the fabrication process (Thoppey et al., 2011).

3.2.7 Melt differential electrospinning

Different from solution electrospinning, melt electrospinning is performed in the absence of a toxic solvent, thus making it a green nanofiber production method. An umbrella-shaped spinneret is used in this process to generate multiple jets with a short interjet distance. The molten polymer is fed into the melt distributor and distributed around the circumference and on the top of the umbrella-shaped nozzle. The molten polymer is then transferred from the umbrella-like spinneret's top to its bottom. Once the umbellate circumferential surface is uniformly covered with the melt film, multiple jets are self-generated around the edge of the umbrella nozzle and subsequently projected to the receiver plate under high supply voltage (Mingjun et al., 2019). The illustrations of nanofibers fabricated though various electrospinning methods are summarized in Table 1.

Table 1. Examples of different nanofiber fabrication techniques

Electrospinning methods	Examples of fabricated nanofibers	References
Needle-based electrospinning		
Coaxial electrospinning	PMMA/PAN nanofibers	(Bazilevsky et al., 2007)
	Tetra-layered SAN/PAN/SAN/PAN nanofibers	(Lee et al., 2014)
	Shellac nanofibers containing ferulic acid	(Wang et al., 2015)
Triaxial electrospinning	PCL/PVP nanofibers	(Han and Steckl, 2013)
	EC nanofibers containing ketoprofen	(Yu et al., 2015)
Bicomponent electrospinning	PVP/PCL nanofibers	(Jin et al., 2014)
	PCL/gelatin nanofibers	(Denis et al., 2015)
	PVDF/PI nanofibers	(Cai et al., 2019)
Multi-needle electrospinning	PVA/chitosan nanofibers	(Nuryantini et al., 2014)
	TPU nanofibers	(Xu et al., 2020)
Conjugate electrospinning	poly(L-lactide)/nano-b-tricalcium phosphate (n-TCP) nanofibers	(Xinsong et al., 2008)
	PVDF-HFP nanofiber	(Sun et al., 2011)
Centrifugal electrospinning	chitosan/PCL nanofibers	(Erickson et al., 2015)
	PLGA/PI blend mixed with HAp and PEG nanofibers	(Muniz et al., 2020)
Needleless electrospinning		
Bubble electrospinning	PVA nanofibers	(Yang et al., 2009)
	PAN nanofibers	(Cheng et al., 2019)
Blown bubble electrospinning	nylon6/66 nanofibers	(Hao et al., 2014)
Rotary cone electrospinning	PVP nanofibers	(Lu et al., 2010)
Edge electrospinning	PEO nanofibers	(Thoppey et al., 2010)
Melt differential electrospinning	PP, PE and PLA nanofibers	(Mingjun et al., 2019)
	PPS nanofibers	(Chen et al., 2020)

Note: PMMA = poly (methyl methacrylate), PAN = polyacrylonitrile, SAN = styrene acrylonitrile, EC = ethyl cellulose, PVDF = polyvinylidene fluoride, PI = polyimide, PVA = polyvinyl alcohol, TPU = thermoplastic polyurethane, PVDF-HFP = poly (vinylidenefluoride-co-hexafluoropropylene, PLGA = polylactic-co-glycolic acid, PEO = polyethylene glycol, PP = polypropylene, PE = polyethylene, PPS = polyphenylene sulfide

4. POLYMERS USED FOR PREPARATION

Electrospun nanofibers have been produced from a variety of synthetic and natural polymers as described below.

4.1 Synthetic polymers

Some synthetic polymers, such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA) PCL and polyurethane, are biocompatible, biodegradable, and cost effective (Kundu et al., 2013). Given their diverse physicochemical properties, synthetic polymers have been extensively used for nanofiber productions (Barot et al., 2014). Synthetic polymers, including PLA, polyurethane, polystyrene, PCL, polyvinyl chloride, poly(methyl methacrylate), poly(lactic-co-glycolic acid), poly(ethylene-co-vinylacetate), poly(ethylene terephthalate) poly(ethylene oxide), polyacrylonitrile, and cellulose acetate, have been well studied (Hadipour-Goudarzi et al., 2014; Liao et al., 2015; Unnithan et al., 2012; Unnithan et al., 2014; Vasita and Katti, 2006; Zahedi et al., 2009). However, natural polymers are promising to develop nanofibers that could mimic a biological environment (Barot et al., 2014).

4.2 Natural polymers

The structures of nanofibers are highly similar to those of the macromolecular substances in the human body, such as ECM; thus, nanofibers prepared from natural polymers might interact favorably with the biological environment to stimulate natural cell and tissue responses (Barot et al., 2014). Natural polymers, including gelatin, chitosan, dextran, hyaluronic acid, collagen, silk fibroin, and shellac, have been commonly used to fabricate nanofibers (Chinatangkul et al., 2017; Hadipour-Goudarzi et al., 2014; Liao et al., 2015; Unnithan et al., 2012; Unnithan et al., 2014; Vasita and Katti, 2006; Zahedi et al., 2009). However, polymeric nanofibers that originate from animals increase the risk of batch variability, antigenicity, and disease transmission (Barot et al., 2014).

4.3 Polymer blends

Polymer blends have been widely applied to create new materials with modified or improved physicochemical properties and to provide materials with the desired mechanical and biological properties at the lowest price. Blending might improve processability and performance.

In the blending process, a number of structurally distinct polymers or copolymers are blended together and interacted with secondary forces such as hydrogen bonding, charge-transfer complexes, and dipole-dipole forces. The morphology, permeability, degradation, and mechanical characteristics of polymer blends will differ from those of homopolymers.

Polymer blends can be broadly divided into three types according to their miscibility: miscible, immiscible, and compatible. Miscible polymer blends exhibit a single-phase structure. The properties of mixtures will be the average values between the values of its contents relying on the quantity of each polymer present. Conversely, immiscible polymer blends display phase separation. The low adhesion between both blend phases leads to poor structural integrity and low mechanical properties. These blends are useless if not compatibilized. To create polymer blends, immiscible polymer blends are modified using various methods to decrease the interfacial tension, provide adhesive force between two phases, and preserve the desired morphology against thermal or shear effects during processing. Modification might be performed by incorporating polymers or copolymers through physical methods, such as high stress, heat treatment, and irradiation, or through reactive extrusion or injection molding. When the interface and morphology of an immiscible blend are altered, a polymer blend is formed. The properties of compatibilized blends are a synergistic combination of favorable characteristics from each polymeric material (Utracki, 2002).

Natural polymer blends are preferrable because of their ECM similarity and biocompatibility. A previous study obtained fibrous scaffolds with enhanced cell adhesion and proliferation by blending gelatin and chitosan (Pezeshki-Modaress et al., 2018). Aside from natural polymer blends, synthetic polymer blends have been widely employed to formulate electrospun nanofibers owing to their scalability, electrospinnability, and high mechanical and electrical properties. For example, PCL/PLA-3D blend scaffolds have been successfully developed for bone tissue engineering with potential mechanical characteristics, and an improvement in cell viability and osteogenic differentiation has been observed (Yao et al., 2017). A mixture of natural and synthetic polymers has been extensively studied to fabricate nanofibers possessing the native structure and favorable properties of each polymer. A previous study applied a blend of corn protein (zein), gum arabic (GA), and PCL to fabricate skin tissue scaffolds based on the protein and polysaccharide nature of zein and GA and the excellent mechanical properties of PCL (Pedram et al., 2018).

5. DEVELOPMENT OF ELECTROSPUN NANOFIBERS FABRICATED FROM NATURAL POLYMERS AND THEIR APPLICATIONS

As previously stated, natural polymers have been mostly employed in biomedical fields on account of their favorable biological features. Examples of natural polymers which have been reported to have been electrospun into nanofibers, include shellac, chitosan and gelatin.

Shellac is a natural biomaterial derived from the hardened excretion of the lac *Kerriar Lacca* insect, which lives on certain trees in China, India, and Thailand. It is a nontoxic polymer generally recognized as safe by the FDA (Okamoto and Ibanez, 1986). With an LD_{50} value of more than 5 g/kg in rats, shellac might be considered safe to animals and even humans (Okamoto and Ibanez, 1986). The structure of shellac consists of polyesters and single esters containing hydroxyl and carboxyl groups. The ionization constant (pKa) is 6.9-7.5. Shellac is insoluble in water but is dissolved in alcohol and alkaline solutions with pH above 7 (Limmatvapirat et al., 2004). In addition, it might be a good film-forming polymer serving as a water vapor barrier, which is related to the content of wax, mostly composed in shellac. Shellac, with a high refractive index of 1.521-1.527, could be effectively applied for the coating of various materials, including medications, cosmetics, fruits, vegetables, and woods to potentiate their attentiveness and appearances. Shellac also provides a strong attractive force with various materials (Luangtana-Anan and Limmatvapirat, 2019).

Shellac can be effectively electrospun into nanofibers. The appearance of electrospun nanofibers is influenced by various parameters, such as solution properties (conductivity, surface tension, and viscosity), processing conditions (applied voltage, feed rate, and distance between tip and collector), and environmental conditions (humidity and temperature) (Ramakrishna et al., 2005). A previous study (Chinatangkul et al., 2017) examined the effects of each parameter, including shellac concentration (35%-40% w/w), applied voltage (9-27 kV), and feed rate (0.4-1.2 mL/h) and their interactions, on the diameter of nanofibers, the number of beads (bead-to-fiber ratio), and the distribution of diameter by using a full factorial design with three replicated center points. According to the findings, shellac content is the most important factor influencing fiber diameter. This effect may be caused by a decrease in electrical conductivity and an increase in solution viscosity, which reduce the stretching ability of the electrospun solution. Consequently, large-diameter nanofibers were obviously generated as displayed in Figure 4. Applied voltage and flow rate were minor parameters. A rise in the applied voltage would induce polymer ejection, which increases fiber diameter. Moreover, the high feed rate can result in a larger volume of drawn solution. The fibers would be therefore fused together.

Bead formation during electrospinning is identified as a defect. Shellac concentration and applied voltage negatively influence bead amount. An increase in shellac content might increase the solvent–polymer interaction rather than the solvent–solvent interaction. Consequently, the beaded nanofibers noticeably change to beadless nanofibers (Figure 4). The number of electrical charges increases with increased applied voltage, leading to the fast pulling out of the solution from the tip of needle. As a result, smooth fibers can be attained. However, the distribution of fiber diameter is not significantly influenced.

A previous study developed shellac nanofibers incorporated with an antimicrobial lipid (monolaurin, ML) for wound dressing to prevent microbial infection, which is the leading cause of delayed wound healing, and to reduce possible antibiotic resistance (Chinatangkul et al., 2018). In this study, the main and interaction impacts of shellac concentration (35%-40% w/w), ML content (1%-3% w/w), flow rate (0.4-1.2 mL/h), and applied voltage (9-27 kV) on the morphology of fibers were evaluated using a full factorial design with three replicated center points.

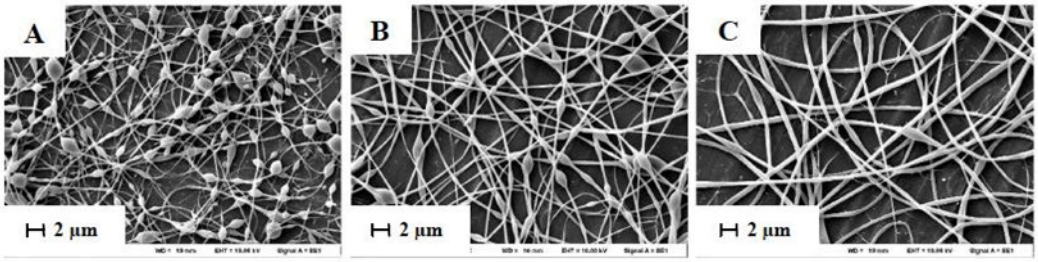

Figure 4. SEM images of shellac nanofibers at the concentrations of (A) 35% w/w, (B) 37.5% w/w, and (C) 40% w/w (Chinatangkul et al., 2017)

Shellac concentration is the most important factor influencing fiber diameter and bead amount (Figure 5). The diameter of nanofibers is also influenced by the amount of loaded ML. As shown in Figure 6, an increase in ML content results in a large fiber diameter because of the interaction between shellac and ML. The incorporated ML will be intercalated among the shellac chains, leading to the impaired stretching ability of the solution. However, the effects of feed rate and applied voltage on the diameter and bead amount of fibers have been largely neglected. An advantage of fabricating shellac fibers loaded with ML is that it potentiates its antimicrobial activities against *Staphylococcus aureus* and *Candida albicans*, which are primarily found in wounds.

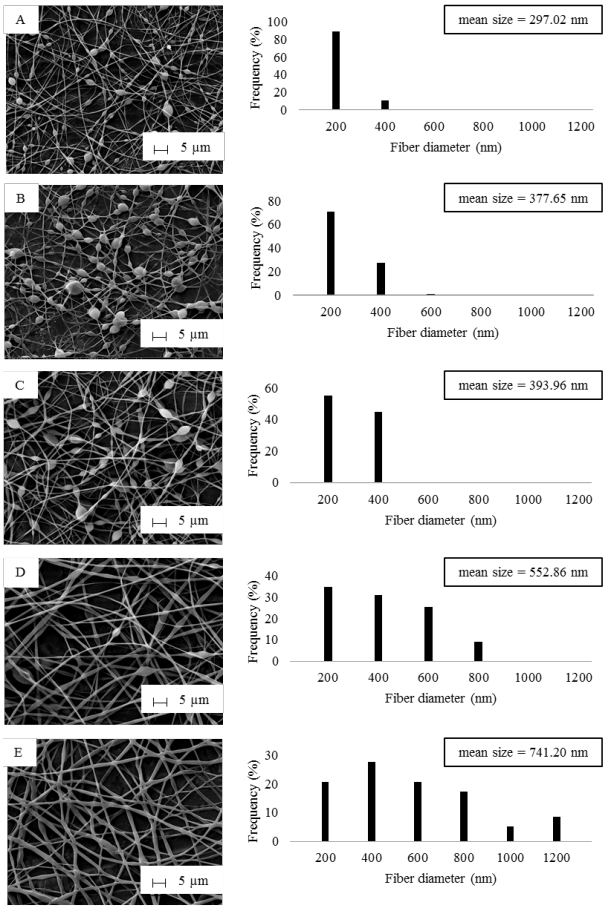

Figure 5. SEM photos and size distribution of shellac-monolaurin nanofibers at the weight ratio of (A) 35:1, (B) 35:3, (C) 37.5:2, (D) 40:1, and (E) 40:3 (Chinatangkul et al., 2017)

As mentioned above, polymer blends have been widely used in various fields, including wound healing and tissue engineering, to produce high-performance materials. Although shellac nanofibers can potentially be employed as drug carriers, fibers using only shellac exhibit some drawbacks because of their absence of hydrophilicity, cell affinity, and good mechanical properties. Thus, to mitigate these problems, several hydrophilic polymers have been selectively added to shellac nanofibers.

Shellac (48% w/v) was combined with gelatin (10% w/v) and poly(N-isopropylacrylamide) (PNIPAm) to fabricate bioactive thermoresponsive polymer blend

nanofibers for wound healing (Vannuruswamy et al., 2015). The thermoresponsive polymer PNIPAm has a low critical solution temperature (LCST) between 32°C and 33°C. PNIPAm is hydrophobic above the LCST and hydrophilic below the LCST. Thermosensitivity can be a factor affecting cell attachment and easy removal of the dressing. A previous study encapsulated the antibacterial drug nadifloxacin into polymeric nanofibers. The drug release profile of the blended nanofibers showed a constant, prolonged duration for 140 h. In addition, the regeneration of tissue treated with the developed nanofibers loaded with nadifloxacin is faster than that of tissue treated with the fiber mats without drug and commercial nadifloxacin cream.

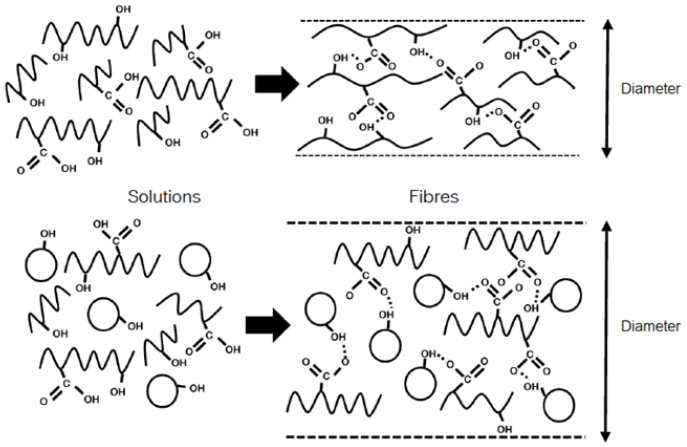

Figure 6. Schematic diagram illustrating the effect of monoluarin on fiber diameter (Chinatangkul et al., 2017)

Aside from wound healing management, the electrospun shellac nanofibers were also effectively implemented for controlled drug release. Wang et al., 2015 prepared shellac nanofibers containing the antioxidant ferulic acid through coaxial electrospinning and used them as an oral colon-specific sustained-release formulation. During spinning, a solution of shellac (75% w/v) and ferulic acid (15% w/v) was employed as a core fluid, and a mixed solution of ethanol and N, N-dimethylformamide was used as a shell fluid to avoid the clogging of the spinneret. The results of the *in vitro* dissolution test illustrated that the release of ferulic acid from shellac nanofibers at pH 2.0 is minimized because of the gastric insolubility of shellac, whereas the release of ferulic acid is sustained in a neutral phosphate buffer solution for over 8 h through the erosion mechanism of shellac (Wang et al., 2015).

Another study employed shellac nanofibers as a sustained-release drug carrier. In this research (Ma et al., 2018), sandwich-structured nanofiber membranes comprising a shellac membrane layer in the middle of two layers of PCL fiber membranes were fabricated and treated by ethanol vapor to enhance their properties. Salicylic acid, which was exploited as a model drug, was added to the shellac solution prior to electrospinning. The resultant nanofiber mats were transparent and featured strong mechanical properties. In addition, the release of salicylic acid from the prepared sandwich-structured nanofibers was observed to have been sustained. The PCL/shellac/PCL sandwich-structured nanofiber membranes incorporated with salicylic acid were further used for skin care applications.

Chitosan, a linear cationic polysaccharide with a pKa value of 6.3, is generated from the deacetylation of chitin, the hard-outer skeleton of arthropods, by treating with alkaline agent. The physical characteristics of chitosan such as solubility and viscosity are directly dependent on the molecular weight, the degree of deacetylation, the side chain of amino and acetamido groups and the purity of material. Chitosan is soluble in dilute acids including acetic, formic, lactic, oxalic and hydrochloric acids (Salas et al., 2017). In addition, chitosan activates neutrophils, macrophages and fibroblasts which allows for improved wound healing (Senel and McClure, 2004). Chitosan also exerts the antimicrobial activity and the hemostatic property related to its cationic nature (Dai et al., 2011). Due to its biodegradable and biocompatible properties, chitosan might gain significant attention for its potential to be fabricated into functional nanofibers.

Regarding the structure of chitosan containing free amino groups, it appears to be a positively-charged polyelectrolyte in acids with pH values of 2-6, resulting in an increase in viscosity, and thus a decrease in spinnability. To resolve this issue, chitosan can be treated with alkali in order to hydrolyse its polymeric chains leading to a decline in the molecular weight allowing for the ease of spinnability. According to the study of Homayoni et al., 2009, a solution of treated chitosan dissolved in 70-90% acetic acid might contribute to a steady electrospun jet. The optimum diameter was achieved at 140 nm with the chitosan hydrolyzed for 48 h with a low molecular weight of 2.94×10^5 g/mol. Additionally, the fiber diameter was strongly influenced by the concentration of acetic acid in the solvent. As the acetic acid concentration was increased, the fiber size was found to be decreased (Homayoni et al., 2009).

Similar to shellac, the application of chitosan is quite limited due to its water insolubility and low mechanical properties. Blends of chitosan with other polymers might therefore be required. In previous work, nanofibrous scaffolds comprising chitosan and PCL were prepared for promoting skin regeneration with the aim of combining the intrinsic biological features of chitosan with the mechanical durability of PCL. The results revealed that the obtained chitosan-PCL scaffolds could reduce wound recovery time and improve complete wound closure when compared with Tegaderm™, a commercial medical dressing (Levengood et al., 2017).

Gelatin, a partially hydrolyzed collagen, is widely applied in the food, pharmaceutical and cosmetic industries due to its non-antigenicity, biocompatibility, biodegradability and cost effectiveness. In order to increase its water-resistant ability, the cross-linking treatment of gelatin nanofibers would be desirable. The agents commonly used for the cross-linking procedure are glutaraldehyde, hexamethylene, acyl azides, diisocyanate and carbodiimide (Jalaja and James, 2015). Gelatin nanofibers incorporated with vitamin E D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) and vitamin A palmitate and cross-linked with glutaraldehyde have been previously fabricated. The prepared gelatin nanofibers demonstrated a moderate hydrophilic characteristic. The release of vitamins from gelatin fibers was observed to be sustained over more than 60 h. Moreover, the fibers had an effective antibacterial effect against *E. coli* and *S. aureus*. The electrospun nanofibers could successfully stimulate the adhesion and proliferation of fibroblasts, and also promote the formation of collagen (Li et al., 2016).

6. CONCLUSION

Nanofibers have piqued the interest of researchers due to their wide potential application in a variety of capacities, as evidenced by the growing number of studies focusing on the development of nanofibers, particularly those fabricated from biocompatible natural polymers. This review summarizes the current development of electrospun nanofibers and their application in several fields.

Nanofibers have been successfully fabricated through several methods. Electrospinning is widely used because of its potential to be developed for mass production. Given their microporous structure, excellent pore interconnection, and high surface area-to-volume ratio, electrospun nanofibers could be effectively employed in a diverse range of applications. Numerous polymers, including natural and synthetic materials, have been extensively electrospun into nanofibers. Natural polymers resemble natural ECM and are biocompatible. Synthetic polymers exhibit high mechanical and electrical properties. Polymer blending has been used to fabricate novel materials with the complementary properties of various polymers. However, polymer blends are usually thermodynamically immiscible. Electrospinning might be a potential technique to address this issue.

Due to their desirable biological properties, natural polymers have been the preferred choice for use in various biomedical fields. Shellac has been generally employed in various applications because of its ability to easily form an excellent protective film. With respect to the unique structure of nanofibers, the transformation of shellac into nanofibers contributes to the improvement of its properties. Although shellac can be practicably electrospun into nanofibers, defects appear in the morphology and properties of shellac fibers obtained by this method. Thus, the blending of shellac and other polymeric materials, especially water-soluble polymers, is required to improve cell attachment, drug loading capacity, and mechanical characteristics. Smooth fibers with less beads are also generated through this method, instead of beaded fibers. As a result of the protective properties of shellac and the unique structure of nanofibers, electrospun shellac nanofibers have been successfully utilized in wound healing management and modified drug delivery.

Aside from its biodegradable and biocompatible properties, chitosan also provides native antimicrobial and hemostatic activities. These features make chitosan a potential material for producing functional nanofibers. However, the spinnability of chitosan solution seems to be poor as a result of its high viscosity. Chitosan hydrolyzed with an alkali agent could be easily electrospun into nanofibers as a consequence of its reduction in molecular weight. Because of its water insolubility and low mechanical strength, blends of chitosan with other polymers might be desirable.

Another attractive natural polymer is gelatin. Cross-linking treatment would be required in order to enhance the water-resistant ability of gelatin nanofibers. With its similarity to ECM, gelatin nanofibers could potentially promote cell adhesion and proliferation leading to rapid tissue regeneration. Further investigation focusing on the development of electrospun nanofibers from natural polymers for other fields, especially air filtration, are increasingly needed to face the challenges of worsening air pollution and the COVID-19 pandemic.

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