

Review Article

Advances in Electrospinning of Natural Biomaterials for Wound Dressing

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Received 31 October 2019; Revised 23 January 2020; Accepted 20 February 2020; Published 27 March 2020

Academic Editor: Ilaria Armentano

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Electrospinning has been recognized as an efficient technique for the fabrication of polymer nanofibers. Various polymers have been successfully electrospun into ultrafine fibers in recent years. These electrospun biopolymer nanofibers have potential applications for wound dressing based upon their unique properties. In this paper, a comprehensive review is presented on the researches and developments related to electrospun biopolymer nanofibers including processing, structure and property, characterization, and applications. Information of those polymers together with their processing condition for electrospinning of ultrafine fibers has been summarized in the paper. The application of electrospun natural biopolymer fibers in wound dressings was specifically discussed. Other issues regarding the technology limitations, research challenges, and future trends are also discussed.

1. Introduction

A wound is defined as a disruption of the continuity of the skin or mucosal surface due to physical or thermal damage. Depending on the size, depth, and extent of the epidermal and dermal layers of the skin, it usually heals within a predictable and expected time frame within 8-12 weeks [1, 2]. The skin plays an important role in protecting the body from external environmental disturbances such as pathogens and chemicals [3]. Once the structure or function of the skin is defective, the body is susceptible to microbial invasion and wound infection, which delays wound healing and may even endanger life [4]. Surgery, burns, or chronic diseases can damage skin integrity, affect homeostasis, and cause wound infection [5]. However, wound healing is a very complicated process, and both acute and chronic skin injury treatments face great challenges in clinical practice [6]. Therefore, it is of great clinical significance to develop new skin substitutes to promote skin repair and shorten the course of treatment [7]. Conventional dressings, such as cotton and gauze, have the advantages of low cost and high absorbency. However,

they only act passively during the healing process by simply isolating the wound from the contaminants [8, 9]. In addition, traditional dressings can cause dehydration of the wound, and increased adhesion can also cause discomfort and pain to the patient and delay wound healing [10]. With the development of technology, there are various types of dressings for different wounds, and choosing specific materials for the wound is important for better wound healing. There is also an increasing demand for medical dressings, the traditional cleaning and isolation have been far unable to meet the requirements. Therefore, many medical dressings with different structures and different functions have emerged and applied clinically, such as natural dressings, synthetic dressings, medical dressings, and tissue engineering dressing [11]. The number of research reports on biomedical wound dressing has been increasing year by year. In 2000, in order to further standardize wound treatment, the US Food and Drug Administration (FDA) treated the wet environment as a standard requirement, which put new demands on medical dressings [12]. It also underlines the research significance of biological dressing. Compared with traditional

TABLE 1: The characteristics of electrospun nanofiber.

Ideal characteristic	Advantage	References
Fiber diameter (50~500 nm)	ECM-like structure and nanosize	[24]
High specific surface area	Promotes hemostasis of damaged tissues	[25]
High porosity (60%-90%)	Conducive to cell respiration and gas penetration	[26]
Cross-linked porosity	Can meet the need of cutting	[27, 28]
Mechanical strength	Similar to human skin tissue	[40]

medical dressings, biological dressings mainly show the following advantages [13]:

- (1) It has good moisture absorption
- (2) It can effectively maintain exudate around the wound but does not form effusion
- (3) It has light adhesion to wound tissue and is not easy to scab, which can reduce the damage to new tissue when the dressing is removed
- (4) The raw materials used have certain antibacterial properties, showing good antibacterial effects
- (5) It can prevent wound infection again, which is unlikely to cause disease
- (6) The dressing materials should be biocompatible, absorb excess exudates, and possess bioactive properties to promote wound healing (e.g., antibacterial behavior) [13, 14].

Various constructions of wound dressings have been explored to facilitate wound healing, such as sponges, hydrogels, hydrocolloids, and films [14]. The electrospun nanofibrous membrane has great potential for wound dressing with the advantages of three-dimensional support structure, small pore size, and high volume ratio [15–17]. The three-dimensional supportive structure could mimic the structure of the natural extracellular matrix, which is conducive to cell growth, adhesion, and proliferation [18]. The small pore size and high porosity of the nanofiber mats could facilitate the gaseous exchange and bacterial isolation during the wound-repairing state [19]. The high surface-to-volume ratio of nanofibers has been proved to be beneficial for the loading and delivery of drugs [20].

Electrospinning is a nanofiber production method by spraying and stretching polymer solutions or melts by means of high-voltage electrostatic action [21, 22]. Compared with other polymer nanofiber manufacturing technologies (such as phase separation method or self-assembly method), electrospinning technology has simple operation and low cost [23]. The characteristics of electrospun nanofibers (as shown in Table 1) make them more suitable for wound dressings.

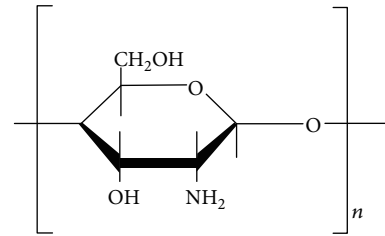


FIGURE 1: Schematic representation of chitosan.

Electrospun polymers for wound dressings are classified into synthetic polymers and natural polymers [29]. Synthetic polymers, including poly(lactic-co-glycolic acid) [30], polycaprolactone (PCL) [31], polyvinyl alcohol (PVA) [32], polyethylene glycol (PEG) [33], polylactide (PLA) [34], poly-L-lactic acid (PLLA) [35] etc., have good mechanical properties and excellent formability, and they are nontoxic in biology. At the same time, synthetic polymers also have the shortcoming of lacking cell binding sites. Natural materials such as gelatin [36], collagen [37], cellulose [38], chitosan [39], silk fibroin [40], mainly from plants, and animals have excellent biocompatibility, and there are biological sites on the surface that can be specifically recognized by cell integrins which can promote cell adhesion migration and proliferation and accelerate tissue regeneration and reconstruction [41]. Biological dressings not only have better water permeability and air permeability but also can resist the invasion of bacteria and prevent infection. They are obviously superior to traditional medical dressings in wound care and skin regeneration, which has attracted more and more attention. This review article briefly introduces the advantages of electrospun nanofibrous membrane applied to wound dressings and then emphatically discusses the researches and developments related to electrospun biopolymer nanofibers including processing, structure and property, characterization, and applications. The technology limitations, research challenges, and future trends are also discussed finally.

2. Preparation a Biomedical Dressing by Electrospinning

2.1. Research on the Electrospinning of Chitosan Composites. Chitosan is a polysaccharide macromolecule formed by partial deacetylation of chitin. It is the only basic natural polysaccharide material, and it is biodegradable and nontoxic [42]. It has a wide range of sources, mainly in the exoskeleton and crustaceans of arthropods. The molecular structure is given in Figure 1. Chitosan is the only natural cationic polymer that has received extensive attention in the biomedical field with its unique cationic properties [42]. In addition to the basic characteristics of ideal wound dressings such as biocompatibility, biodegradability, and low toxicity [43, 44], it is also involved in various stages of wound healing and is considered to be a potential wound healing promoter [45]. During the initial healing phase, CS exhibits its unique hemostatic properties and promotes the infiltration and migration of neutrophils and macrophages [46, 47]. In the late stage of wound healing, it can inhibit scar formation and promote good

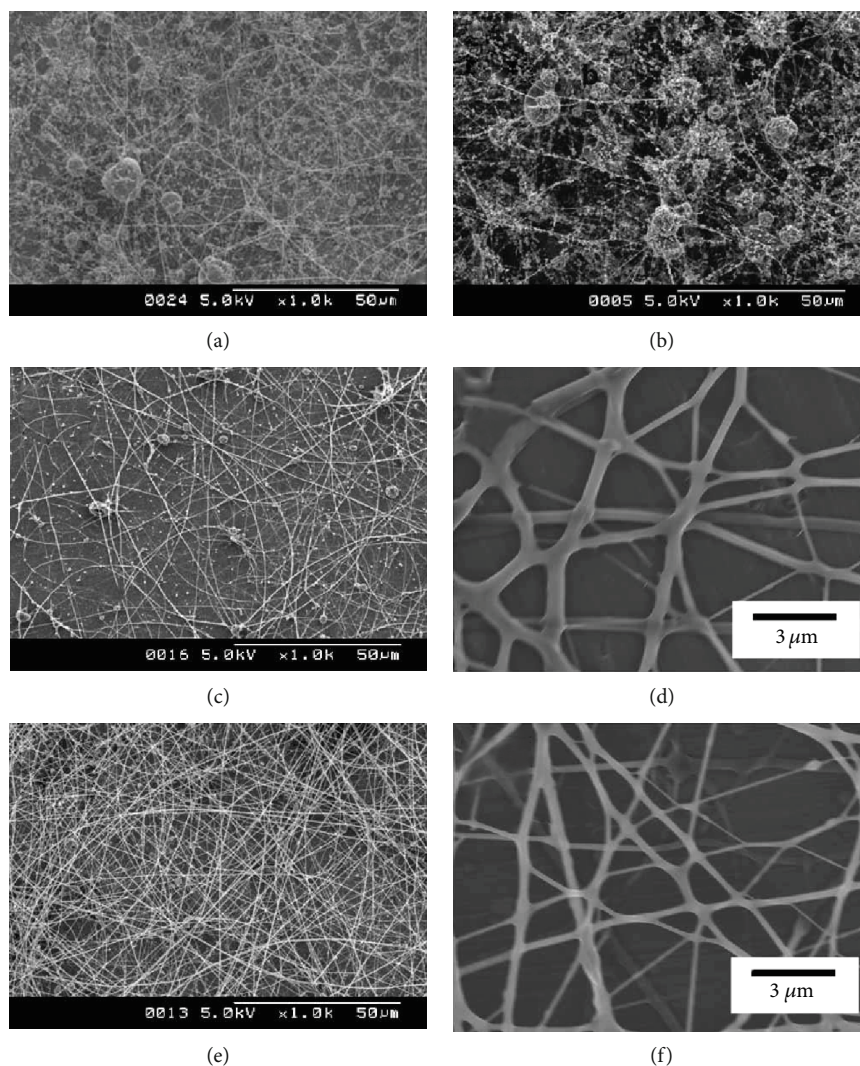


FIGURE 2: Morphological changes in the electrospun fibers of chitosan10. Chitosan10 was dissolved in trifluoroacetic acid (TFA) at the specified concentration; then the chitosan-TFA solutions were electrospun. Chitosan10 concentrations were 5 wt% (a; magnification, $\times 1000$), 6 wt% (b, $\times 1000$), 7 wt% (c, $\times 1000$; d, $\times 10000$), and 8 wt% (e, $\times 1000$; f, $\times 10000$). (With permission from John Wiley and Sons).

epithelial regeneration of tissue [48]. Therefore, CS-based nanocomposites are widely used in wound healing, tissue engineering, and drug delivery [49]. Chitosan for artificial skin can increase the absorption of serum proteins on wound leaching and facilitate wound healing [6].

As soon as the degree of acetylation (DA) is lower than 0.5, it becomes soluble in acidic aqueous solutions with $\text{pH} < 6.5$. From those solutions, it may be easily processed into different structure and morphology: beads, capsules, fibers, films, sponge, or nanoparticles with adjustment of pH over $\text{pH} = 7.5$ where chitosan becomes insoluble. For many applications, the exact chemical structure of chitosan is important and controls the physicochemical properties. It highly depends on the average molar mass (MW), average DA, and distribution of the acetyl groups along the chain (blockwise or random acetyl distribution) [50].

2.1.1. Electrospinning of Chitosan. Ohkawa et al. [51] first used TFA solution as solvent to electrospin chitosan nanofi-

bers from chitosan solution in 2004. The chitosan10 ($\overline{M}_v = 1.3 \times 10^6$; degree of deacetylation, 0.77) was dissolved at concentrations ranging from 3 to 9 wt% in the following solvents: neat formic acid (FA), dichloroacetic acid (DCA), TFA, aqueous acetic acid (0.2 M AcOH), hydrochloric acid (0.1 M HCl), and their mixtures with methanol, ethanol, 1,4-dioxane, dichloromethane, N,N-dimethylformamide, or dimethylsulfoxide. Only when TFA was used as the solvent, chitosan fibers were deposited onto the collector. The SEM photographs of the deposited chitosan are represented in Figure 2. The morphology of the deposited chitosan depended on its concentration in the TFA solution. When the chitosan concentration was 6 wt% or less, the beads and fibers coexisted in the SEM images (Figures 2(a) and 3(b)). At a chitosan concentration of 7 wt%, fibers were predominantly deposited while the bead fraction remarkably decreased (Figures 2(c) and 3(d); average diameter, 490 nm; diameter distribution, 330–610 nm). Electrospun chitosan nanofiber was obtained at 8 wt% (Figure 2(e); average

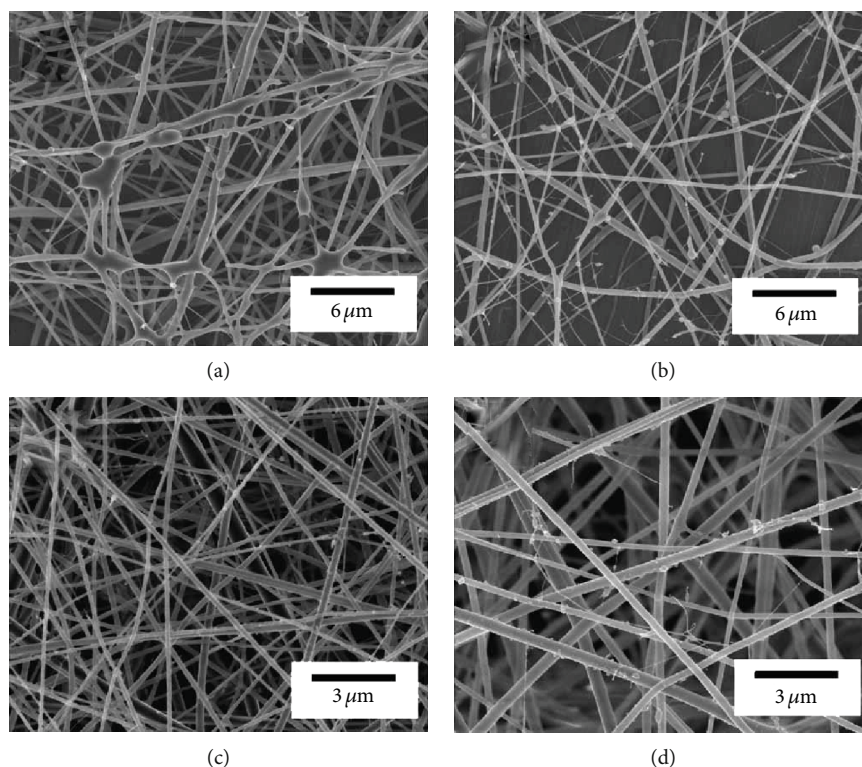


FIGURE 3: Effects of the coexisting dichloromethane (MC) in the prespun chitosan-TFA solution on the morphology of the electrospun chitosan fibers. Concentration of chitosan10 was fixed at 8 wt%. Chitosan10 was dissolved in a series of the TFA:MC mixed solvents and then the chitosan-TFA-MC solutions were electrospun. The volume ratios of TFA:MC were 90 : 10 (a; magnification, $\times 5000$), 80 : 20 (b, $\times 5000$), and 70 : 30 (c, $\times 5000$; d, $\times 10000$). (Licensed by John Wiley and Sons).

diameter, 490 nm; diameter distribution, 390–610 nm). There are two possible reasons why the electrospinning of chitosan is successful with TFA: (i) TFA forms salts with the amino groups of chitosan and this salt formation destroys the rigid interaction between the chitosan molecules, making them ready for the electrospinning process; (ii) the high volatility of TFA is advantageous for the rapid solidification of the electrified jet of the chitosan-TFA solution. However, in the case of 8 wt% chitosan-TFA solution, small beads (Figure 2(e)) and interconnected fibers (Figure 2(f)) were still found. One possible optimization approach was to mix a volatile organic solvent with TFA. Hence, a TFA and dichloromethane (MC) mixed solvent was examined (Figure 3). When the network morphology prepared from the TFA : MC = 80 : 20 solvent (Figure 3(b); average diameter, 380 nm; diameter distribution, 200–660 nm) was compared with that from 90 : 10 (Figure 3(a); average diameter, 390 nm; diameter distribution, 230–650 nm), the network of chitosan fibers became more homogenous. As shown in Figures 3(c) and 3(d), the finest fibers (average diameter, 330 nm; diameter distribution, 210–650 nm) were obtained with the TFA:MC ratio of 70 : 30. In addition, trifluoroacetic acid itself is corrosive and toxic, and solvents remaining in the fiber may affect the subsequent use.

In another study by Sangsanoh et al. [52], mixed TFA and dichloromethane (DCM) in a ratio of 70 : 30 (v/v) was used as the solvent. The addition of methylene chloride improved the homogeneity of the electrospun chitosan fiber. Under the best experimental conditions, the average fiber diameter

was 160 ± 20 nm. Concentrated acetic acid is an effective organic solvent other than TFA.

Gu et al. [53] studied the effect of ultrasonic treatment on electrospinning of chitosan solution. The results showed that the length of sonication changed the pore size and thickness of electrospun chitosan nanofibers, and under optimal conditions, the porosity was greatly increased, the hydrophilicity of chitosan fibers increased significantly, and the water absorption time was reduced from 110 s to 9 s.

Since chitosan is difficult to electrospin directly, it is usually blended with other compatible polymers to improve its spinnability [54].

2.1.2. Electrospinning of Chitosan/PEO. Sarkar et al. [55] dissolved Chitosan (710 kDa) with a deacetylation degree of less than 90% and PEO (200 kDa) with a mass ratio of 4 : 1 in acetic acid and produced fibers with an average diameter less than 78 nm.

Kuntzler et al. [56] produced nanofibers from a 3% chitosan/2% PEO blend containing 1% phenolic compounds. The nanofibers had an average diameter of 214 ± 37 nm, and the potential antibacterial activity of the nanofibers was confirmed by their inhibition of *Staphylococcus aureus* ATCC 25923 (6.4 ± 1.1 mm) and *Escherichia coli* ATCC 25972 (5.5 ± 0.4 mm).

Chen et al. [57] dissolved chitosan with different ratios and different molecular weights in a 50% aqueous acetic acid solution, and the amino group on polycation would

protonize, which would endow chitosan electrical properties. The chitosan molecules then moved in the direction of the electric field under the action of electrostatic force and form a shell of PEO/chitosan nanofibers to produce core-shell nanofibers.

2.1.3. Electrospinning of Chitosan/PVA. Biranje et al. [58] studied the relationship between the properties of CS (chitosan)/PVA nanofiber membranes and the solution viscosity and applied voltage. The 2% (*w/v*) chitosan solution in 1% (*v/v*) acetic acid and 5% (*w/v*) PVA in distilled water were blended, and electrospinning of nanofibers could be done with the CH/PVA mass ratios ranging from 40/60 to 10/90. It was found that a uniform nanofiber membrane was obtained with an average fiber diameter of 80–300 nm in an electric field of 20–25 kV.

Hang et al. [59] studied the electrospinning of mixed solution of chitosan and PVA with silver ions. It was found that the addition of silver ions improved the spinnability of the mixed solution and the antibacterial property of the fibers. When the concentration of chitosan in the mixed solution was less than 6%, the conductivity of the solution to which silver ions were added was higher than that of the solution without silver ions, and the opposite was true when the concentration of chitosan in the mixed solution was more than 6%. Since chelation inhibited the ionization degree of the amino group in chitosan, the conductivity of the solution was reduced.

2.1.4. Electrospinning of Chitosan/SF. Hao et al. [60] studied the electrospinning of chitosan (CS) in formic acid with silk fibroin (SF) and found that when the CS concentration increased to 4%, the average diameter of the fibers is between 103–337 nm. At the same time, the conformational transformation of SF nanofibers took place with the addition of CS, and the trend of the β -sheet structure was confirmed.

Delezuk et al. [61] studied the induction of conformational changes of silk fibroin (SF) by chitosan and used it as a substrate for immobilized phytase for phytic acid detection. CS/SF-LBL films were prepared from three chitosan (CS) samples with different molecular weights, and the structure of high molecular weight chitosan (CS) was observed from random coil to sheet structure. The CS/SF-LBL film deposited on the interdigitated gold electrode was coated with a layer of phytase, and the impedance spectrum was used as the detection principle. The data were processed by multidimensional projection technology, and the plant acid could be detected within a range of 10–9 M. This high sensitivity might be due to the suitability of the CS/SF matrix, indicating that molecular level interactions between chitosan and SF could be exploited in other biosensors and biologics. Controlling the properties provided by the combination of chitosan and SF is promising for the development of novel biosensors and biologics.

2.1.5. Wound Dressing Applications of Electrospun Chitosan. Trinca et al. [62] produced double-layer stents by using electrospinning technology. The inner layer was mechanical support composing of a mixture of polycaprolactone (PCL) or

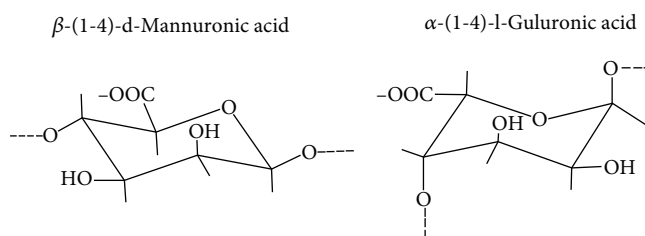


FIGURE 4: β -(1 \rightarrow 4)-d-Mannuronic acid and α -(1 \rightarrow 4)-l-gulonic acid chemical structure.

polycaprolactone/cellulose acetate (PCL/CA), while the outer layer was made of chitosan/polyethylene oxide mixture (CS/PEO) which acted as a mechanical dressing. PCL and PCL/CA fibers had diameters ranging from 1 to 4 μ m, while CS/PEO fibers had diameters less than 200 nm. The mechanical properties of the scaffold were determined by PCL or PCL/CA layer, and its tensile strength was 1.4–1.8 MPa, Young's modulus was 10–15 GPa, and elongation at break was above 430%. The use of 10 wt% CA in the PCL/CA blend increased the tensile strength and Young's modulus without loss of maximum elongation. The performance of the stent met the application requirements of skin lesion dressings, and the cytotoxicity to L929 fibroblasts was also low, which promoted sufficient cell proliferation.

Alavarse et al. [63] prepared polyvinyl acetate/chitosan and polyvinyl acetate/chitosan/tetracycline hydrochloride (TCH) dressing pads by electrospinning, and the polymer blend formed a fiber mat with three-dimensional cross-linked nanofibers. The drug was uniformly bonded along the nanofibers without significant changes in the morphology and thermal properties of the mat. In addition, during the cross-linking of the nanofiber mat, the exposure of the glutaraldehyde vapor caused a decrease in surface porosity and at the same time improved the roughness of the felt. The addition of tetracycline nanofibers showed a uniform distribution of the drug along the nanofibers and microbeads. In vitro indirect MTT assay also showed that the drug-loaded nanofiber scaffold developed had good cell compatibility, and it was confirmed by the scratch test that the scaffold could promote healing as an antibacterial wound dressing.

2.2. Research on the Electrospinning of Alginate Composites. Alginate is mainly found in the cell wall and intercellular viscose of brown algae, and also in some bacteria, such as pseudomonas and nitrogen-fixing bacteria that produce mucoid capsules. It is a long-chain polymer composed of β -(1 \rightarrow 4)-d-mannuronic acid and α -(1 \rightarrow 4)-l-gulonic acid [64]. The chemical structure is shown in Figure 4. Alginate is processed from alginic acid extracted from brown algae. Among them, calcium alginate has the property of absorbing a large amount of liquid and can absorb up to 20 times of its own weight of exudate, which is 5–7 times that of ordinary gauze [65]. Alginate can efficiently absorb excess exudate and provide a moist environment during the wound healing process thanks to its excellent water absorption [66, 67].

Alginate is not easily electrospun due to its high electrical conductivity, high surface tension [68], and the chain

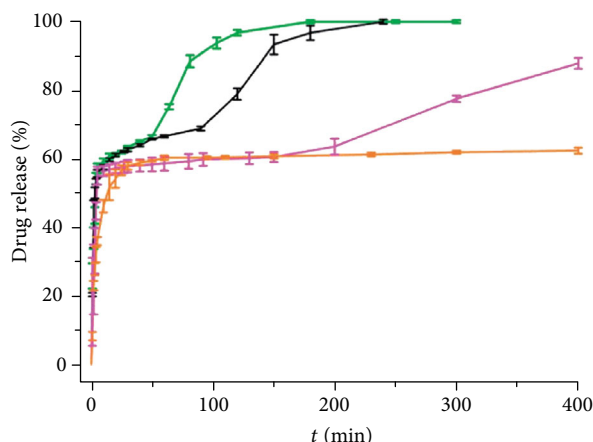


FIGURE 5: Drug release from fibers with varied SA contents at pH 3: F4 (6.3% SA; green line); F1 (9.1% SA; black line); F5 (11.8% SA; purple line); and F6 (14.3% SA; orange line). For clarity, data are shown out only to 400 min, although experiments were performed for up to three days. Three independent experiments were performed (each with a separate fiber mat), and results are reported as mean \pm SD (Licensed by Royal Society of Chemistry).

entanglement in its aqueous solution [69]. Therefore, synthetic polymers such as polyvinyl alcohol (PVA), polyoxymethylene (PEO) were added to improve the electrospinnability and mechanical strength of alginate [70], while PVA was also identified as a favorable wound dressing material [71, 72]. The combination of sodium alginate (SA) and polymer can improve the interaction force between molecules and entangle the segments, which makes it easier to form electrospun nanofibers. To obtain a better healing effect, the addition of antibacterial agents such as silver nanoparticles, metal oxides, and antibiotics to nanofiber dressings has become a recent research hotspot [73–75].

2.2.1. Electrospinning of SA/PEO. Jeong et al. [76] mixed cell-adhesive peptide-modified SA and unmodified SA with PEO to synthesize SA/PEO composite nanofibers, cross-linked with CaCl_2 in 5:1 ethanol/water solution, and then soaked in deionized water for 5 days. When the optimum concentrations of SA and PEO were 0.2% and 0.4%, respectively, and the volume ratios of the mixed solution were 20:80, 40:60, 50:50, and 60:40, uniform nanofibers were obtained.

Kaassis et al. [77] prepared a novel, highly adjustable pulse delivery system by electrospinning a mixed solution of polyethylene oxide (PEO), sodium alginate (SA), and sodium ibuprofen (SI). The resulted fiber skeleton exhibited a novel three-dimensional network structure, and a two-stage pulsatile drug release was obtained, as shown in Figure 5. The amount released could be precisely adjusted by changing the sodium alginate and ibuprofen sodium content in the mixture. Therefore, the materials could be used for pulsatile drug release into the stomach in the fed state, particularly important, for elderly patients.

2.2.2. Electrospinning of SA/PVA. Tang et al. [78] added the PVA and SA powders in distilled water at a content of 7.2% w/v and 0.8% w/v, respectively, to obtain a mixture. The mix-

ture was swollen at room temperature for 1 hour and then stirred at 90°C for 3 hours to give a clear and transparent solution. A volume of honey was added to the PVA/SA solution with a defined concentration of honey (0%, 5%, 10%, 15%, or 20% (v/v)). Subsequently, the honey/SA/PVA mixture was stirred at room temperature for 12 hours to obtain a homogeneous solution. It was observed that the nanofiber membrane exhibited a smooth and single-shaped three-dimensional structure by SEM, and the average diameter of the nanofibers increased as the honey content increased. In addition, MTT measurements indicate that honey/SA/PVA nanofiber membranes had good biocompatibility.

De et al. [79] prepared a 2% (w/v) alginate solution by dissolving alginate in distilled water and adding a corresponding amount of MgO under vigorous stirring to obtain a 10% (w/w) MgO composition. PVA was then dissolved in distilled water at 80°C and stirred for 3–4 hours to prepare a 10% (w/v) PVA solution. The solutions were mixed together in a weight ratio of 3:2, stirred for 4 hours, and then sonicated (30 min, $J = 8$ Hz) to obtain a uniform MgO dispersion. To compare the effects of particle reinforcement and chemical cross-linking, the electrospun alginate fiber mat was cross-linked by immersion in 20 ml of 2% (v/v) glutaraldehyde solution for 2 hours and the sample was dried under vacuum for 24 hours at 40°C. The Alginate/MgO scaffolds consisted of randomly oriented, ultrafine, nearly imperfectly formed alginate nanofibers with diameters ranging from 60 to 250 nm, similar to alginate scaffolds with a pore size of 2–50 μm . On the other hand, the cross-linked alginate scaffold had dense and well-fused fibers.

2.2.3. Wound Dressing Applications of Electrospun Alginate.

Some reports showed that silver nanoparticles are effective against pathway-ogenic organisms namely *B. subtilis*, *Vibrio cholerae*, *E. coli*, *P. aeruginosa*, *S. aureus*, *Syphilis typhus*, etc. [80–83]. Many arguments have been given to explain the mechanism how silver nanoparticles (AgNPs) inhibit and kill microorganisms, but the most convincing explanation is the formation of free radicals which has also supported by the appearance of the 336.33 peaks in the electron spin resonance (ESR) spectrum of AgNPs [84]. The generation of free radicals is quite obvious because they can attack membrane lipids in a living system; then they break down, destroy, and eventually inhibit the growth of these microorganisms. Some researchers [85, 86] believe that the silver bactericidal and bacteriostatic method is similar to silver ions, but the effective concentration is different. Silver ions released from silver nanoparticles may penetrate bacterial cell components such as peptidoglycan, DNA, and proteins and prevent them from further replication [87]. Therefore, the key to nanosilver antibacterial is the oxidation rate and release rate of silver ions.

In Stojkowska et al.'s study [88], Ag/alginate colloid solutions and nanocomposite hydrogel microfibers with electrochemically synthesized AgNPs were used to treat secondary burns in rats and compared with related commercial products for wound care. All the treated wounds healed faster than the controls (19 days and 21 days vs. 25 days, respectively) without any adverse effects of silver ions or nanoparticles. The obtained macroscopic results

and histopathological analysis showed that both the colloidal solution and the microfibers had shown statistically equivalent results as the respective commercial products, although the amount of silver applied to the wound was about two orders of magnitude lower.

Kyzioł et al. [89] prepared alginate nanofibers in the presence of poly(ethylene oxide) (PEO), a surfactant Pluronic F-127, and a model drug (ciprofloxacin hydrochloride, CpHCl), all mixed prior to electrospin. It was demonstrated that the addition of a carrier polymer (PEO) and a small amount of surfactant are necessary to obtain uniform alginate fibers with cylindrical shape and regular morphology. The stable alginate fibers loaded with CpHCl were examined by scanning electron microscopy, and the average diameter of the fibers ranged from 109 nm (unloaded fibers) to 161 nm (loaded fibers).

In a study, honey was incorporated into an alginate/PVA-based electrospun nanofibrous membrane to develop an efficient wound dressing material. Nanofibrous membranes with increased honey content show enhanced antioxidant activity, suggesting that nanofiber dressings can control the overproduction of reactive oxygen species [78].

2.3. Research on the Electrospinning of Gelatine Composites.

Gelatin is a fibrous protein consisting of a unique amino acid sequence obtained by hydrolysis from natural collagen, which results in the loss of the original alpha-helical conformation by disrupting the intermolecular bonds. Regardless of the hydrolysis process that converts the collagen into gelatin, both biopolymers have up to 20 different ratios of different amino acids in the primary structure. This primary structure provides RGD (L-arginine-glycine-L-aspartate), three amino acid-recognition sequences for integrin-mediated cell adhesion. Low-cost collagen derivatives have good biocompatibility and biodegradability and are also nonimmunogenic. Therefore, gelatin has many applications in the food and pharmaceutical industries [90]. Gelatin properties depend on the source of the collagen (usually cattle or pigs), the age of the animal, the type of collagen, and the type of collagen to gelatin conversion (acidic and alkaline hydrolysis). Two types of gelatin are generally available, depending on the pretreatment procedure (before the extraction process). Acidic pretreatment (type A) hardly affects the amide group, while alkaline pretreatment (type B) targets the amide groups of asparagine and glutamine and hydrolyzes them to carboxyl groups, thus converting many of these residues for aspartic acid and glutamic acid [91]. At the isoelectric point (IEP), gelatin has a neutral net charge as a balance between the positive charge from the NH_3^+ ion and the negative charge from the COO^- ion. IEP is an intrinsic property of gelatin and is determined by the pretreatment of the raw materials and the type of process. Type A gelatin typically exhibits an IEP in the range of 6–9.5, while form B has an IEP in the range of 4.5–5.6. Due to the electrostatic attraction of the oppositely charged groups near the IEP, some properties reach an extreme value close to the IEP [92].

2.3.1. Electrospinning of Gelatin. Gelatin can only be electrospun from a solution in which the gelatin is in a random

crimp conformation. Gelatin gels in an aqueous solution at 30°C, making it impossible to electrospin at room temperature. Therefore, the aqueous solution needs to be heated to above the gel-sol transition point. In addition, the instability of the polymer jet and the formation of droplets, as well as the high surface tension of the aqueous solution, make electrospinning gelatin difficult. The high boiling temperature of water introduces another problem. Incomplete water evaporation before reaching the collector results in fiber fusion and heterogeneity. Another way to obtain nanofibers is to use certain organic solvents. Except for some harmful and toxic organic solvents (usually 2,2,2-trifluoroethanol (TFE), trifluoroacetic acid (TFA), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)), an effective way to obtain an electrospinning solution is to use an acidic solvent such as acetic acid and aqueous formic acid [93]. An important advantage of gelatin over other structural proteins (i.e., collagen) is that gelatin will not be denatured by the effect of applied voltage during electrospinning [94].

Gelatin nanofibers prepared by electrospinning generally have many disadvantages such as brittleness, poor variability, and poor moisture resistance. In order to regulate the gelatin nanostructure, composition, and properties and expand the functional application of gelatin, research on gelatin hybrid electrospinning technology has received more and more attention [95–97].

2.3.2. Electrospinning of Gelatin/PEO. Barchuk et al. [98] studied the effect of gelatin on the structure, phase composition, and morphology of the electrospun chitosan/PEO nanofibers. Particular attention was paid to the surface chemistry, surface structure, and surface morphology of nanocomposite fibers, as these parameters were critical for biomedical applications and final surface modification. Gelatin and PEO prevented chitosan crystallization, and chitosan/PEO had a significant effect on the surface properties of gelatin nanofibers, especially after cross-linking. During the heating process, decomposition of the gelatin on the surface of the nanofiber occurred, which caused a large number of cracks on the surface, as well as a significant change in surface chemistry, resulting in a decrease in surface adhesion. Furthermore, after cross-linking between the fibers, it was also observed that the region was a continuous gelatin layer, which resulted in a significant decrease in the porosity of the nanoweb.

2.3.3. Electrospinning of Gelatin/PCL. Coimbra et al. [99] used PCL as the core and functional gelatin as the shell to prepare core-shell fiber mesh by coaxial electrostatic spinning and then photo-cross-linking under UV light aiming to be used in vascular tissue regeneration. The suitability of the meshes for the pretended biomedical application was evaluated by assessing their chemical/physical properties as well as their haemo- and biocompatibility in vitro. The obtained results revealed that meshes' shell prepared with a higher content of gelatin showed fibers with diameters presenting a unimodal distribution and a mean value of 600 nm. Moreover, those fibers with a higher content of gelatin also displayed lower water contact angles and therefore higher hydrophilicity. Furthermore, gelatin included in

the fibers also induced an increased performance while interacting with blood, thus reducing the hemolytic and thrombogenic character of the materials. In addition, the physiological responses of NHDF cells to PCL/gelatin MA fibers were also characterized by MTS analysis. The results showed that all materials were biocompatible and cell viability was unaffected by the material, indicating its potential for biomedical applications.

Zhou et al. [100] reported that aqueous sodium hydroxide (NaOH) solutions of different concentrations were introduced at a tiny amount into the GT/PCL hybrid dissolved in trifluoroethanol (TFE). Compared with unmodified GT/PCL fibers, the wettability and mechanical properties of alkali-modified GT/PCL nanofibers were greatly improved. Cell-culture experiments showed that the murine IPSC-MSCs had favorable interactions with the alkali-modified GT/PCL scaffolds compared to the unmodified ones. The alkalinized nanofibers were found to have a positive effect on cell adhesion and proliferation.

2.3.4. Electrospinning of Gelatin/Silk Fibroin. Marcolin et al. [101] proposed an innovative method to obtain small diameter tubular structures that were naturally and biologically compatible. The biocompatibility and good mechanical properties of electrospun silk protein tubular substrates (SFts) for tissue engineering applications were combined with the excellent cellular interaction properties of gelatin. In fact, an innovative noncytotoxic gelatin gel, cross-linked under mild conditions by Michael-type addition reaction, was used to coat the SFt matrix and obtain an SFt/gel structure (ID = 6 mm). SFts/gels showed uniform gelatin coating on electrospun fiber tubular structures. Finally, SFt/gel compatibility in vitro was confirmed by the good viability and diffusion morphology of L929 fibroblasts for up to 7 days. These results suggested that SFt/gel was a promising off-the-shelf graft for small diameter blood vessel regeneration.

2.3.5. Wound Dressing Applications of Electrospun Gelatin. The gelatin nanofiber membrane material not only has obvious small size effect, high porosity, large specific surface area, and supramolecular alignment effect but also has good biocompatibility, structural compatibility, and biodegradability. Composite fiber materials can be prepared by compounding gelatin with other materials, such as fungicides, anti-inflammatory drugs, and growth factors, which can increase the effect of dressings, effectively improve the hemostatic speed of wounds, and fully bridge the wound surface, reducing the stimulation of external environment on the wound.

Morsy et al. [102] introduced novel antibacterial electrospun gelatin-based mats by combining gelatin, glycerol, glucose, and silver nanoparticles (AgNPs), which together could exhibit optimal physical-chemical characteristics as long-term electrospun fibrous mats. Therefore, AgNPs were synthesized in situ within the acidic electrospun solutions during preparing electrospun gelatin-glycerol-AgNPs (GEL-GLY-Ag) and gelatin-glycerol-glucose-AgNPs (GEL-GLY-GLU-Ag) mats. The results showed that the felt layer of electrospun gelatin matrix composite had a free-beaded dense fiber structure, high water absorption, and good degrada-

tion performance. The AgNPs could be successfully synthesized in situ within electrospinning solutions, and the results confirmed that in situ-prepared AgNPs enhanced the antibacterial activity of electrospun fibers against positive and negative bacteria.

Yao et al. [103] dissolved gelatin powders in formic acid (88 wt%) with a concentration of 17 wt% and PVA in hot deionized water at a concentration of 10 wt%. The PVA aqueous solution was then added to the gelatin solution with a gelatin/PVA ratio of 9/1 (v/v). After that, keratin powders were dispersed in the mixed solution at a concentration of $2 \mu\text{g ml}^{-1}$ and stirred overnight at room temperature to ensure complete dissolution. The blended polymer solution was loaded into a syringe with a metal needle and then spun toward a commercial PU wound dressing for 2 hours using the electrospinning machine. After electrospinning, the fibers were cross-linked in 50 wt% glutaraldehyde vapors for 45 min. The thickness of the nanofibrous mat was about $160 \mu\text{m}$. The results of the MTT cell activity assay revealed that residue released from electrospun gelatin/keratin composite nanofibers enhanced cell proliferation. Furthermore, the interaction between fibroblasts and gelatin/keratin composite pads was more favorable as compared to a gelatin mat.

2.4. Research on the Electrospinning of Silk Fibroin Composites. Silk fibroin (SF) extracted from silkworm has recently received attention due to its unique biological behavior, biocompatibility, biodegradability, high water and oxygen uptake, low immunogenicity, and strong mechanical properties [104, 105]. It can be transformed from the α -helix to the β -sheet by the silkworm. With the presence of β -sheet structure, SF fiber has excellent mechanical properties and good biocompatibility, oxygen permeability and biodegradability, and so on [106–108]. SF can be processed into fibers, membrane, hydrogel, or gel spongy body, which can be applied in the external wound care, anticoagulant, sustained drug release, tissue framework material, and other fields [108].

2.4.1. Electrospinning of Silk Fibroin. There are three main solvents for electrospinning of SF: hexafluoroisopropanol (HFIP), formic acid (FA), and water. In addition, trifluoromethane (TFA) was first used as a solvent for electrostatic spinning of SF. With HFIP, the electrospinning could be successfully processed, but HFIP is very expensive. In addition, HFIP, FA, and TFA are three toxic solvents, and residues in the material can affect the application of the drug. Therefore, electrospinning without the use of organic solvents can result in better biomedical materials. However, there are several problems with the electrospinning of aqueous solution, such as processing with low SF concentration and slow evaporation of water [109].

Feng et al. [110] prepared silk fibroin (SF) fiber mats by electrospinning using mixed solvent of hexafluoroisopropanol (HFIP) and formic acid (FA). The results showed that the SF fiber mats had an average diameter of 2.0 and $0.3 \mu\text{m}$. The electrospinning solvent not only affected the secondary structure of the as-spun SF fiber mat but also indirectly affected the structural transformation of the fiber mat. SF fiber mats electrospun with FA showed more β -sheet

structure after ethanol treatment. The solvent of HFIP or FA had little effect on the thermal properties of the SF fiber mat. Both membranes supported cell adhesion and growth, and no significant difference was observed.

Gaviria et al. [111] evaluated the effect of manufacturing parameters on silk fibroin (SF) nonwoven fabrics obtained by electrospinning. In addition, the relationship between the secondary structure and the thermal stability of the protein material and the morphological characteristics of the obtained nonwoven fabric were analyzed. The silk fibroin in a 10% *w/w* formic acid solution was electrospun at 8 cm, with various ratios of voltage/distance and flow rate. The best morphology of the SF nonwoven fabric was obtained at $R = 1 \text{ kV cm}^{-1}$ and low flow rates, and these process parameters were related to the higher crystal structure content of the material. The results showed that the nonwoven fabric obtained under the controlled process parameters had great potential for various applications.

SF has many excellent characteristics; however, its secondary structure leads to low crystallinity and poor mechanical properties of the fiber membrane, which greatly limits its practical application. To solve this problem, SF must be modified. In recent years, many attempts have been taken up. For instance, blending SF with other natural or synthetic polymer materials can improve overall performance [112].

2.4.2. Electrospinning of Silk Fibroin/PVA. Cao et al. [113] used a coaxial electrospray technique to produce drug-loaded PVA/SF nanoparticles with different core-shell structures. The encapsulated drug release profile could be altered by varying the PVA ratio in the nanoparticles. Due to the barrier of the carrier polymer, doxorubicin (DOX) was released slowly and steadily after the initial burst release after 72 hours of incubation. In addition, PVA/SF nanoparticles also showed pH-dependent release, and more drugs could be released in acidic media. Measurement of apoptosis showed that sustained release of DOX resulted in high cytotoxicity of tumor cells in a time-dependent manner.

Sah et al. [114] developed three-dimensional porous SF, SF/PVA, and soluble eggshell protein- (SEP-) SF/PVA scaffolds using salt-leaching technology and characterized them. The results showed that the physical and biological properties of the SF scaffold were improved by mixing SF with PVA (50:50) and subsequently modifying it by SEP. The hybrid scaffold exhibited an interconnected porous structure. SEP hindered the swelling and biodegradability of the hybrid stent. In addition, cell compatibility, cell viability, and preliminary bioactivity assays indicated that the system evaluated was nontoxic, biologically tolerant, and potentially biocompatible. The noninflammatory response to the host ICR mouse model further confirmed the *in vivo* biocompatibility of the scaffold. The results of this study indicated that SF/PVA and SEP-SF/PVA stents were highly promising for tissue engineering applications.

2.4.3. Electrospinning of Silk Fibroin/PLA. He et al. [115] made tussah silk fibroin (TSF)/poly(lactic acid) (PLA) composites with different composition ratios by electrospinning. By adding 10% PLA, the spinnability of the TSF solution

was significantly improved, the average diameter of the fiber was reduced from 583 nm to 178 nm, and the fiber diameter uniformity was remarkably improved. In addition, the mechanical properties of electrospun nanofibers increased significantly after blending 10% PLA, while thermal properties remained stable. When the PLA content exceeds 15%, the average diameter of TSF/PLA composite nanofibers increased and the fibers seemed to be polarized. Moreover, the mechanical properties of the fibers decreased with the increase of PLA content, and the fibers showed more mechanical characteristics of the PLA component.

2.4.4. Electrospinning of Silk Fibroin/PEO. Rajabi et al. [116] used a mixed aqueous solution of SF/PEO for the preparation of nanofiber scaffolds by electrospinning. In addition, laminin (LN) was immobilized on the surface of the SF/PEO nanofiber scaffold using O₂ plasma treatment in order to improve the hydrophilicity of SF/PEO and provide a cell adhesion motif to produce a promising nerve scaffold. The untreated sample exhibited a smooth surface and a circular cross-section, and after the MeOH treatment, an increase in surface roughness and a decrease in porosity occurred. Finally, SCs proliferation assays and morphological studies demonstrated that by controlling the hydrophilicity of the scaffold and providing LN molecules, synergistic effects of cell adhesion, diffusion, and proliferation onto the surface of the electrospun laminin-functionalized SF could occur. The results of PEO nanofiber scaffolds showed that the SF conformation and surface hydrophilicity of SF/PEO nanofibers were improved after methanol and oxygen plasma treatment. Immunostaining observations showed a continuous application of LN on the stent. Improving surface hydrophilicity and laminin functionalization significantly increased cell proliferation, and this was more pronounced after 5 days of culture. The electrospun laminin-functionalized SF/PEO nanofiber scaffold might be a promising candidate for peripheral nerve tissue regeneration.

2.4.5. Application of Electrospun Silk Fibroin in Wound Dressing. Yu et al. [117] prepared the 80:20 collagen/chitosan (CL/CS) and 50:50 silk fibroin/chitosan (SF/CS) nanofiber scaffolds by electrospinning. Compared with the control group (gauze dressing), CL/CS and SF/CS stents had good biocompatibility and promoted wound healing.

Zhang et al. [118] prepared a novel HPRP- (helicobacter pylori origin-) A2 peptide/silk fibroin (SF) matrix composite nanofiber through a full water electrospinning process. HPRP-A2 was an antimicrobial peptide. HPRP-A2 incorporation had little effect on morphological and biocompatible SF nanofibers. Interestingly, the nanofiber composite matrix of Gram-positive and Gram-negative bacteria showed impressive antibacterial activity. Furthermore, based on animal data, HPRP-A2/SF composite nanofibers exhibited excellent properties in accelerating wound healing.

3. Conclusions

Natural biomaterials have attracted more and more attention due to their good biocompatibility, biodegradability, unique

antibacterial, hemostatic properties, and renewable characteristic. However, a single biomaterial has shortcomings such as poor mechanical properties and a single function. Therefore, the modification of natural biological materials, compounding with other materials, and drug loading are the research hotspots of new medical biological dressings in the future.

The nanofibers prepared by electrospinning technology have high specific surface area, high porosity, liquid absorption, and semipermeability. It can simulate the structure and biological functions of the natural extracellular matrix which promotes cell adhesion, migration, and proliferation. With the excellent biocompatibility and biodegradability and good mechanical strength and physical properties of natural polymers, it is widely used in the field of skin substitutes and wound dressings. However, the biological activity and therapeutic effect of the dressing made by electrospinning are still insufficient. In order to solve this problem, bioactive substances such as growth factors, vitamins, antibacterial agents, and the like may be added to the electrospun fiber, and the slow release of active substances in the dressing can not only inhibit infection but also accelerate wound healing and tissue regeneration. It is foreseeable that the electrospun composite nanofibers with bioactive agents will be the development direction of the wound dressing field in the future.

Although the advantages of electrospinning are obvious, natural biomaterials still have disadvantages such as poor spinnability and low mechanical strength. The research in the past ten years has not been well developed. The main reasons are as follows:

- (1) Natural biomaterials are rarely soluble in organic solvents due to their crystal structure or strong polarity. Water can be used as the main solvent but it is difficult to remove during the electrospinning process
- (2) Natural biomaterials require complex, time-consuming, and energetic pretreatments prior to electrospinning, such as controlling the size of the morphology, the number of impurities, and the molecular weight.

Many natural biomaterials easily form strong hydrogen bonds with water in aqueous solution and have high viscosity at low concentrations, which are not good for electrospinning. The most feasible way to improve the spinnability of natural biomaterials is to reduce their surface tension and improve their movement ability in the electric field. In order to solve this problem, it is important to choose a solvent which can evaporate quickly, and thus the biopolymer molecular structure and key functions are well maintained. Besides, physical blending or chemical modification of bio-based polymers is necessary to improve their processing property and electrospinning property, while the biocompatibility has to be carefully considered. In addition, there is a need to develop electrospinning equipment that can provide higher efficiency. So far, relevant research is still in the early stage of exploration. It is necessary to continue to study in depth to expand its application areas. In short, there is still a long way to go in the commercial application of electrospinning for medical wound dressings.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors sincerely acknowledge the financial support from the National Natural Science Foundation of China (51273005), the Project of Top Young Talents of Beijing Excellent Talents Training Program (2018), and the Innovation Teambuilding Program of Beijing Institute of Fashion Technology (BIFTTD201904).

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