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REVIEW ARTICLE

Novel Advances in 3-D Printing Technology in Drug Delivery

State-of-the-Art Review of Advanced Electrospun Nanofiber Composites for Enhanced Wound Healing

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Abstract

Wound healing is a complex biological process with four main phases: hemostasis, inflammation, proliferation, and remodeling. Current treatments such as cotton and gauze may delay the wound healing process which gives a demand for more innovative treatments. Nanofibers are nanoparticles that resemble the extracellular matrix of the skin and have a large specific surface area, high porosity, good mechanical properties, controllable morphology, and size. Nanofibers are generated by electrospinning method that utilizes high electric force. Electrospinning device composed of high voltage power source, syringe that contains polymer solution, needle, and collector to collect nanofibers. Many polymers can be used in nanofiber that can be from natural or from synthetic origin. As such, electrospun nanofibers are potential scaffolds for wound healing applications. This review discusses the advanced electrospun nanofiber morphologies used in wound healing that is prepared by modified electrospinning techniques.

Keywords coaxial electrospinning · core–shell nanofiber · emulsion electrospinning · janus nanofiber · layer-by-layer · multi-layer nanofiber · side-by-side electrospinning · wound healing

Introduction

The skin is the largest organ in the body and accounts for 15% of the total body weight. It is the first line of defense that plays an important protective role against physical, chemical, and biological external [1]. The skin consists mainly of the epidermis, dermis, and hypodermis with the presence of other sublayers [2].

Skin wounds result from the disruption and damage of the skin layers [3]. Wounds can be acute or chronic. In acute wounds, the skin can self-heal and undergo normal healing stages. While in chronic wounds, self-healing property is insufficient and stages of healing is interrupted [4].

Wound dressings act as protective barriers to the applied surface and should be biocompatible, biodegradable, prevent microbial infection and resemble the extracellular matrix (ECM) of normal tissue, and provide an optimum environment for accelerated healing [5]. An ideal wound dressing should have an elastic mechanical structure but strong enough for easy handling and comfortable wear [6]. Too soft dressings are difficult to handle. On the other hand, high strength wound dressings often stick to wounds and may cause secondary injury [7].

Current treatments such as cotton, gauze films, foams, hydrogels, and hydrocolloid have low cost and high absorption capacity and play role in isolation of wound from contaminations [8]. Those treatments are often cause adhesion of the wound and delay on wound healing leading to decrease patient compliance [9]. Therefore, in order to improve the skin permeability of the drugs and to achieve better therapeutic effects, researchers have designed a variety of nanoparticle drug delivery agents for transdermal use, such as nanosheets, liposomes, hydrogels, wafers, nanospheres, dendrimers,

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nanosized colloids, and nanofibers [10]. Nanofibers resemble extracellular membrane (ECM) with large specific surface area, high porosity, good mechanical properties, and controllable morphology and size [11, 12].

Electrospun nanofiber properties used for wound healing including hydrophilicity, flexibility and strength, biocompatibility, and specific cell interactions are largely determined by the chemical composition of the polymers used [13]. Many different polymers used together with various bioactive ingredients could be introduced as electrospun nanofibers for wound healing purposes. Based on their origin, polymers can be classified as natural and synthetic polymers [14]. Natural polymeric dressings can be fabricated from protein polymers (e.g., gelatin [15], egg white [16], casein [17], whey protein [18] collagen [19, 20], silk fibroin [21], zein [22], keratin [23], marine [24], and soy protein [25]), plant polysaccharide (e.g., cellulose [26, 27], starch [28], and pectin [29, 30]), animal polysaccharide (e.g., chitosan [31–33] and hyaluronic acid [34–36]), fungal polysaccharide (e.g., pullulan [37, 38]), bacterial polysaccharides (e.g., dextran [39]), and alginates [40]. Synthetic polymeric dressings include polyvinyl alcohol (PVA) [41, 42], polyurethane (PU) [43, 44], polycaprolactone (PCL) [45], polylactic acid (PLA) [46], polyacrylic acid (PAA) [47], polyacrylonitrile (PAN) [48–50], poly-l-lactic acid (PLLA) [51], polyvinyl pyrrolidone (PVP) [52], polyethylene oxide (PEO) [53], polyethylene glycol (PEG) [54], polylactic-co-glycolic acid (PLGA) [55], polyglycolic acid (PGA) [56], polydopamine (PDA) [57], polyamide-6 (PA-6) [58], polyhydroxy butyrate (PHB) [59], polyvinylidene fluoride (PVDF) [60], poly-L-lactide-co-caprolactone (PLCL) [61], epsilon poly-lysine (ε-PL) [62], etc.

M. Wang *et al*. fabricated nanofibrous membrane of chitosan and PVA loaded with antibiotics at different ratios successfully, and they found that when low-molecular-weight chitosan to PVA ratio equaled 50/50, smooth and homogeneous fibers were obtained for potential wound healing applications [63]. H. Ezhilarasu *et al*. developed PCL/aloe vera (AV) nanofiber containing curcumin PCL/AV/CUR and tetracycline hydrochloride PCL/AV/TCH. The resulted fibers were nontoxic and have good mechanical properties within a range that resembles human skin properties that make them potential for wound healing applications [64]. F. Mwiiri , J. Brandner, and R. Daniels loaded birch bark dry extract (TE) on low-molecular-weight PVA fiber mats that showed significant increase in wound healing more than TE oleo gel with high drug permeation in a sustained release manner [65, 66]. Zaeri S, Karami F, and Assadi M prepared PVA solution containing 4% wt/vol propranolol and the result showed thin fibers that have good porosity and hydrophilicity with no toxic effects [67]. PU/PVA-gel nanofibers incorporated with cerium oxide (CeO_2) nanoparticles and cinnamon essential oil (CEO) that showed good porosity, suitable fluid uptake capability with a slow degradation rate, and antibacterial effect on gram positive and gram negative bacteria [68].

In this context, nanofibrous scaffolds produced by electrospinning technique could potentially provide an excellent dressing for wound healing.

Wound Healing Phases

Wound healing process includes four subsequent phases: hemostasis, inflammation, proliferation, and remodeling with a timescale of seconds to hours, hours to days, days to weeks, and weeks to months, respectively [69, 70] (Fig. 1).

In hemostasis phase, the main goal is to prevent excessive blood loss and to protect vital function of the organ. Exposed extracellular matrix (ECM) components activate platelets, and three main steps occur: (a) platelet migration to the injured tissue; (b) secretion of alpha and dense granules containing adenosine diphosphate (ADP), thromboxane A2, and thrombin; and (c) aggregation. Chemical mediators released stimulate coagulation cascades. Thrombin catalyzes the conversion of fibrinogen to fibrin that promotes blood clot formation. This blood clot formed composed of platelets entrenched in a mesh of cross-linked fibrin fibers linked together by fibrinogen with smaller amounts of plasma fibronectin, vitronectin, and thrombospondin [71–75]. Activated platelets release multiple pro-inflammatory cytokines and chemokines, such as interleukin factors (IL-1α, IL-1β,

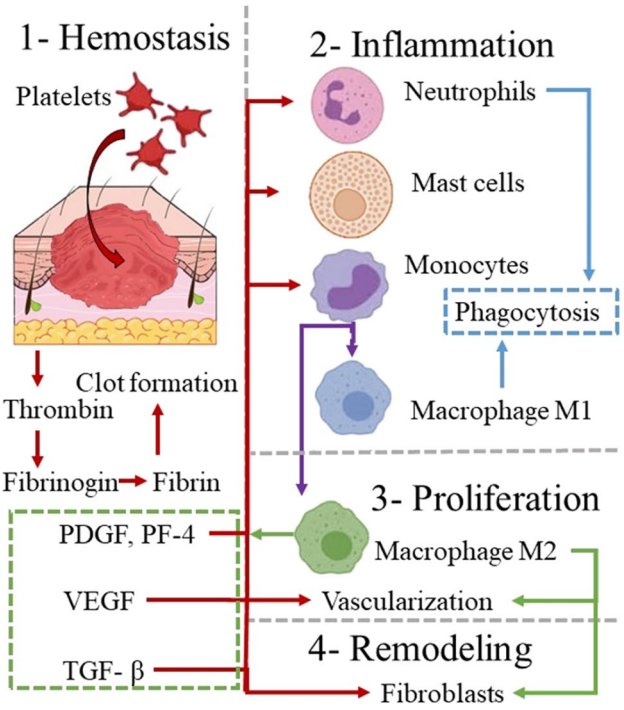

Fig. 1 Schematic diagram of wound healing phases

IL-6, and IL-8) and tumor necrosis factor-α (TNF-α), and anti-inflammatory chemokines such as platelet factor-4 (PF-4), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), and pro- and antiangiogenic factors such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) [76–79].

Inflammation phase divided into two stages, early stage and late stage, for the protection wounds against bacteria and removal of apoptotic tissues. The released mediators recruit neutrophils to the injury site first, followed by the accumulation of monocyte as well as mast cells [80]. At first, neutrophils kill and phagocytose bacteria and damaged matrix proteins within the wound bed [81]. Neutrophils also recruit TNF-1 and IL-1 which aid in the healing process [82]. Subsequently, neutrophils start to diminish, and monocytes differentiate into macrophages M1 and then migrate into the extravascular space to phagocytose bacteria as well as tissue debris [83]. Macrophages are divided into two categories based on their nature and function: inflammatory (M1) macrophages and anti-inflammatory (M2) macrophages. M1 macrophages are usually activated through various pro-inflammatory signals, such as tumor necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), and lipopolysaccharide (LPS); M1 phenotype secretes cytotoxic agents (nitric oxide), pro-inflammatory cytokines IL-1, IL-6, IL-12, IL-23, and TNF-α. M2 macrophages on the other hand are activated by IL-4 and IL-13, and they have various subtypes: M2a (alternatively activated macrophages), M2b (type 2 macrophages), and M2c (deactivated macrophages) [84]. The activation of M2a, M2b, and M2c macrophages occurs in response to IL-4 and IL-13, immune complexes and bacterial lipopolysaccharide (LPS), and glucocorticoids and TGF-b, respectively [85].

M2 macrophages contribute in cell proliferation phase by releasing of several growth factors such as PDGF, VEGF, TGF-β, insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), and fibroblast growth factor-2 (FGF-2) for the promotion of wound healing via angiogenesis and skin re-epithelialization [86]. M2 macrophages also act as regulatory cells by activating keratinocytes, fibroblasts, and endothelial cells that migrate into the clot and synthesize a new extracellular matrix components such as fibrin, collagen III, fibronectin, glycosaminoglycans, proteoglycans, and the matrix protein hyaluronan which contributes wound closure and initiate the formation of granulation tissue [87, 88].

In remodeling phase, replacement of collagen III by the stronger collagen I and rearrangement of collagen fibers leads the skin to reach its maximum elasticity and strength [89]. It also involves replacement of granulation tissue with the scar tissue by the fibroblasts and is completed to restore skin integrity [90].

Electrospinning Process

Many technologies have been developed to generate nanofibers including bioprinting, wet spinning, dry spinning, and electrospinning [91]. Electrospinning is a simple, cost-effective, and versatile setup process which depends on electrostatic concept in the presence of high electrical field [92]. Electrospinning device is mainly composed of high voltage power source, syringe that serves as reservoir for storing polymer solution, needle (spinneret) for dispensing of solution, and collector to collect nanofibers [93] (Fig. 2a).

Firstly, a high voltage is applied, and polymer solution is expelled from needle, and a strong electric field is formed between the needle and collector. Secondly, the continuous application of high voltage makes the polymer solution elongates to form a cone called Taylor cone. Thirdly, charged droplets of Taylor cone eject from the tip of the needle. Finally, the polymer solution is stretched and evaporated by the electric force and deposited on the collector to form nanofibers [94]. Insufficient entanglement of polymers due to instability of liquid jet and altered surface tension caused incomplete evaporation of solvent solution before reaching collector and led to the formation of beads instead of fibers [95–97] (Fig. 2b).

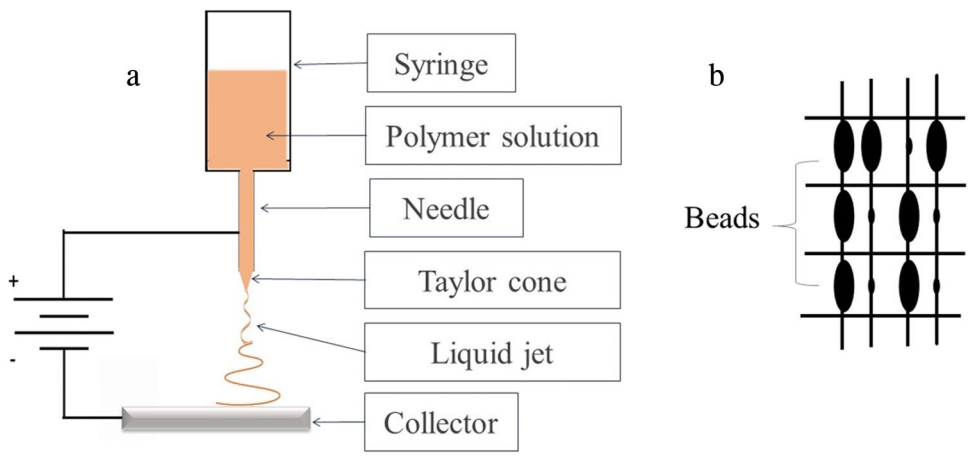

Fig. 2 Schematic diagram of **a** electrospinning process and **b** beaded fibers

Electrospinning can be divided blend electrospinning, coaxial electrospinning, emulsion electrospinning, and side-by-side electrospinning [98, 99]. Blending electrospinning is the conventional and the most common drug incorporation method, especially for miscible polymer–drug solutions [100]. It involves dispersing or dissolving drugs in the polymer solution to form a homogenous solution [101]. Their drug release kinetics depends on the morphology and distribution of drug in the resulted fibers in addition to drug–polymer interaction which influence the release behavior as drugs blended electrospun nanofibers have frequently show burst release pattern [102, 103]. X. Chen *et al*. incorporated tannic acid TA by electrospinning into PCL nanofibers, and release study showed initial burst release of tannic acid that increased with increasing drug distribution in the polymer [104]. However, beside the burst release limitation, the direct contact of drug to solvent may lead to denature and decrease activity of sensitive bioactive agents (e.g., proteins and cytokines) that make a necessity for more recent electrospinning methods [105].

In contrast to conventional electrospinning, where polymer and drug are blended into one solution in which, coaxial electrospinning uses a core solution and a shell solution [106]. Coaxial electrospinning is an electrospinning technique in which the core solution and shell solution are placed into the core syringe and shell syringe, respectively [107] (Fig. 3a). The core–shell structure fabricated by coaxial electrospinning provides improved mechanical strength, declined the initial burst release, and protected drug from degradation by avoiding direct exposure to solvents by encapsulating the drug in the nanofiber [108–110]. Coaxial technique have many advantages such as the high encapsulation efficacy, the high variety in the selection of drugs and materials, and the simple procedure and cheapness [111]. Emulsion electrospinning is another method to encapsulate the drug inside a core of a core–shell fiber by electrospinning of oil-in-water (O/W) or water-in-oil (W/O) emulsions using the ordinary single needle instead of the two needles of coaxial electrospinning [112, 113] (Fig. 3b). In side-by-side electrospinning, two polymer solutions exposed to the electrical field in the presence of side-by-side needles for the different solutions, which makes it very easy for them to parting from each other allowing incorporation of solutions with different chemical properties (e.g., hydrophilic and hydrophobic) [114–116] (Fig. 3c).

Many techniques used to characterize and evaluate morphological, mechanical, chemical, and structural properties of the produced electrospun nanofiber [117]. Morphological properties include diameter, size distribution, and pore size distribution [118]. Diameter and size distribution of nanofibers can be measured by transmission electron microscopy (TEM) [119], scanning electron microscopy (SEM) [120], and atomic force microscopy (AFM) [121]. Pore size distribution and porosity can be measured by mercury intrusion porosimeter [122], liquid extrusion porosimeter [123], nuclear magnetic resonance [124], or capillary flow porometer [125]. Chemical properties of nanofibers can be characterized by Fourier transform infrared spectroscopy (FT-IR) [126], Raman spectroscopy [127], thermogravimetric analysis (TGA) [128], differential scanning calorimetry (DSC) [129], and differential thermal analysis (DTA). Structural evaluation can be characterized by X-day diffraction (XRD) technique [130]. Mechanical properties of the nanofibers can be characterized by tensile strength test according to the ISO 5270:1999 standard test methods using uniaxial tensile testing device [131, 132].

Electrospinning Parameters

Many parameters can affect electrospinning process which can be classified into process parameters (applied voltage, flow rate, diameter of needle to collector distance), solution parameters (concentration, molecular weight, viscosity, and conductivity), and environmental parameters (humidity and temperature) [133].

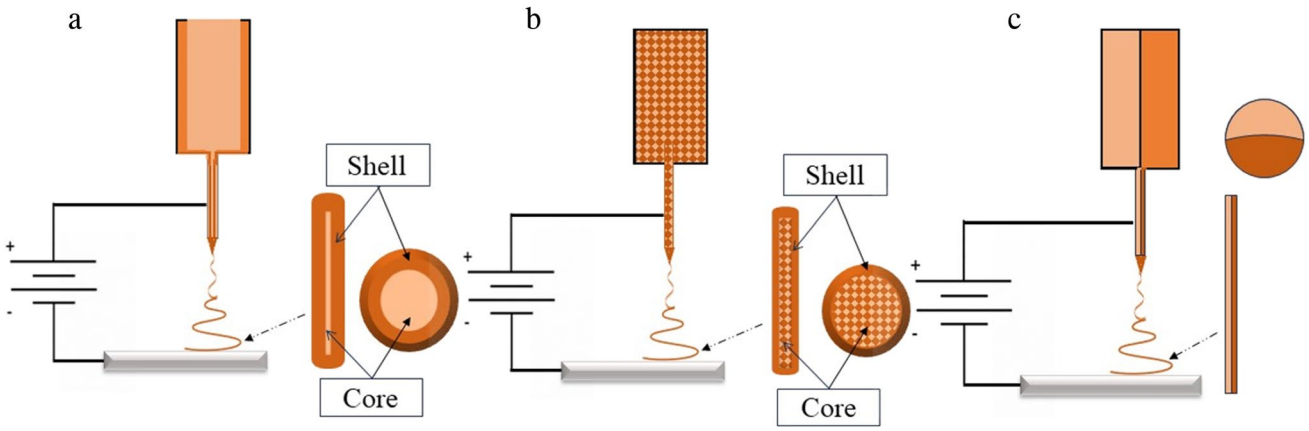

Fig. 3 Schematic diagram of **a** coaxial electrospinning, **b** emulsion electrospinning, and **c** side-by-side electrospinning

Process Parameters

The increase of applied voltage more than critical value will result in increase in diameter and formation of beaded fibers. This effect is attributed to that with the same flow rate, the size of Taylor cone decrease, and the velocity and length of the jet increase [134]. The application of high voltage to the polymer solution breaks the balance of its surface tension and creates a charge on the surface of the liquid. Reciprocated charge repulsion and the contraction of the surface charges to the counter electrode cause a force opposite to the surface tension. As the intensity of the electric field is increased, the hemispherical drop formed at tip of the needle tip gets converted into conical shape [135]. At voltage value lower than the critical value, the electrical force will not be enough to form the homogenous fibers [136].

L. Miranda Calderon *et al*. fabricated rifampicin-loaded methacrylic nanofiber and noticed that when decrease voltage from 20.3 to 14.2 KV lowered nanofiber diameter [137]. C. Kumar *et al*. developed of composite electrospun nanofibers based on PCL and collagen hydrolysate loaded with ferulic acid and increased applied voltage up to 18 kV that led to increased fiber diameter and further increase to 25 kV resulted in electrical bubbles due to the stagnant potential exceeding the confined air resistance [138]. M. Ignatova, N. Manolova, and I. Rashkov also noticed increased fiber diameter by increasing voltage [139]. N. Chinatangkula *et al*. designed shellac nanofiber loaded with monolaurin, and they noticed that moving capacity of polymer solution towards the tip was poor when the applied voltages was below 9 kV [140].

A minimum flow rate is required to produce fibers with lower defects and smaller diameter. At high flow rate, a larger drop is produced that results in a faster movement of solution to the collector lead to gradual increase in the volume of the Taylor cones, and the length of the straight fluid jets shortened as a result incomplete evaporation of the solvent occur and solvent-wet fibers produced that increase the probability of beads formation and increase fiber diameter [141, 142].

X. Wu *et al*. loaded magnesium l-ascorbic acid 2-phosphate and α-tocopherol acetate (MAAP/α-TAC) on PAN nanofibers to the form of core–shell structure and by increasing the flow rate of MAAP/α-TAC core solution and bead formation increased [143]. M. Almukainzi produced PEG/PVP nanofibers and noticed that nanofibers with increased diameter produced by increasing flow rate under the same conditions [144]. F. Davani *et al*. fabricated core–shell nanofiber by PEO, chitosan, and vancomycin in shell and PVP, gelatin, and imipenem/cilastatin in core compartments. They noticed that by increasing flow rate of both core and shell solutions, nanofibers with increased diameter produced [145]. M. Hajikhani, Z. Emam-Djomeh, and G. Askari encapsulated PLA\PEO\cefazolin inside within PVP shell, and when flow rate of core solution is less than 0.1 mL\h, extra thin fibers were formed that reduce cefazoline loading. On the other hand, when increase to more than 0.2 mL/h, it will cause jet break. In the case of shell solution, a flow rate of less than 0.6 mL/h resulted in the formation of numerous beads in the nanofibers due to insufficient solution to fully cover the surface of the core fibers. On the other hand, an excessive flow rate of about 1 mL/h resulted in the formation of large droplets on the tip of the needle that can fell on the collector and destroy the fabricated fibers [146].

Needle to collector distance determines the morphology of electrospun nanofibers. An optimized distance should be applied to allow all of the solvent to evaporate and to prevent bead formation [141]. The increase in the distance between needle and collector causes reduction in the electrostatic field strength and led to complete evaporation of the solvent occurs which make polymer solution fully stretched hence results in increased fiber diameter [147–149].

X. Zhang *et al*. fabricated silk fibroin nanofiber and showed that at 6 cm, continuous fibers with small number of beads were formed, while in distance above 9 cm, a smooth, bead-free, and fine fiber was formed. However, distance above 15 cm showed to be unsuitable for electrospinning [150].

Solution Parameters

Optimized polymer concentration range should be used. Below this range, only droplets are formed rather than fibers. This may occur because the polymer solution is not reaching the collector due to entangled polymer chains are broken under surface tension and electric field forces. On the other hand, when concentration is above this range, uncontrolled fibers morphologies may appear [151].

T. Baykara and G. Taylan developed core–shell nanofiber with PVA as shell solution and *Nigella sativa* seed oil as the core solution. Increasing concentration of PVA solution resulted in continuous and thicker fibers with low number of beads [152]. N. Chinatangkul *et al*. used shellac solution to develop nanofiber, and they noticed that by increasing shellac concentration, bead formation decreased [153]. B. Poornima and P. Korrapati incorporated ferulic acid and resveratrol into PCL\chitosan core–shell nanofiber. The found that chitosan optimum concentration was 2%, and when concentration was higher than 2% large, beaded fibers formed, while concentration less than 2% resulted in spray formation instead of fibers [154]. Z. Li *et al*. prepared core–shell fibers with small unilamellar vesicles (SUVs)\sodium hyaluronate in the core and PVP in the shell. Optimum sodium hyaluronate concentration was 2%, and when concentration was 1%, droplets were formed instead of fibers. On the other hand, increasing concentration to 3% caused blockage of needle during electrospinning process [155].

The molecular weight, controlled by the length of the polymer chain, therefore smooth and uniform fibers can

be obtained if the molecular weight is appropriate. With extremely low molecular weight, beads are highly probable to be formed. Conversely, very high molecular weight increases fiber diameter and affects their morphology [156]. Viscosity is dependent on solution's concentration and molecular weight. In extremely low viscosity, only droplets are formed, and fiber formation is interrupted. High viscosity prevents polymer solution flow through the needle [157, 158].

F. Zulkifli *et al*. fabricated hydroxyethyl cellulose (HEC)/PVA, and when the amount of HEC in the HEC/PVA increased from 30 to 50%, the viscosity of the solution was also increased [159]. W. Sarhan and H. Azzazy fabricated honey\chitosan\PVA nanofiber and found that increasing chitosan concentration from 1.5 to 3.5% resulted in highly viscous solution that is unable to spin [160]. L. Moradkhannejhada *et al*. prepared PLA nanofiber loaded with curcumin, and then PEG of different weights have been added. PEG addition led to a decrease in average weight of nanofibers because of the decreased viscosity of PLA solution; therefore, the jet solution with low viscosity can increase instability and consequently lead to fibers with small diameter. On the other hand, average size of nanofibers have been increased by increasing the PEG weight [161]. Z. Hadisi, J. Nourmohammadi, and S. Nassiri developed Lawsonia inermis–gelatin–starch nanofiber in which with an increase in gelatin content, the viscosity of the solution increased. They noticed that at low viscosities, the molecular entanglements between polymeric chains are not enough to form a uniform fiber, and thus, beads were formed [162]. M. Wang *et al*. PVP/PVDF core–shell shows the viscosity of neat PVDF and PVP is low, and once mixing the two solutions, the viscosity increased significantly. This change in viscosity resulted in good chain entanglement between the two substances, which lead to advanced electro-spinnability [163].

Polymer solution conductivity is dependent on intrinsic polymer properties, solvent, and ionizable salts. An increase in electric conductivity tends to decrease fiber diameter. Above the critical limit, polymer solutions become very unstable in the presence of strong electric fields, resulting in a broad diameter fibers and may prevent the formation of Taylor cone [164].

A. Abdel Gawad *et al*. fabricated PVA nanofibers from chitosan and iodoacetamide and complexes. Increasing the chitosan content increased conductivity due to progression of NH_3^+ groups from $-NH_2$ in acidic medium which increases the charge density on the surface of the ejected jet formed during electrospinning, and therefore, it decreases diameter of the formed fibers [165]. Similar results are obtained by M. Ganesh [166].

Environmental Parameters

The humidity (RH%) influences the diffusive equilibrium between solvent and water vapor, affecting the fiber morphology. A decrease in the RH% humidity leads to fibers with decreased diameter. However, an excessive decrease in humidity tends to accelerate the evaporation rate of solvent and induce inadequate extension of the jet resulting in thicker nanofiber [167]. In contrast, humidity higher than certain limit inhibits solvent evaporation so that water vapor may penetrate into the jet leading to thinner fibers [168]. A highly humid environment may affect electrospinning and contribute to the formation of pores on the nanofibers surface. Additionally, high humidity in the environmental atmosphere can prevent blockage at the needle caused by quick evaporation of volatile solvent during electrospinning [169]. R. Augustine *et al*. loaded connective tissue growth factor (CTGF), and they found that humidity can lead to formation of secondary pores on fibers due to condensation of droplets from air and subsequent difference in the rate of evaporation of the solvent from the surface [170].

The temperature affects the rate of evaporation and the viscosity of polymer solution. The elevated temperature increases viscosity leading to increasing evaporation time and limiting further jet stretching. For low temperature, they decrease the viscosity and facilitate formation of thinner fibers [171].

Applications of Electrospun Nanofiber as Wound Healing Dressings

Morphology and structure of nanofibers play an important role in cell behavior by improvement of cell attachment and proliferation [172, 173]. Nanofibers are characterized by their similar structure to ECM, increasing cell viability, allowing gas exchange, and absorbing excess exudates from the wound as they have large surface area and high porosity [174]. They also have inert cell property which allow painless removal of wound dressing and protect newly formed skin layer combined with minimal scars [175].

Core–shell Nanofiber

Coaxial electrospinning and emulsion electrospinning are two new techniques for the fabrication of core–shell nanofibers, where the outer shell layer can encapsulate and prevent the release of the active components in the inner core layer [176].

Y. Li *et al*. suggested PLA\chitosan core–shell nanofiber as a potential scaffold for wound healing [177]. S. Afshar *et al*. prepared PLA\chitosan core–shell nanofiber by coaxial electrospinning loaded with curcumin. PLA-chitosan core–shell nanofiber showed better mechanical properties than that of neat chitosan nanofiber. Chitosan shell layer showed a burst release, and around 80% of drug released in less than 10 h. In contrast, curcumin inserted in the PLA exhibited a two-stage release behavior: an initial burst release of about 25% in the first 4 h followed by a sustained

release in the second stage [178]. A. Joshi *et al*. used coaxial electrospinning to prepare PCL\gelatin core–shell nanofiber loaded with heparin. Compared to single-phase gelatin nanofiber, PCL\gelatin nanofiber showed improved mechanical and swelling properties. After that heparin\PCL\gel treated with bFGF that showed more accelerated healing than non-treated group [179]. C. Gao developed PCL/gelatin-ciprofloxacin/Fe_3O_4 multi-functional dressing that allowed controlled release of drug and improved re-epithelialization, granulation tissue formation, and collagen deposition at the wound site [180].

A. Basar *et al*. prepared ketoprofen-containing PCL and PCL/gelatin binary electrospun fibers by solution and emulsion electrospinning, respectively. PCL nanofiber exhibited a burst release profile that released approximately 90% of the drug after only 12 min. In contrast, PCL\gelatin binary structure extended release for about 4 days. Furthermore, electrospun PCL/gelatin binary nanofiber improved attachment and wettability more than PCL nanofiber [181]. M. Hussein *et al*. prepared core–shell and loaded phenytoin into PCL shell layer and silver-chitosan nanoparticles into PVA core layer that showed two-stage release behavior in addition to improved biocompatibility and mechanical properties [182]. X. Bai *et al*. prepared zeolite imidi framework (ZIF-8)-coated PCL/ε-PL core–shell nanofibers and found that ZIF-8 and ε-PL exhibited dual antibacterial properties and enhanced wound healing process [183].

C. Wang *et al*. fabricated core–shell nanofibers based on core layer involving gelatin, quaternary ammonium salt-grafted sulfonated chitosan and EGF/bFGF, shell layer of PCL, and polydopamine. This nanofiber improved mechanical properties and antimicrobial effect. Wounds treated with core–shell nanofiber exhibited the smallest wound area with superior angiogenesis effect and increased collagen deposition accompanied with decreased inflammatory mediators [184]. C. Cui *et al*. used coaxial electrospinning to encapsulate ciprofloxacin into PCL\chitosan core–shell nanofiber that showed ideal porosity and good mechanical properties. Nanofiber scaffolds showed three-stage release with an initial burst release of ciprofloxacin during the first 12 h, followed by a gradual release over more than 8 days. After 15 days, the release of ciprofloxacin reached a plateau at 56%. They also showed enhanced healing process with improved well-organized granulation tissue, better epithelialization, less lymphocyte, and neutrophil infiltration which were observed in the wounds [185]. N. Zandi *et al*. prepared core–shell nanofiber with gelatin with phenytoin as a shell layer and PVA\gelatin with lysozyme as a core layer, and release profiles can be considered in three stages including an initial burst release within 8 h followed by gradual release lasting to 33 h and then reached plateau [186].

M. Najafiasl *et al*. fabricated nanofibers using PVA/sodium alginate (SA) as core layer and chitosan as shell layer loaded with D-panthenol which exhibited enhanced mechanical properties and accelerated wound healing process [187]. A. Khan *et al*. incorporated ZnO nanoparticles and oregano essential oil into PLCL core–shell nanofiber, and results revealed good antibacterial activity and accelerated wound healing process. The untreated wound exhibited an elevated level of IL-6 which indicated inflammation in the wound area. Compared to untreated group, wounds treated by core–shell nanofiber showed complete epithelialization, and angiogenesis with highly organized collagen fibers in addition to that inflammatory activity decreased significantly, and scar was replaced by newly formed epithelium [188].

J. Wang *et al*. loaded nanohydroxyapatite (n-HAP) with tetracycline and subsequently encapsulated in chitosan\gelatin nanofiber. Compared to tetracycline\n-HAP and tetracycline\chitosan\gelatin which showed burst release of >90% of drug within 4 days, they showed sustained release where only 45% released within 4 days [189]. Z. Xie loaded chitosan and PEO nanofiber with VEGF- and PDGF-encapsulated PLGA nanoparticles embedded inside them. This scaffold has a biphasic release pattern: an initial burst release of VEGF followed by sustained release of PDGF. They facilitated easy detachment and promoted fast cell growth and proliferation in addition to complete wound closure within 2 weeks with less inflammatory cell presence and higher fibroblast cells. Furthermore, collagen deposition is shown to be more mature with more hair follicle formation [190].

Z. Dong *et al*. biological prepared ethyl cellulose-modified zein with tea carbon dots (TCDs) and calcium peroxide (CaO_2) that shown to significantly accelerate the wound closure rate and the production of sebaceous glands and hair follicles. They also promoted the transformation of macrophages from M1 to M2 in diabetic rat wound models, shortened the duration of the inflammatory stage, and facilitated further wound healing [191]. C. Lee *et al*. prepared core–shell nanofiber loaded with insulin as core and PLGA\vildagliptin as shell. The core–shell nanofiber demonstrated improved wettability, porosity, surface area, and mechanical properties. It exhibited initial burst release in the first day followed by continuous release until day 30. The nanofiber promoted diabetic wound healing and reduced fibrotic effects [192].

S. Homaeigohar *et al*. developed PAN core–shell nanofiber together with bovine serum albumin (BSA) and calcium-deficient hydroxyapatite (HA) and showed to be nontoxic and resemble ECM of the skin with good mechanical properties [193]. M. Aljohani coated chitosan silver nanoparticles within poly-lactate calcium salt (PLCS) that revealed good water permeability and displayed high antimicrobial efficiency against gram positive and gram negative bacterial pathogens [194]. A. Aldalbahi *et al*. fabricated PVDF\cellulose acetate nanofiber that contains gold nanoparticles and displays enhanced

cell spread and proliferation [195]. Z. Li *et al*. prepared core–shell nanofiber by cellulose acetate as shell and naproxen-loaded liposomes\sodium hyaluronate as core which showed biphasic release pattern with initial burst release of 47.1% naproxen in the first 8 h followed by sustained release of residual drug for about 12 days [196]. H. Zhang *et al*. synthesized 5-fluorouracil (5-Fu)-loaded dendritic mesoporous bioglass nanoparticles (dMBG) in PEO\poly (ether-ester-urethane) urea core–shell nanofiber that found to have good wettability and mechanical properties. The nanofiber effectively inhibits hypertrophic scars, accelerates wound healing process, and promotes angiogenesis and collagen deposition [197].

G. Jin *et al*. encapsulated multiple epidermal induction factors (EIF) such as the epidermal growth factor (EGF), insulin, hydrocortisone, and retinoic acid with gelatin and PLCL nanofiber that showed to promote cell proliferation. Compared to EIF blended nanofibers that showed burst release over a period of 15 days, there was no burst release which was detected from EIF core–shell nanofibers [198]. A. Li *et al*. loaded epigallocatechin-3-O-gallate (EGCG) in PLCL\gelatin core–shell nanofiber and results appropriate biocompatibility, antibacterial, and antioxidant ability, which could support cell viability and proliferation. Compared to gauze, wounds treated with core\shell nanofibers showed accelerated wound closure, angiogenesis, and re-epithelialization [199]. M. Movahedi *et al*. prepared PU\starch core–shell nanofibers and showed to have improved mechanical properties compared to starch nanofibers and higher cell proliferation compared to PU nanofibers. Wounds treated with the scaffold showed accelerated wound closure and presence of hair follicles and sebaceous glands [200].

Janus Nanofiber

Janus nanofiber involves two separate compartments which allow incorporation of solutions with different chemical properties [201]. F. Ao *et al*. designed Janus nanofiber contains hydrophilic and hydrophobic properties. They used ethyl cellulose as hydrophobic layer and ethyl cellulose\gelatin as hydrophilic layer [202].

K. Zhang *et al*. loaded curcumin in quaternized chitosan/PVA Janus nanofibrous aerogel, and the result showed uniform, homogenous, and biocompatible fibers with enhanced mechanical properties and liquid absorption capacity, while it retains the inherent soft texture and ECM architecture from nanofibers. It also showed noticeable antioxidant and anti-inflammatory effect. They were able to decrease TNF-α expression and increase IL-10 and VEGF expression [203]. Y. Shi *et al*. fabricated PVA\PLGA Janus nanofiber with copper sulfide nanoparticles (CuS), mupirocin (M), and valsartan (V) to form PLGAV-CuS/PVAM that showed good cytocompatibility and antibacterial activity. In the early stage of wound healing, the hydrophilic layer of the Janus fibrous membrane enables continuous and slow release of hydrophilic antimicrobial drugs (M), thereby avoiding infection [204]. X. Ji *et al*. incorporated Rana chensinensis skin peptides (RCSPs) and silver nanoparticles (Ag-NPs) into PCL\PVP Janus nanofibers that showed good wettability, mechanical properties like ECM, antibacterial activity, and effectively enhanced wound healing [205]. L. Li *et al*. prepared Janus nanofiber with PVA/hydroxylpropyl trimethyl ammonium chloride chitosan (HACC) on the hydrophilic side and thermoplastic polyurethane (TPU) on the hydrophobic side that showed to have good unidirectional wettability properties and high elasticity [206].

Multi-layer Electrospun Nanofibers

Multi-layer nanofibers are prepared by electrospinning of a second polymer solution on the same collector directly after the first electrospun nanofiber has been collected [207]. Each layer of produced multi-layer structures has its own biological, physical, and chemical properties to improve nanofiber characteristics [208]. A dense top layer can protect the wound site from mechanical stresses, dehydration, and microbial infections, while the sublayer is designed to resemble ECM in order to accelerate wound healing and improve cell proliferation [209–211]. Multi-layer nanofibers provide sustained release profile and prevent burst release when compared to single-layer structures [212]. Furthermore, multi-layer structures have the ability to load and release various drugs with different release profiles in each layer due to differences in morphological characteristics and degradability of different layers [213]. Layer-by-layer self-assembly nanofibers are formed by applying oppositely charged molecules to nanofibers followed by electrostatic interaction that results in molecules adsorption to the surface of nanofiber and formation of a multi-layer structure [214–216]. Table I shows the recent potential multi-layer nanofiber for wound healing.

Conclusion

Ideal wound dressing should have an elastic mechanical structure but strong enough for easy handling and comfortable wear. Nanofibers is characterized by its good mechanical strength and inert cell property allowing painless removal with minimal scars. They also resemble the ECM of the skin and provide a large surface area so they can absorb excess exudates from the wound. Many technologies have been developed for nanofibers preparation. Many parameters can affect electrospinning process that classified to process parameters (applied voltage, flow rate, diameter of needle to collector distance), solution parameters (concentration, molecular weight, viscosity, and

Table I Potential Multi-layer Nanofiber for Wound Healing

Type	Top layer	Intermediate layer	Bottom layer	Reference
Bi-layer	PCL/quaternized silicone (PQS)	-	PVA/collagen/ quaternized chitosan (PCQC)	[217]
	PVA\chitosan\ CuNPs	-	PVP	[218]
	PU	-	Gelatin\keratin	[219]
	PCL\hyaluronic acid	-	Chitosan\zein\salicylic acid	[220]
	PLA	-	PLA\natural rubber\curcumin	[221]
	PVA-aloe vera-tetracycline\chitosan-PVA\collagen core–shell nanofiber	-	Gelatin\Calenula essential oil	[222]
	Methacrylated gelatin (MeGel)/ PLLA	-	*Salvia miltiorrhiza* Bunge-Radix Puerariae herbal compound (SRHC)-loaded MeGel hydrogel	[223]
	PCL\α-tocopherol	-	PLA	[224]
	PCL\ quaternized silicon nanofiber	-	Collagen\quaternized chitosan sponge	[225]
	PLGA	-	PVA\gel\vancomycin-thrombin	[226]
	Thermoplastic polyurethane nanowovens		PU\AgNPs	[227]
	Chitosan	-	PVA\gelatin\curcumin-Lithospermi Radix extract	[228]
	Sodium alginate\PVA	-	Chitosan\PVA\deferoxamine	[229]
	Sodium alginate\PVA	-	Solvent cast film of PVA\sodium alginate	[230]
	PCL	-	Collagen\skin graft hydrogel	[231]
	Silk fibroin	-	Human amniotic membrane (AM)	[232]
	PCL\fish collagen	-	Chito-oligosaccharides	[233]
Tri-layer	PLGA\collagen	PLGA\vancomycin, gentamycin, and lidocaine	PLGA\collagen	[234, 235]
	PU	Gelatin\PRGF	PU	[236]
	Collagen	Silk fibroin	Bioactive glass	[237]
	PVA	chondroitin sulfate	Gelatin	[238]
	PVA\gentamicin	Gelatin\capsaicin	PVA\chitosan iodoacetamide	[239]
	Cellulose acetate\PEO\ciprofloxacin	Silk fibroin nanofiber	Cellulose acetate\PEO\ciprofloxacin	[240]
	PCL	PCL\gelatin\AgNps	PCL\gelatin	[241]
	Stearic acid	PAA-aloe vera sponge\ insulin-like growth factor-1 (IGF1)	Aloe vera nanofiber\carbon nanotubes	[242]
	PCL	PCL\collagen	Collagen\Melilotus officinalis extract	[243]
	PCL	Carboxyethyl chitosan\PVA\chamomile\PCL	Carboxyethyl chitosan\PVA\chamomile	[244]
	PLA	PVA\cerium oxide nanoparticles	PLA	[245]
	Gelatin	PVA\sodium alginate	Chitosan\PVA\silk fibrin	[246]
	PCL nanofiber	Micro-skin	PCL microwells	[247]
Layer-by-layer	Fibroblasts and keratinocytes	-	PCL\collagen nanofiber	[248]
	Transforming growth factor (TGF)-β1	-	PCL\collagen nanofiber	[249]
	ε-PL	-	PGA\PL6-curcumine core–shell nanofiber	[250]
	Gold nanoparticles	Lysozyme	Cellulose acetate nanofiber	[251]

conductivity), and environmental parameters (humidity and temperature). Electrospinning is a simple, cost-effective, and versatile setup process which depends on electrostatic concept in the presence of high electrical field. Conventional method involves dispersing or dissolving drugs in the polymer solution to form a homogenous solution. However, this method frequently shows burst release patterns and may lead to denature and decrease activity of sensitive bioactive agents. That gives

the need for more advanced electrospinning techniques like coaxial electrospinning, emulsion electrospinning, and side-by-side electrospinning. Coaxial electrospinning and emulsion electrospinning are used for the fabrication of core–shell nanofibers, where the outer shell layer can encapsulate and prevent the release of the active components in the inner core layer. Janus nanofibers synthesized by side-by-side electrospinning incorporate two separate solutions with different chemical properties. Multi-layer nanofibers can be prepared either by electrospinning of a second polymer solution directly after the first nanofiber is collected or by self-assembly of oppositely charged molecules that adsorb on the surface of the nanofiber. In this context, we believe that electrospun nanofibers are promising dressings for wound healing applications.

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Data Availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflict of Interest The authors declare no competing interests.

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