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Nanofibers for Biomedical and Healthcare Applications

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Unique features of nanofibers provide enormous potential in the field of biomedical and healthcare applications. Many studies have proven the extreme potential of nanofibers in front of current challenges in the medical and healthcare field. This review highlights the nanofiber technologies, unique properties, fabrication techniques (i.e., physical, chemical, and biological methods), and emerging applications in biomedical and healthcare fields. It summarizes the recent researches on nanofibers for drug delivery systems and controlled drug release, tissue-engineered scaffolds, dressings for wound healing, biosensors, biomedical devices, medical implants, skin care, as well as air, water, and blood purification systems. Attention is given to different types of fibers (e.g., mesoporous, hollow, core-shell nanofibers) fabricated from various materials and their potential biomedical applications.

1. Introduction

Nanotechnology is considered as one of the most important parts of science and technology in the twenty-first century that can be compared with the industrial revolution. Nanotechnology has a very significant impact on the worldwide economy, industry, and the human-made equipment and lifestyle in near future.[1–13]

Nanofibers are one of the interesting groups of nanomaterials with two similar external dimensions in the nanoscale (≤100 nm) and the third dimension significantly larger.[14] Nanofibers exhibit a lot of wonderful features such as large surface area, possibility to surface functionalization, tunable porosity, a wide range of material selection, and superior mechanical performance.[15,16] These remarkable properties make the nanofibers ideal candidates for a wide range of biomedical applications including tissue-engineered scaffolds (e.g., skin, cartilage, bone, blood vessel),[17,18] dressings for wound healing,[19,20] biomedical devices,[21] biosensors,[22,23] and drug delivery systems.[24,25]

One of the main and interesting biomedical applications of nanofibers is tissue engineering and wound healing. Nowadays, nanofiber tissue-engineered scaffolds are considered as a satisfactory solution to aid the health and quality of life for millions of patients worldwide with end-stage organ failure or tissue loss.[26,27] Nanofiber scaffolds provide many appropriate properties such as high porosity, large surface area, biocompatibility, mechanical properties, and biocompatibility to cells which are needed for tissue regeneration and sustained release of drugs or growth factors.[28] Nanofibers afford great flexibility in selecting biodegradable or non-degradable materials to give amazing properties such as finer control over drug release kinetics for drug delivery applications. There is a possibility to immobilize enzymes, antimicrobial peptides, antibiotics, and growth hormones to nanofibers, or loading into the core of nanofibers.[29–35] Nanofibrous mats provide a structure similar to native extracellular matrix with high interconnected porosity (60–90%),[36] great absorbance, balanced moisture, and gas permeability that bring an appropriate environment to protect the wound from exogenous infection. The ability of loading bioactive compounds into nanofibers provides a great environment to treat infections in the wound regions, prohibition of bacterial biofilm formation, prolonging drug release, and decreasing the time of wound healing process.[37–39]

Nanofibers have been used in wound dressing to promote wound healing, hemostasis, skin regeneration, and treatment of diabetic ulcers.[40] Nanofiber holds more moisture in its structure and keeps the surface of the wound wet during the healing process. This prevents sticking the nanofibers to the wound surface. Moreover, the porous nanofiber network allows oxygen to diffuse more easily into the wound surface.[41] Nanofiber membrane may be incorporated into wearable blood purification systems for the removal of toxins from the blood of kidney failure patients.[42] Biosensors based on nanofibers show great promise for future applications in healthcare testing, disease diagnostics.[43] Nanofibers are a natural fit for gas masks and protective textiles, as high air permeability is desired to improve user comfort, and high aerosol efficiency is needed to provide adequate protection from aerosolized threats.[44] Nanofibers provide 3D architecture with the desired

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surface properties regarding the intended application within the body in addition to mechanical strength and physiological acceptability.[45,46]

The present review summarizes the nanofiber fabrication techniques, unique properties, and applications of nanofibers in biomedical and healthcare fields including tissue-engineered scaffolds, dressings for wound healing, biomedical devices, implants, drug delivery systems and controlled drug release, protective and medical textiles, and nanofiber for air, water, and blood purification. Some of the key challenges in drug delivery, as well as the promise of drug-loaded nanofibers, are highlighted. The requirements in nanofibers as drug carrier such as biocompatibility, biodegradability, and drug release, are discussed. Currently available nanofibrous mats for drug delivery applications ranging from cancer treatment, tissue engineering, biosensors, to wound dressings are also reviewed.

2. Nanofiber Fabrication Techniques

Nanofiber fabrication techniques are varied and utilize mechanical, chemical, thermal, and electrostatic fabrication methods. Various bottom-up and top-down approaches were proposed to produce nanofibers. In the bottom-up approaches, ions, atoms, molecules, and even nanoparticles themselves can be used as the building blocks for the formation of nanofibers, for example, gas-phase production. Top-down approaches involve slicing or successive cutting of a bulk material by attrition or milling to produce nanofibers, for example, production of cellulose nanofibers from wood pulp.[47,48] Different materials, that is, polymers, carbon, metal, and metal oxides have been used for fabrication of nanofibers. However, large-scale production of nanofibers with well-defined morphology and high yield is still an important challenge. Nanofiber fabrication techniques can be generally classified into two main categories: i) physical, chemical, and biological techniques; and ii) spinning and non-spinning fabrication techniques. In the next sections, these categories will be discussed in more detail. To date, various physicochemical properties such as length, diameter, inter-fiber spacing, Young's modulus, and adhesion energy were included for designing the nanofibers.

2.1. Physical, Chemical, and Biological Techniques

Nanofiber fabrication techniques can be classified into physical, chemical, and biological techniques based on the forces and actions applied to produce the nanofibers. Each technique has specific advantages and drawbacks.

Physical methods apply high energy radiations, mechanical pressure, electrical energy or thermal energy to cause material melting, abrasion, evaporation or condensation to form nanofibers. Most common examples of physical fabrication techniques are physical vapor deposition,[49] laser ablation,[50] and spinning fabrication techniques.[51] Physical vapor deposition techniques such as plasma sputtering,[52] thermal evaporation,[53] and pulsed laser deposition[54] have been used to prepare metal oxide nanofibers and carbon nanofibers. In this technique, the material goes from a solid or liquid phase to a vapor phase and then re-condensed to form nanofibrous structures and thin films. The

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evaporated atoms or molecules undergo collisions with gas atoms or molecules and are converted into a homogeneous mixture to get nanofibers. Ball milling,[55] cryo-crushing,[56] or high-pressure homogenization[57] are commonly used as physical methods (top-down techniques) to produce cellulose nanofibers from natural sources. For example, the production of cellulose nanofibrils (CNF) by fibrillation of cellulose plant cell fibers employs the mechanical isolation of individual fibrils by processes of grinding, cryo-crushing, or high-pressure homogenization.[58,59]

Chemical methods involve chemical reactions between two or more reacting species to form nanofibers. Such a chemical reaction can occur simultaneously or be caused by an external force such as high energy radiations, electrical energy, or thermal energy to form nanofibers. Typically, catalysts and growth controlling agents are used during or shortly after the formation of precipitates to control the growth of primary particles to nanofibers. Chemical vapor deposition (CVD),[60] electrochemical deposition,[61] polyol synthesis,[62] phase-separation,[63] microemulsion,[64] sol-gel method,[65] hydrothermal synthesis[66] are some of the most commonly used chemical methods for nanofiber synthesis. CVD is often used for production of metal oxide and carbon nanofibers from vapor phase via catalytic reactions at high-temperature condition. Ultrasound irradiation and microwave have been recently employed for wet chemistry synthesis of nanofibers.[67,68] Soft templates (e.g. surfactants and polymers)[69] or hard porous templates (e.g. anodic aluminum oxide membranes, AAO)[70] are often used in combination with the chemical methods (e.g., sol-gel, electrochemical deposition, and chemical vapor depositions) to produce a range of nanofibers (e.g., metals, carbons, semiconductors, metal oxides, conductive polymers). **Figure 1** shows schematic representation for the use of hard and soft templates for synthesis of nanofibrous structures.

Biological methods involve biological reactions between nanofiber raw materials and bioactive species such as bacteria or enzymes in the presence or absence of external forces such as mechanical pressure, high energy radiations, electrical energy, or thermal energy. In the case of biological treatments, cellulosic materials are treated with cellulolytic enzymes like cellulase that cleave the fiber structures to simpler ones. Bacterial cellulose (BC) nanofibers produced by aerobic bacteria received ample attention due to its unique physiochemical properties compared to plant cellulose (**Figure 2**).[72] Biological synthesis of cellulose nanofibers uses nontoxic and benign raw materials in conjunction with green technology and is therefore eco-friendly and more acceptable than chemical and physical fabrication techniques.[73,74] However, the large-scale industrial production of BC is still in a state of development.

2.2. Spinning and Non-Spinning Fabrication Techniques

Most of the physical and chemical fabrication techniques listed above are non-spinning techniques. Spinning techniques employ outside forces such as electric force, centrifugal force, or compressed gas to draw threads of polymer solutions or polymer melts up to fiber diameter ranges from few nanometers to several micrometers.[75] Nanofiber spinning has shown great scientific and industrial interest due to its versatility, cost-efficiency, and potential to be used in a wide range of applications from environmental improvement to biomedical application. Nanofiber spinning techniques can be further classified into two major categories.

2.2.1. Electrospinning Technique

Electrospinning is the most commonly used method to produce nanofibers because of the straightforward setup (Figure 2). Electrospinning technique consists in placing a polymer solution into a syringe and then pushing it to the tip of the syringe by external pumping applied by a mechanical piston. When the solution droplet is formed at the metallic needle, an electric voltage bias is applied between the metallic needle and a collector placed in front of it.[76] As the applied voltage is gradually increased, the electric forces overcome surface tension and a jet is produced and finally, the droplet elongates into a Taylor

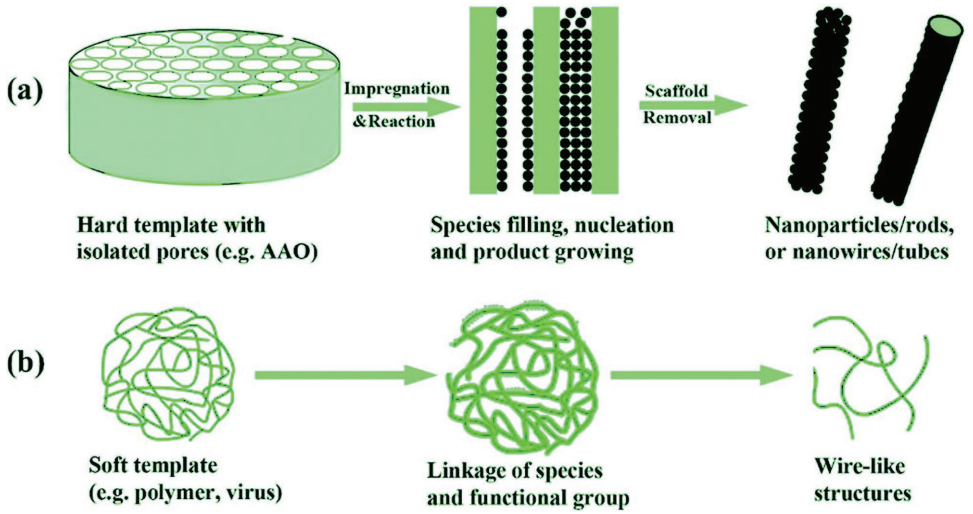

Figure 1. Schematic description of a) Hard and b) Soft template synthesis of nanofibrous structures. Reproduced with permission.[71] Copyright 2008, American Chemical Society.

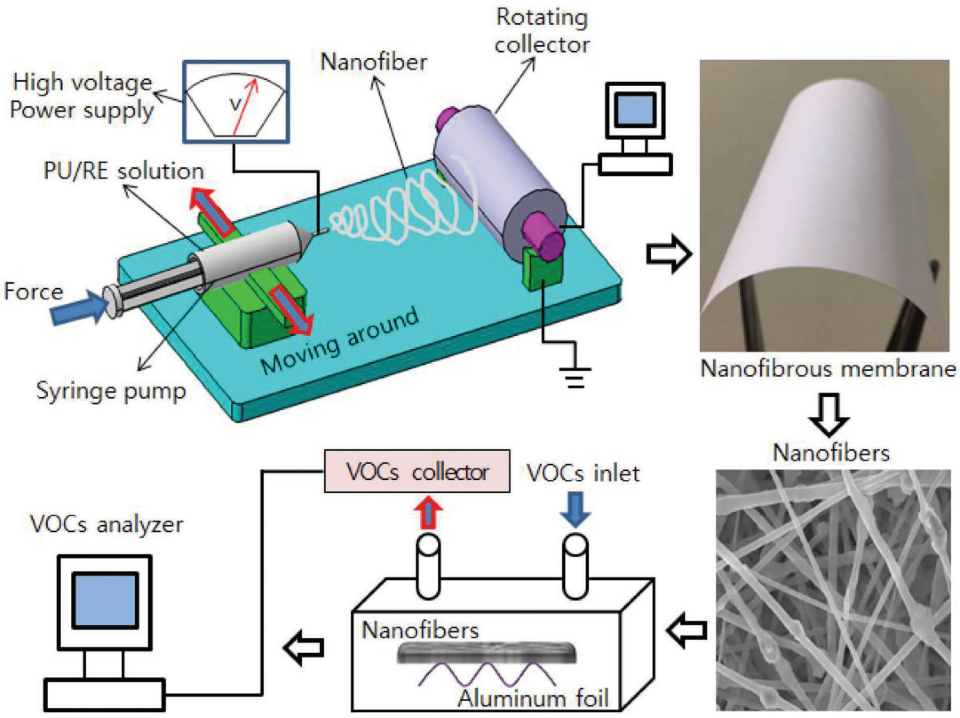

Figure 2. Simple electrospinning setup. Fabrication of polymer nanofiber membranes by electrospinning and removal of volatile organic compounds (VOCs) from air. Reproduced with permission.[77] Copyright 2017, MDPI.

cone, from which polymer nanofibers are produced and then deposited on the collector. The jet is accelerated and stretched through the atmosphere with the evaporation of the solvent. Finally, the nanofiber mat is deposited on the surface of an oppositely charged grounded collector.

Today, electrospinning equipment is rapidly moving to commercialization. Bubble electrospinning,[78] melt electrospinning,[79] coaxial electrospinning,[31] self-bundling electrospinning,[80] nanospider electrospinning[81] are the most common electrospinning techniques. Polymer nanofibers (50–1000 nm) can be produced using fiber electrospinning techniques (wet or hot melt electrospinning spinning).[82] In wet electrospinning certain solvent or a mixture of solvents will be used to dissolve the polymer. This solvent will evaporate due to its low boiling point leaving behind the polymer in fiber form. Comparing with hot melt electrospinning process, the wet electrospinning is an expensive method since it requires extra equipment to prepare the mixture adds to that the solvent recovery process.[82,83] The fiber diameter, morphology, alignment, as well as molecular orientation are affected by the nature of the collector, applied voltage, distance between nozzle and collector, and dispersion flow rate.[84] Some researchers have reported on needleless electrospinning systems using rotating disks, rollers, balls, and bubbles to obtain huge amounts of nanofibers.[85] Among several nanofiber processing techniques, co-electrospinning, side-by-side electrospinning, multi-jet electrospinning, coaxial electrospinning, emulsion electrospinning are recognized as the easiest and effective methods for drug delivery and biomedical applications.[86]

Several techniques have been developed to overcome the limitation of the standard electrospinning method (**Figure 3**). Multi-needle electrospinning (MNEs) has been used to improve the productivity. However, in some cases, the strong repulsion among the multi-jets lead to poor fiber quality.[87,88] Air-jet assisted bubble electrospinning uses blowing air and electronic force to produce fine fibers. This method has been used commercially as a one-step process to convert polymer resin directly into a nonwoven mat of fibers. Blowing of the air can significantly improve the performance of the electrospinning process. Coaxial electrospinning (CEs) are used to produce core-shell nanofibers, where a polymer solution (shell) and a compound solution (core) can be utilized as precursor solutions and co-spun. The emulsion electrospinning (EEs) method allows for two immiscible solutions to be electrospun into nanofibers. However, the resulting fibers are usually difficult to produce uniformly, due to the greater number of variables to be accounted to create the emulsion.[89] The bicomponent spinning (BCS) can be used for the fabrication of small nanofibers as well as to create multicomponent nanofibers. While modifying or changing the electrospinning process conditions, different shapes can be obtained, such as biaxial aligned, uniaxially, porous fibers, ribbon, necklace-like, hollow, nano-webs, a nanowire in hollow fibers, and multichannel tubular.[90]

Aside from the electrospinning techniques and type of collector, there are several factors that affect the fiber diameter and morphology: i) electrospinning parameters, for example, applied electric field, distance between the needle and collector, flow rate, and needle diameter; ii) solution parameters, for example, solvent, polymer concentration, viscosity and solution conductivity; iii) environmental parameters, for example, relative humidity and temperature. **Figure 4** shows the different morphologies obtained for electrospun nanofibers prepared using different electrospinning conditions.[91]

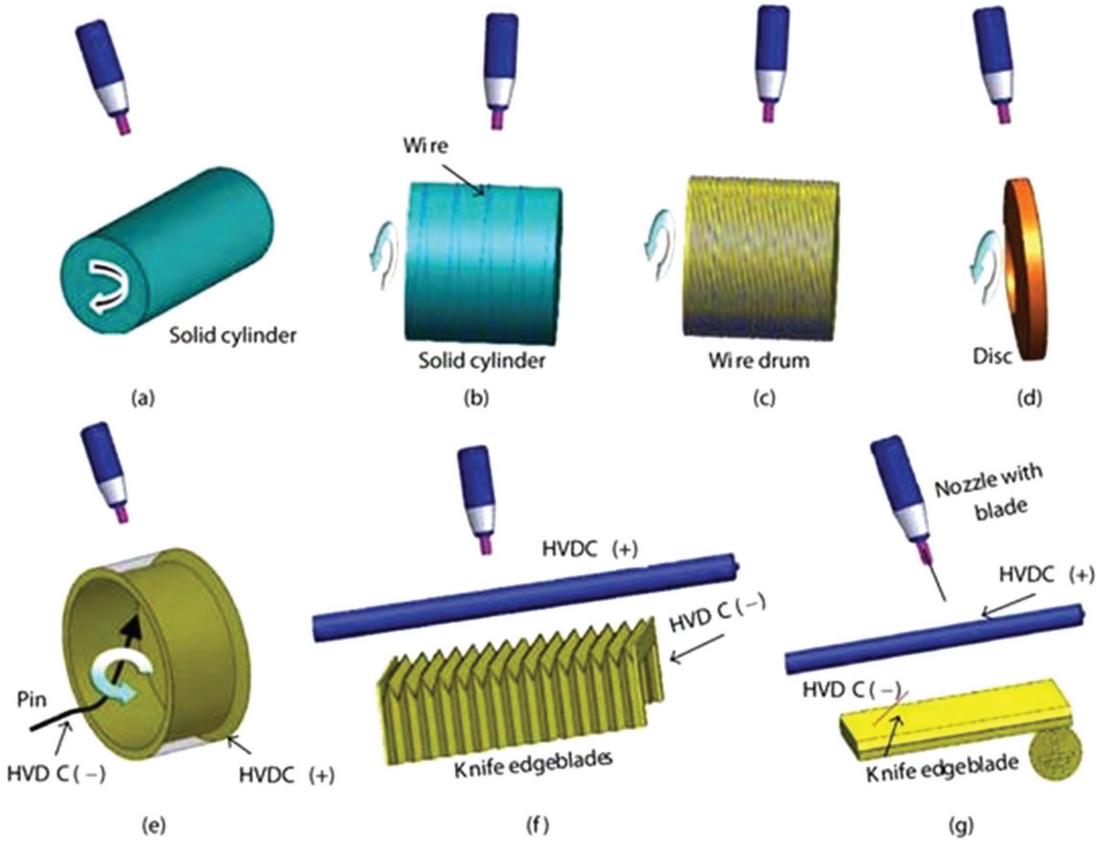

Figure 3. Schematic representation of different electrospinning techniques and types of collectors used for electrospinning. a) Solid cylindrical, b) wire winded on an insulated cylinder, c) wired drum, d) disc collector, e) sharp pin inside the rotating collector, f) knife-edged electrodes, and g) knife-edged electrode and needle system. Reproduced with permission.[90] Copyright 2011, Hindawi.

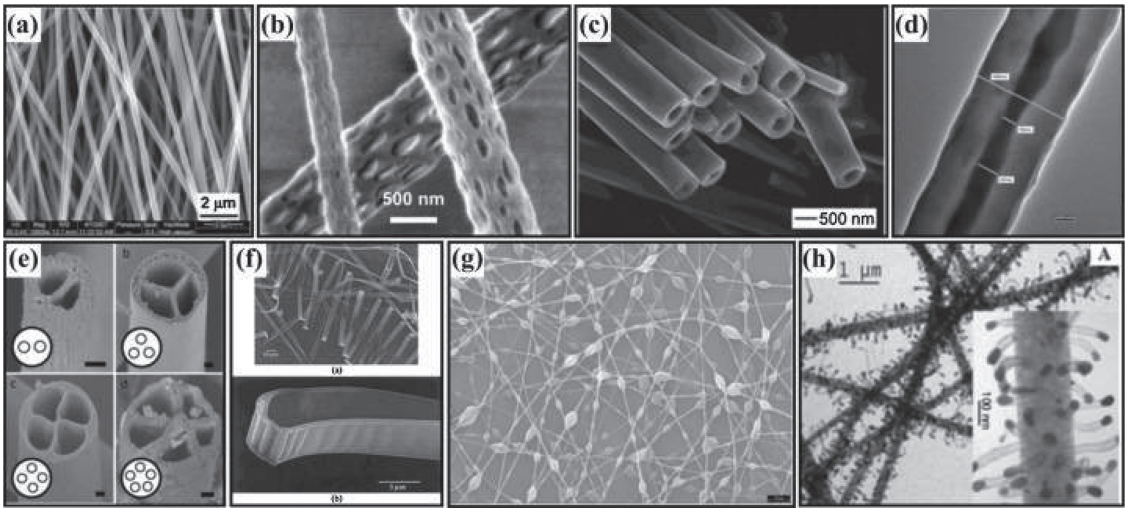

Figure 4. Different morphologies of electrospun nanofibers. a) SEM images of well-aligned PVA nanofibers; b) parallel electrode collector with a gap between two conductive substrates. c) Dual rings collector. d) Two oppositely placed metallic needles with opposite voltages. e) Collection of aligned magnetized nanofibers with magnetic field. f) Collector of rotating disc with high speed. g) Rotating wire drum collector. h) Yarn collection by using an electrically grounded water bath. Reproduced with permission.[91] Copyright 2016, Elsevier.

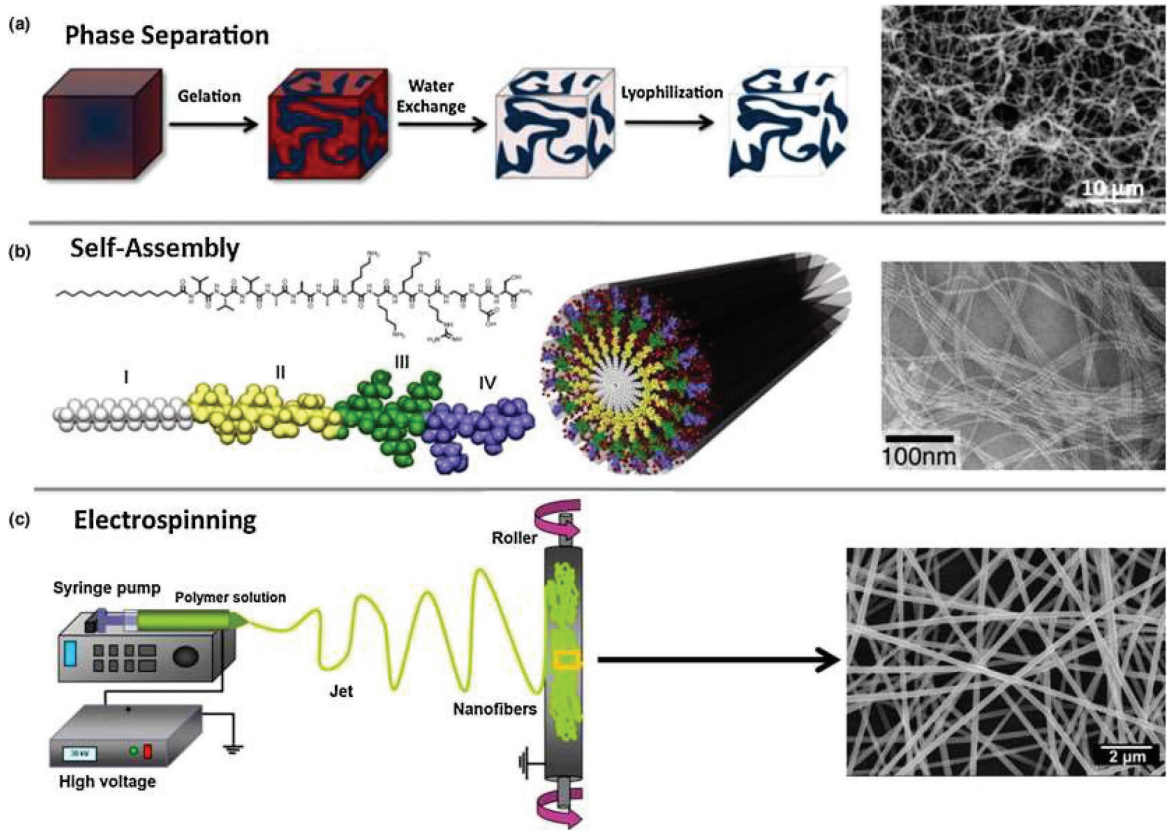

Figure 5. Schematic of some fabricating techniques such as a) phase separation, b) self-assembly, and c) electrospinning to fabricate nanofibril structures in synthetic scaffolds. Reproduced with permission. [108] Copyright 2013, Elsevier.

2.2.2. Non-Electrospinning Techniques

Non-electrospinning techniques use centrifugal force or compressed gases instead of an electric field to generate nanofibers These techniques limit the use of a solvent, increase the productivity, and lower the production cost. Blowing bubble spinning (gas-jet spinning),[92] centrifugal spinning,[93] and fiber drawing[94] are three of the most common non-electrospinning nanofiber production techniques. As a high-output nanoscale fiber production method, centrifugal spinning offers high fiber production rates, but it cannot produce high-quality fibers. Centrifugal spinning is not recommended for the biomedical field because of the erratic performance of the fibers, which may affect the bioactivity of the fibers.[95] Blown bubble spinning uses blowing air or mechanical force to overcome the surface tension and produce nanofibers.[96]

3. Nanofibers for Tissue-Engineered Scaffolds

There are millions of patients who suffer from end-stage organ failure or tissue loss around the world annually.[97] Autologous and allogeneic natural tissue is generally used for replacement. Patency rates for these procedures are not 100%, about 50–70% generally for coronary artery replacement,[98] these surgeries cost billions of dollars worldwide annually.[99] The low number of donors is another limitation in transplantation. Nowadays, to address these problems tissue engineering brings a good alternative way to transplantation of diseased, failed, or abnormal organ or tissue.[100] Tissue engineering scaffold provides a 3D environment for cell adhesion proliferation and the specific arrangement of cells into complex tissue depends on the functional architecture of the organ. Three key elements are required for tissue engineering; scaffold, cells (differentiated or undifferentiated), and biological signaling molecules such as growth factors (GFs).[101] Various processing techniques (e.g., phase separation,[102] self-assembly,[103] solvent casting,[104] freeze drying,[105] gas foaming,[106] and electrospinning[107] have been employed to fabricate nanofiber scaffolds (**Figure 5**).[108] Among them, electrospinning as a straightforward and cost-effective process has attracted significant attention. Electrospun nanofiber can be fabricated from a wide range of materials with high similarity to the native extracellular matrix in different sizes and functions.[108] Electrospun scaffolds have been employed in a number of different tissue applications including: vasculature,[109–112] skin,[113,114] bone,[115–121] cartilage,[122,123] neural,[124,125] and tendon/ligament (**Table 1**).[126–128]

Scaffolds with 3D structure can be synthesized from natural polymers, synthetic polymers, or blends of synthetic and natural polymers. Chitin, chitosan, alginate, collagen, and gelatin are the most commonly used polymers for the fabrication of nanofibrous scaffolds. Synthetic polymers, such as polyglycolic

Table 1. A number of different tissues fabricated out of synthetic polymers, natural polymers, or blends of natural or synthetic polymers.

	Polymer	Tissue	Cell	Ref.
Natural biopolymers	Collagen and elastin	Skin	Human keratinocytes	[131]
		Blood vessel	Smooth muscle/endothelial cells	[130]
	Fibrinogen-PDO (polydioxanone)	Urologic tissue engineering	Bladder smooth muscle cells	[140]
	Silk	Blood vessel	Human aortic endothelial (HAECand human coronary artery smooth muscle cell (HCASMC)	[141]
	Chitin/chitosan	Bone	Human osteosarcoma cell line MG63	[142]
	Poly(3hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)	Skin	Human skin fibroblasts	[143]
Synthetic polymers	Polyglycolide (PGA)	Cartilage	Canine chondrocytes	[144]
	Polylactide (PLA)	Soft tissue	–	[145]
	Poly(1-caprolactone) (PCL)	Cartilage	Chondrocytes	[132]
			Human mesenchymal stem cells	[122]
		Bone	Mesenchymal stem cells	[115]
	Poly(1-caprolactone) (PCL)/poly(lactic acid) (PCL/PLLA)	Blood vessel	Fibroblasts	[112]
	Poly(1-caprolactone) (PCL)/hydroxyapatite) (PCL/CaCO3 and PCL/HA)	Bone	Human osteoblasts	[133]
	Poly (L-lactide-*co*-glycolide) (PLGA)			
	Cartilage	Chondrocytes		[134]
		Blood vessel	Differentiated smooth muscle cells (SMCs) and endothelial cells (ECs) cells from canine bone marrow. An adult dog over a 3-week period (20–25 kg) as an animal model	[146]
	Polyurethane (PU)			
	Ligament/tendon	Human ligament fibroblast (HLF)		[147]
	Poly(esterurethane)urea (PEUU)	Blood vessels	Rat aortic SMCs	[148]
Blends of natural and synthetic polymers	Poly (L-lactide-*co*-glycolide) (PLGA/chitin)	Skin	Human keratinocytes	[149]
	Poly (L-lactide-*co*-glycolide) (PLGA/dextran)	Skin	Dermal fibroblasts	[150]
	Collagen-blended P(LLA-CL)	Blood vessels	Human coronary artery endothelial cells (EC)	[110]
	Gelatin-grafted poly(1-caprolactone) (PCL) nanofibers	Blood vessels	Endothelial cells (ECs)	[151]
	Collagen-coated poly(1-caprolactone) (PCL) fibers	Blood vessels	Human coronary artery endothelial cells (HCAECs)	[152]

acid, polylactic acid, polycaprolactone, poly(*N*-isopropyl acrylamide), and their copolymers have been also used for fabrication of scaffold (Tables 1 and **2**).[112,115,122,129–135] If necessary, the nanofibers can be further modified via adding bioactive agents (e.g., DNAs, enzymes, and growth factors) either incorporated via encapsulation or covalently conjugated to the matrix polymer to better control the proliferation and differentiation of cells seeded on the scaffolds.[136] Wang et al.[137] evaluated the efficacy of aligned electrospun chitosan fibrous tube as a potential platform for enhancing peripheral nerve regeneration or for the treatment of demyelinating lesions using a Schwann cell-seeded to repair a 10-mm sciatic nerve defect. **Figure 6** shows Schwann cells cultured on both random and oriented electrospun chitosan nanofiber coverslips. Aligned electrospun fibers enhanced Schwann cell maturation more than randomly oriented fibers.[138]As a result, such aligned electrospun scaffolds may be an ideal platform for this purpose.[137]

Cellulose hydrogels maintain high volumes of water or other fluids. The swelling capacity enables it as ideal materials for potential applications in the field of drug delivery, tissue engineering, wound healing, and water treatment. Hirayama et al.[139] developed a cellular building unit made from microstrand-shaped bacterial cellulose (BC microstrand) covered with mammalian cells. The BC microstrands are fabricated by encapsulating (see **Figure 7**). The mechanical strength and porous property of the BC microstrands can be regulated by

Table 2. Different tissue applications of nanofibrous scaffolds.

Application	Nanofiber materials	Cell/signal	Ref.
Blood vessels	A bi-layered tubular scaffold of an oriented and stiff polylactide (PLA) outside fibrous layer and a randomly oriented and pliable poly(ε-caprolactone) (PCL) fibrous as an inner layer	3T3 mouse fibroblasts and human venous myofibroblasts (HVS)	[112]
	Aligned poly(L-lactide-*co*-ε-caprolactone) [P(LLA-CL)] (75:25)	Human coronary artery smooth muscle cells (SMCs)	[109]
	Poly(methacrylic acid) (PMAA)-polyethylene terephthalate (PET) nanofiber mats were modified with gelatin	Endothelial cells (ECs)	[111]
	Poly(ε-caprolactone) (PCL)/gelatin blend	Human mesenchymal stem cells (hMSCs)	[157]
	Polyurethane (PU)	Endothelial progenitor cell (EPC)	[158]
Bone	Microporous, nonwoven poly(ε-caprolactone) (PCL)	Mesenchymal stem cells (MSCs) derived from the bone marrow of neonatal rats	[115]
	Silk fibroin fiber scaffolds containing bone morphogenetic protein and/or hydroxyapatite nanoparticles	Human bone marrow-derived mesenchymal stem cells (hMSCs)	[116]
	Poly(ε-caprolactone) (PCL)	MSCs derived from the bone marrow of neonatal rats	[117]
	Hydroxyapatite/chitosan (HAp/CTS)	Human fetal osteoblast (hFOB) cells	[165]
	Blend of polycaprolactone (PCL), human bone cells (HOS osteosarcoma cell line) hydroxyapatite (HA), and natural polymer gelatin (Gel)	Human fetal osteoblast (hFOB) cells	[166]
	Boron nitride (BN)-reinforced gelatin	Human bone cells (HOS osteosarcoma cell line)	[121]
	Gelatin	Human osteosarcoma cells (HOS)	[120]
Heart	Polyacrylonitrile (PAN)/hydrogel composite	Normal human aortic valve interstitial cells (nHAVIC)	[159]
	Hyperbranched poly-L-lysine dendrimers (HPLys)/polyaniline	Cardiomyocyte	[160]
	Copolymer poly(L-lactic acid)-*co*-poly (ε-caprolactone) (PLACL), silk fibroin (SF)/aloe vera (AV)	Cardiac cell	[161]
	Poly (L-lactide-*co*-glycolide) (PLGA)	Cardiomyocyte	[162]
	Polyurethane (PU)/ethyl cellulose (EC)	Cardiac myoblast H9C2 cells	[163]
	Poly(lactic-*co*-glycolic acid)/multiwalled carbon nanotube (MWCNTs)	Cardiomyocyte	[168]
Cartilage	Poly(vinyl alcohol)/polycaprolactone (PVA/PCL)	Rabbit bone marrow-mesenchymal stem cell (BM-MSC)	[165]
	Lactic acid/glycolic acid	Chondrocyte	[134]
	Polycaprolactone (PCL)	Human mesenchymal stem cells (hMSCs)	[166]
	Poly(ε-caprolactone) (PCL)	Adult bone marrow derived mesenchymal stem cells (MSCs)	[122]
	Poly(lactic acid) (PLLA) nanofibers (NF) were modified with cationized gelatin (CG)	Condrocyte	[123]
Skin	Poly(ε-caprolactone) (PCL) nanofibres with bioactive glass NPs	Human skin fibroblast cells (HSFs)	[159]
	Polyvinyl alcohol (PVA)/gum tragacanth/poly(ε-caprolactone) (PCL) hybrid	NIH 3T3 fibroblast cell	[160]
	Curdlan (β-1,3 glucan) (7 wt%) with polyvinyl alcohol (PVA) (10 wt%)	L6 cells	[113]
	Blend of poly-D,L-lactide (PDLLA) and poly(ethylene glycol) (PEG)	Human dermal fibroblasts (HDFs)	[173]
	Poly[lactic acid-*co*-glycolic acid] (PLAGA)	Human skin fibroblasts (hSF)	[172]
	Blends of chitosan, gelatin, and poly(ε-caprolactone) (PCL)	Human foetal fibroblasts (cell line HFFF2)	[173]

changing the initial density of the bacteria. The fabricated BC microstrands and BC microstrand-based cellular constructs have potential use in various fields such as drug screening, wound healing, and plastic surgery.[139]

The structure and biological function of the scaffold must be similar to the native extracellular matrix.[153] Biodegradability, biocompatibility, nontoxicity, nonmutagenicity, and nonimmunogenicity are necessary properties for an appropriate scaffold. Surface properties (e.g., surface energy, chemistry, charge, surface area) should be able to promote cell adhesion, proliferation, and differentiation.[153] Other important and essential physicochemical parameters of scaffolds needed to develop a useful scaffold are external geometry (e.g., macro-, microstructure, interconnectivity), mechanical properties (e.g., compressive and tensile strength), porosity, and size of pores.[154] Various structural parameters such as fiber diameter, porosity, spatial distribution, and alignment of nanofibers have critical impacts on the mechanical properties of scaffolds. For example,

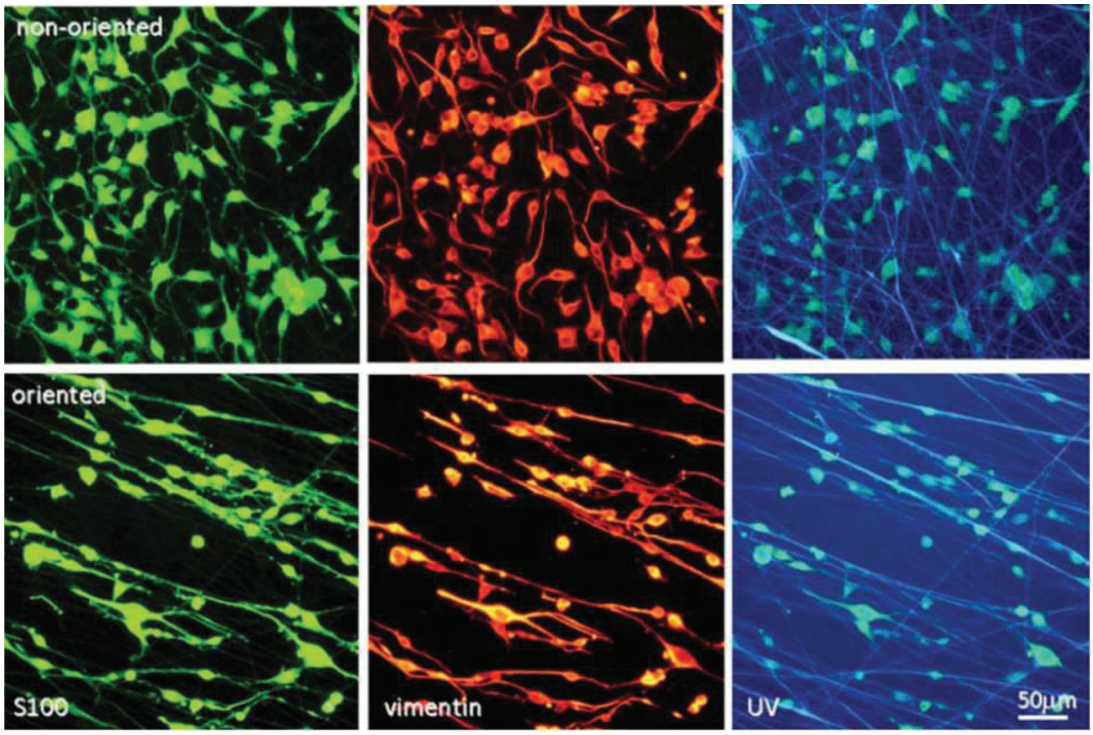

Figure 6. Schwann cell line growth on both random and oriented electrospun chitosan nanofiber coverslips for 4 days. Reproduced with permission.[137] Copyright 2007, Elsevier.

Ju et al.[155] fabricated PCL/collagen bilayer scaffold with desired mechanical properties by controlling nanofiber diameter. Enhancing the scaffold's porosity reduced its Young's modulus from 2.03 to 0.26 MPa by increasing the fiber diameter from 0.27 to 4.45 μm. The large pores on the outer layer of this fabricated PCL/collagen bilayer scaffold promoted smooth muscle cells (SMC) infiltration and small pore on an inner layer-facilitated endothelial cells (EC) attachment (**Figure 8**).[156]

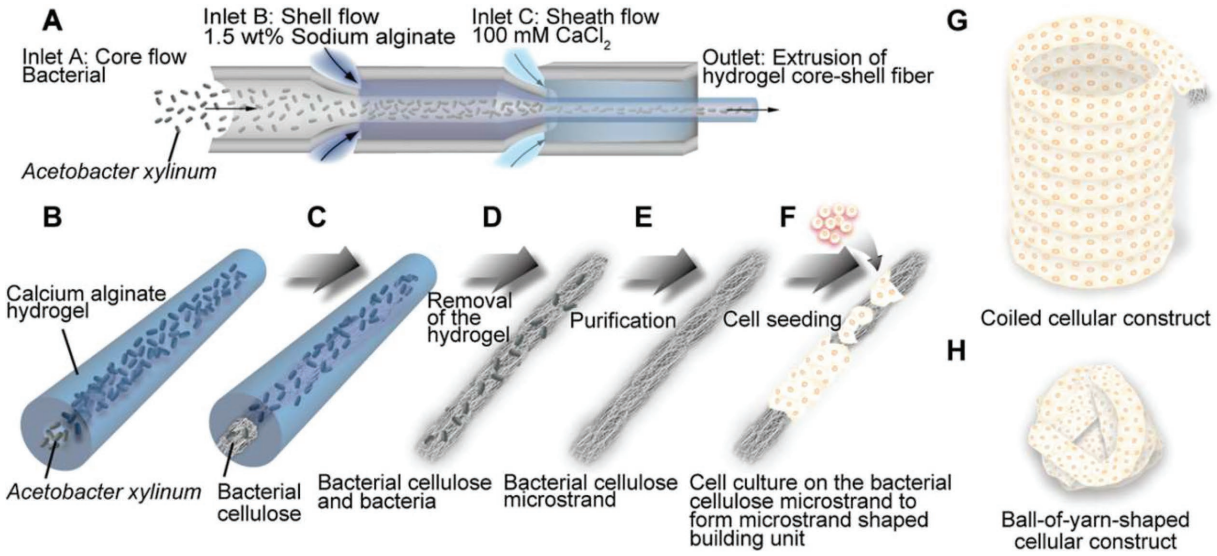

Figure 7. Schematic illustration of the process to fabricate bacterial cellulose microstrands and bacterial cellulose microstrand-based cellular constructs covered with mammalian cells. A) The fabrication process of a bacterial/alginate core-shell hydrogel fiber using a double coaxial laminar flow device. B) The bacterial suspension is confined within the core of bacteria/alginate hydrogel core-shell fiber. C) The bacteria form cellulose nanofiber network within the core of the hydrogel fiber. D) Calcium alginate hydrogel is dissolved by the citric acid solution. E) The bacterial cellulose microstrands are obtained after the removal of the bacteria by NaOH treatment. F) NIH-3T3 cells are seeded onto the bacterial cellulose microstrand. G,H) The bacterial cellulose microstrand-based building units are able to be transformed into a coiled cellular construct (G) and a ball-of-yarn-shaped cellular construct. Reproduced with permission.[139] Copyright 2013, Elsevier.

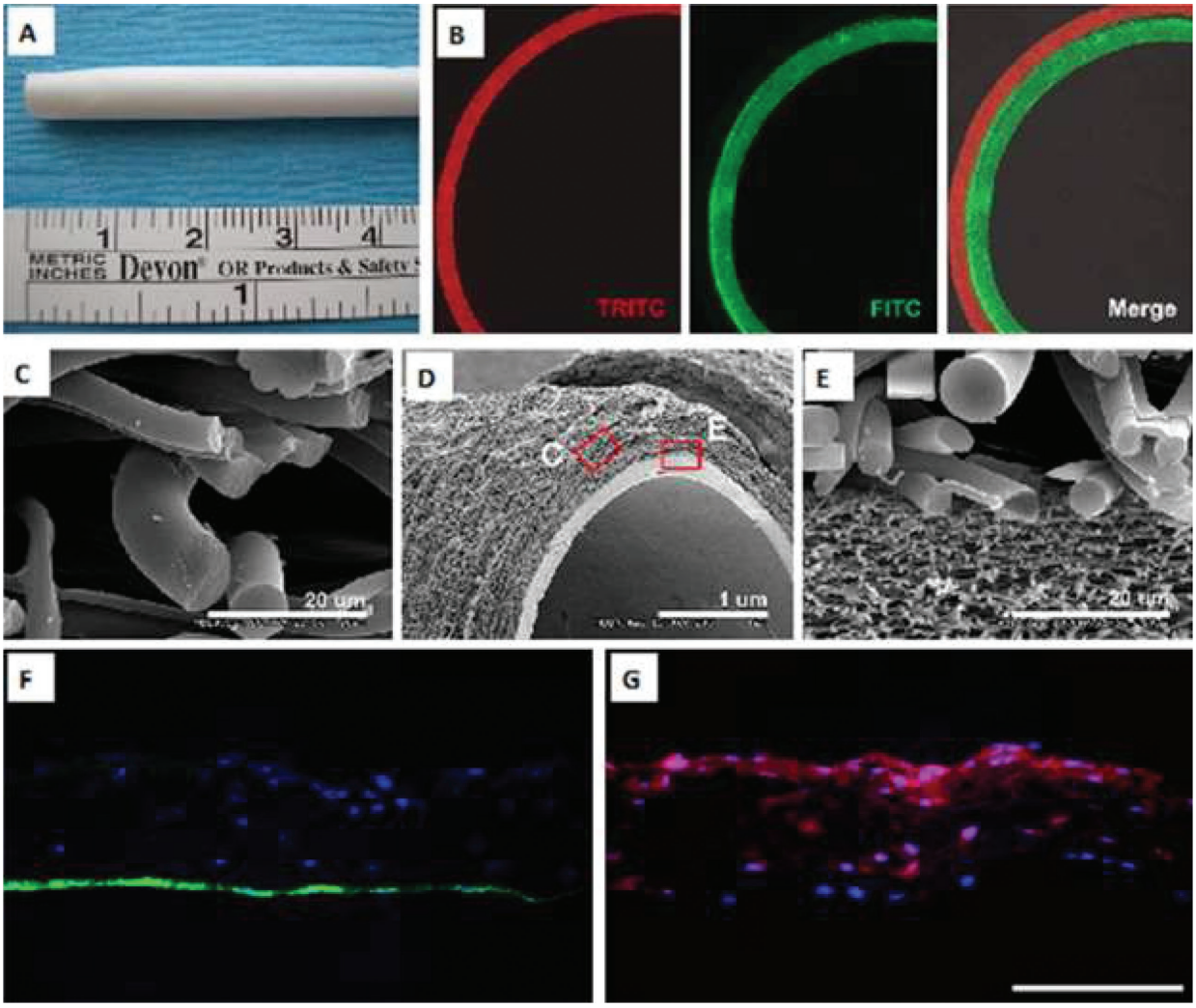

Figure 8. A,B) Macrostructure and fluorescent images of PCL/collagen bilayer electrospun scaffold; C–E) SEM images of different layers of the scaffold outer layer, bilayer, and interface layers, F,G) fluorescent images of EC and SMC seeded scaffold: F) Fluorescent images of EC seeded inner layer (the formation of an EC monolayer confirmed via CD31 expression: green) and G) fluorescent images of SMC seeded outer layer (SMC infiltration into the outer layer demonstrated by a-SMA expression: red). (Scale bar in F and G: 500 Lm). Reproduced with permission.[155] Copyright 2014, Elsevier.

The developing of nanofibers for drug delivery systems faces some challenges including reproducibility, quality control, and cytotoxicity of processing additives in vivo. For water-loving small molecule drugs, their high-water solubility and poor partition and compatibility issues with polymers make their long-term release yet more challenging. Intrinsically, spun nanofibers offer multiple solutions to overcome these challenges if given sustained effort and enough time. Compared to other non-spun, spun nanofiber-based drug delivery systems possess incomparable advantages due to their greater permeability, which allows shorter response time and more precise control over the release rate. The high surface is the major advantage of spun nanofibers, which greatly enhances their response rate to external stimuli, rendering discrete variations in response to the specific stimulus. Drug delivery systems using spun nanofibers can provide growth factor and drug delivery directly to the site to encourage reparation and regeneration and prevent infection.

4. Biosensors and Health Monitoring System

Nanofiber technology has opened a new promising window in the design and fabrication of miniaturized dimension biosensors with high surface to volume ratio for immobilization and sensing, enhanced catalytic properties of electrodes, exceptional ability to boost the desirable sensitivity, specificity, and acceleration of the reaction rate. Among the various types of nanostructured materials, nanofiber-based biosensors have the potential to develop toward even single-molecule biosensing. Retaining the bioreceptor functionality is one of the main challenges associated with the production of nanofiber-based biosensors. To obtain highly sensitive biosensors, the nanofiber mats should provide a large active surface area to ensure that the bioreceptor does not only keep its biological functionality but also remains accessible to the molecules to be detected. To retain the biological functionality of the biosensors, the receptors can be immobilized using various strategies, to optimize the physical and

chemical interactions between the nanofibers and bioreceptors. Surface immobilization has been typically used to immobilize enzymes, antibodies, DNA strands, and aptamers on nanofiber surface. Another approach consists in loading the bioactive molecules inside the nanofiber by electrospinning a blend of enzymes and polymer.[174]

Generally, nanofiber-based biosensors reveal the great potential for applications in disease diagnostics and healthcare testing. Nanofibers have been employed to detect a wide range of analytes including glucose,[22] urea,[175] cholesterol,[176] and microRNA.[177] They have been fabricated with a broad range of materials according to their application.[178] Nanofibers with high porosity and interconnectivity have proved to display good diffusion of analytes, faster electron transfer in comparison with a film made of NPs with the same material, excellent mechanical properties, and high bioactivity of immobilized materials.[179–182] Interest in nanofiber-based biosensors in DNA detection has grown rapidly due to the diagnosis and treatment of genetic disease, viral or bacterial pathogens, and combat with bioterrorism threats and drug discovery.[183]

Recently, nanofiber-based biosensors as miniature, portable, sensitive, and accurate point-of-care diagnostic devices have been employed for the detection of genetic disorders and specific viral or bacterial pathogens. The main reason of much genetic disorder is a mismatch in a single base pair, diagnosis of this mismatch being possible with this kind of biosensor. The specific affinity of DNA or PNA (peptide nucleic acid) for hybridization with its complementary strand has been used in the development of these biosensors.[184] With these devices, some success has been reported for pathogenic microbe detection such as *Escherichia coli* O157:H7[185,186] and bovine viral diarrhea virus (BVDV),[185] malarial parasites,[187] Hepatitis B virus.[188] Luo et al. used the electrospinning method to fabricate electrospun capture membrane made of nanofibrous nitrocellulose and its antibody functionalization (**Figure 9**a).[185] Electrospun-based biosensor on the capture membrane is designed by capillary immunoassay, direct-charge electrical measurement, and integrating magnetic separation, for rapid and quantitative detection of viral and bacterial pathogens (Figure 9b). A pair of electrodes was constructed on the capture membrane via a spray deposition of Ag paint. The biosensor was fabricated by attaching the three-membrane pads onto polyvinylidene chloride (PVDC) substrate using polystyrene adhesive backing (**Figure 10**).[185]

Early and accurate diagnosis of diseases has the vital importance to prevent progress or even death of patients, especially in cancers. The presence of biomarkers or variation of their concentrations are the first symptoms of various diseases. Especially during the early stages of the disease, biomarker concentration is at ultra-low level.[189] Nanofiber-based biosensors provide promising horizon on the early cancer detection such as electrochemical biosensor based on CNTs doped nylon6/poly(thionine) (CNT-PA6-PTH) electrospun nanofibers for K-ras gene mutations detection (in concentration just only 30 fM),[190] Pd functionalized WO_3 nanofibers as a gas sensor sensitive to toluene in lung cancer detection (Rair/Rgas = 1.32),[191] fluorescent chemosensor based on a dendritic zinc porphyrin (Den-Por(Zn)) electrospun nanofibrous membrane for detection of histamine in urine as a biomarker for cancer

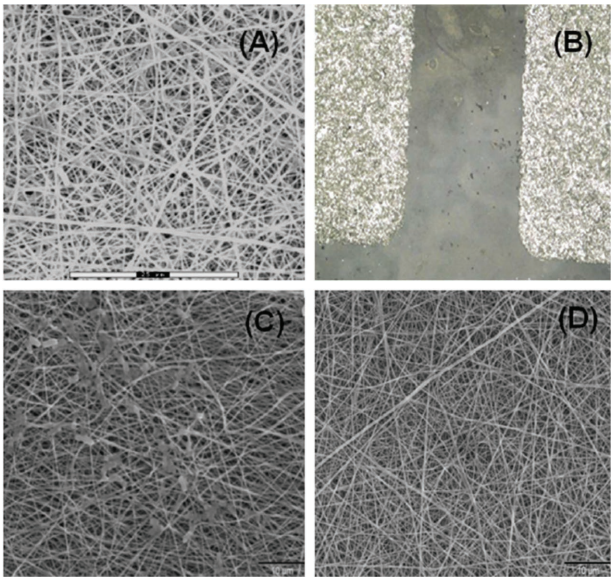

Figure 9. A) SEM image of nitrocellulose nanofibers. B) Ag electrodes fabricated on the electrospun membrane via spray deposition method, C) SEM image of *E. coli* O157:H7 captured on the functionalized electrospun mat, D) no bacteria are observed in the non-functionalized nanofiber mat. Reproduced with permission.[185] Copyright 2010, Elsevier.

detection,[192] anti-epidermal growth factor receptor conjugated mesoporous zinc oxide nanofibers as an immunosensor with unprecedented sensitivity (femtomolar) to detect breast cancer,[193] and electrochemical detection of cathepsin B activity in breast cancer cell lysates using carbon nanofiber.[194] Electrochemical biosensors based on unique properties such as rapid sensing, low cost, portability, and ease of use have been offered in the diagnosis of cardiovascular diseases (CVDs).

Biosensors have been used in the early cancer detection, which is due to their low-cost, fast detection, good portability, and no side effects. In addition, with the quick development of nanotechnology, electrospun nanostructures were applied to amplify bioassay signals, which can observably improve the sensitivity and accuracy of biosensors.[195] Zhang et al.[196] made a cell capture assay based on anti-EpCAM grafted electrospun TiO_2 nanofibers in order to circulate tumor cells detection in colorectal and gastric cancer patients, which significantly enhanced the capture efficiency. Rezaei et al.[197] summarized researches about the diagnosis of CVDs via nanofiber-based electrochemical biosensors.[197] Miyamoto and co-workers[198] developed highly gas-permeable, inflammation-free, lightweight, and stretchable nanofiber sensors that can be directly laminated onto human skin for long periods of time. The sensors are based on nanofiber conductors (nanomesh of 300–700 nm fiber substrates) made by coating water-soluble polyvinyl alcohol (PVA) nanofibers with gold nanoparticles. The process of laminating gold nanofiber mesh onto the skin is as follows: first, gold is evaporated onto electrospun PVA nanofibers, then the PVA is dissolved by spraying water. After removal of PVA nanofibers, gold nanofiber mesh adheres to the skin. The constructed sensor can work as a wireless system that can detect touch, temperature, and pressure with excellent mechanical durability.[198] There is no doubt that the nanofiber-based

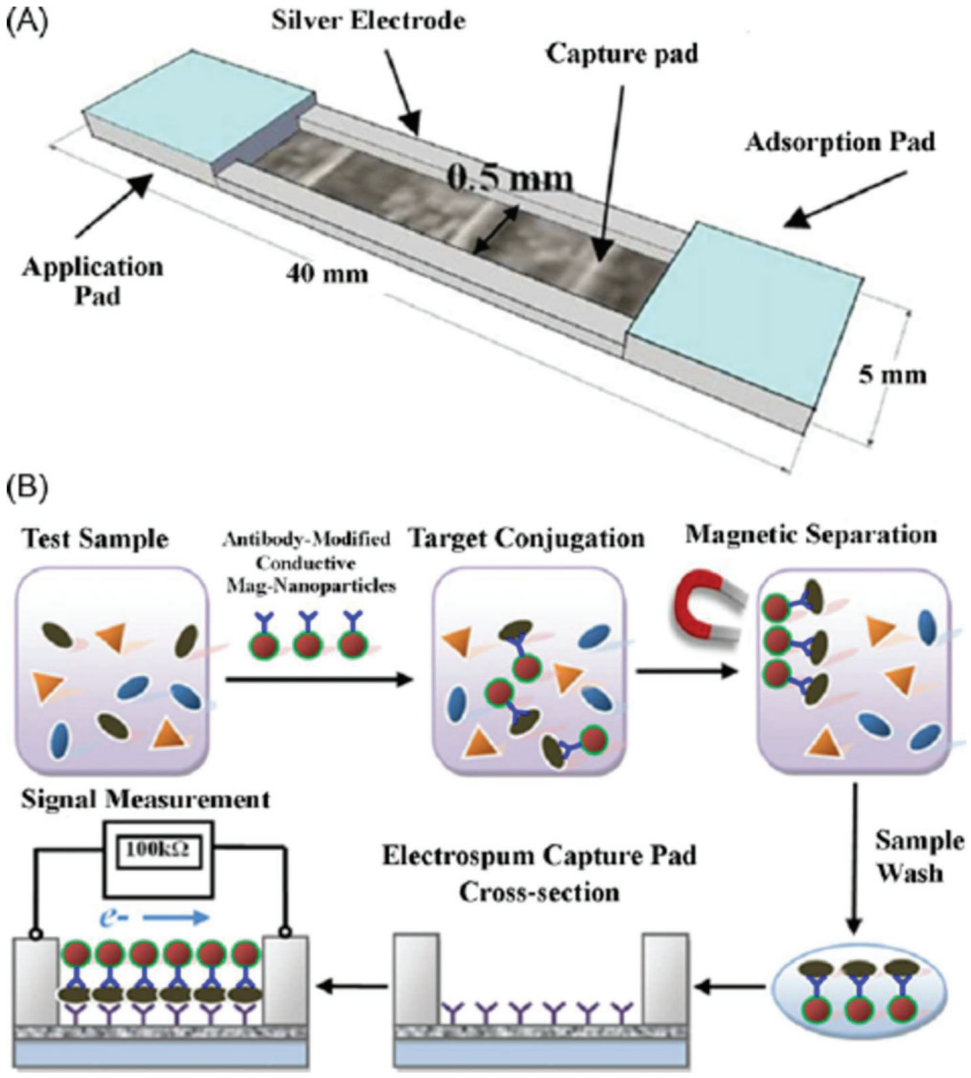

Figure 10. Schematic of the biosensor. A) Structure and membrane assembly consisting of absorption pads and electrospun cellulose nitrate capture pad and cellulose application; and B) the immunosensor based on the antibody functionalized electrospun capture membrane from the lateral flow (B). Reproduced with permission.[185] Copyright 2010, Elsevier.

biosensor has become one of the most powerful techniques for direct, sensitive, and rapid analysis in medicine for diagnosis, preventing many diseases in the future. Nanofibers-based biosensors will overcome challenges that we continuously run into, whether it is a low limit of detection, sample preparation, or similar aspects (**Figure 11**).

5. Drug Delivery Systems

The biomedical application of nanofibers in drug delivery systems is growing fast, due to a various number of unique features and properties of porous nanostructure including high drug loading, encapsulation efficiency, enhanced therapeutic index, localized delivery, reduced drug side effects, ability to modulate drug release by engineering, controlling the processing and solution parameters of synthesis.[199,200] Nanofibers can be produced from a wide range of natural and synthetic polymers.[201] Nanofibers made of natural polymers such as chitosan, cellulose, heparin, gelatin, pectin, collagen, lignin, polysaccharides, and proteins are biocompatible and more capable of mimicking an extracellular matrix,[202,203] whereas the synthetic polymers loaded with drugs can be easily electrospun. Although, natural polymers are more expensive than synthetic polymers. Biodegradable synthetic polymers such as polycaprolactone (PCL), polyesters polyglycolic acid (PGA), polylactic acid (PLA), poly(lactic-*co*-glycolic) acid (PLGA), and naturally biodegradable polymers such as collagen, gelatin, alginate, and chitosan prevalently have been used in electrospun fibers for sustained release (**Table 3**).[204–206]

Simple and versatile fabrication method, high surface-to-volume ratio, interconnected porous structure, and high permeability of electrospun nanofibers provide great potential

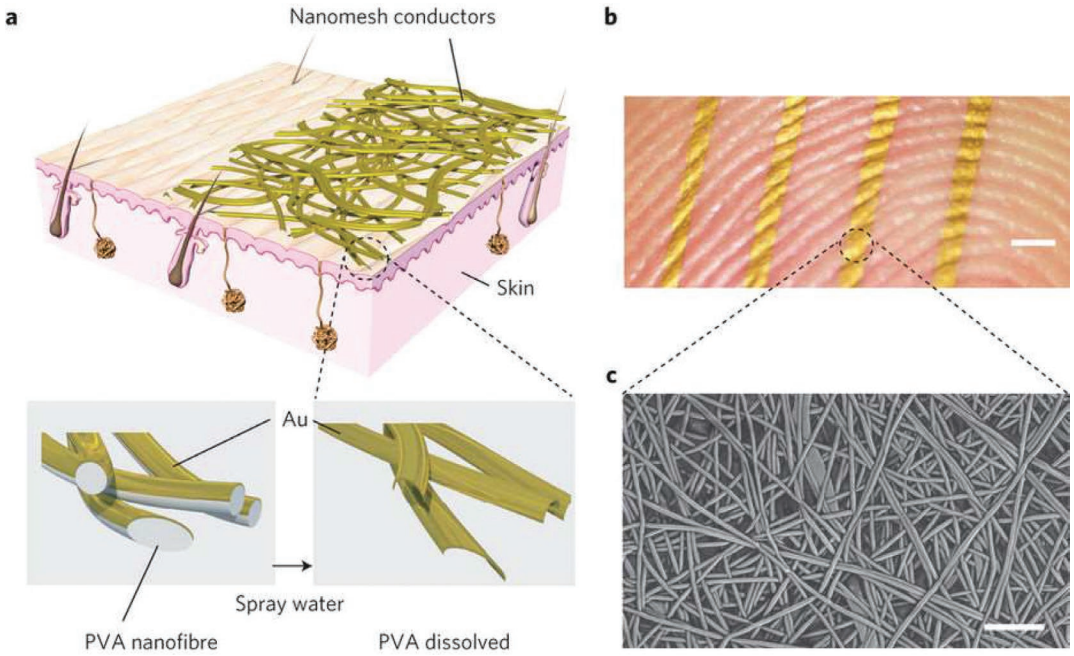

Figure 11. Inflammation-free, gas-permeable, lightweight, stretchable on-skin sensor (electronics) based on nanofiber meshes: a) Schematic of the Au nanofiber mesh conductors. b) Picture of Au nanofiber mesh conductor attached to a fingertip, showing a high level of conformability and adherence to the skin. Scale bar, 1 mm. c) SEM image of Au nanofiber mesh conductor formed by dissolving PVA nanofibers. Scale bar, 5 µm. Reproduced with permission.[198] Copyright 2017, Springer Nature Limited.

Table 3. Different drug incorporation methods using electrospinning.

Drug incorporation methods	Advantages	Disadvantages	Example	Ref.
Blending electrospinning	Simple compared to other encapsulation methods. Controlling drug release by changing the polymer-polymer ratio in the blend.	Blended polymers must be matched hydrophobic-hydrophilic properties of both drug and polymer. The phase behavior of the processed polymer blend is essential should be known clearly.	Poly(D,L-lactic coglycolide) (PLGA) poly(dioxanone) (PDO)/ciprofloxacin hydrochloride (CiH)	[214]
Surface modification electrospinning	Drugs immobilization on the nanofiber surface considered as a workable solution to combat large initial burst release and short release	The nature of polymers and drugs are crucial parameters.	PLGA–chitosan mats were functionalized with graphene oxide decorated with silver nanoparticles	[215]
Emulsion electrospinning	The process is simple. The drug and the polymer are dissolved in appropriate solvents so no need for a common solvent and many combinations of hydrophilic drugs and hydrophobic polymeric are possible.	Not all kinds of drugs can be loaded by this way. In this method, unstable macromolecules like DNA encountered the shearing force or the interface tension between the aqueous and organic phases of the emulsion, so for these reasons, these macromolecules are damaged or degraded.	Chitosan/poly(ethylene oxide)/cinnamaldehye	[216]
Coaxial electrospinning	Biomolecule functionality in the core is preserved by the shell polymer. There is no direct contact between the core ingredient with the biological environment.	The complexity of the design and material parameters. This method needs a special syringe tip.	Polycaprolactone@chitosan/silver nanoparticles	[217]
Coaxial electrospray	Uniform size distribution high encapsulation efficiency, effective protection of drug bio-functionality	Process control is very complex due to the complexity of the multiple design process, the metaphysical nature of the process, and material parameters.	TiO_2/Fe_3O_4, graphene and quantum dots	[218,219]
Electrospray	The possibility of direct drug incorporating into a nanofiber in one-step. It was also proved considered as a safe technique for processing several types of cells. This method is fast and easy. Bulk fabrication is possible.	Sufficient physical interactions between the drug and the polymer are required for attaining sustained and prolonged drug release. Thermal stress in drying, shearing force in the nozzle may induce drug degradation.	PVA/montmorillonite/silver hybrid particles	[220]

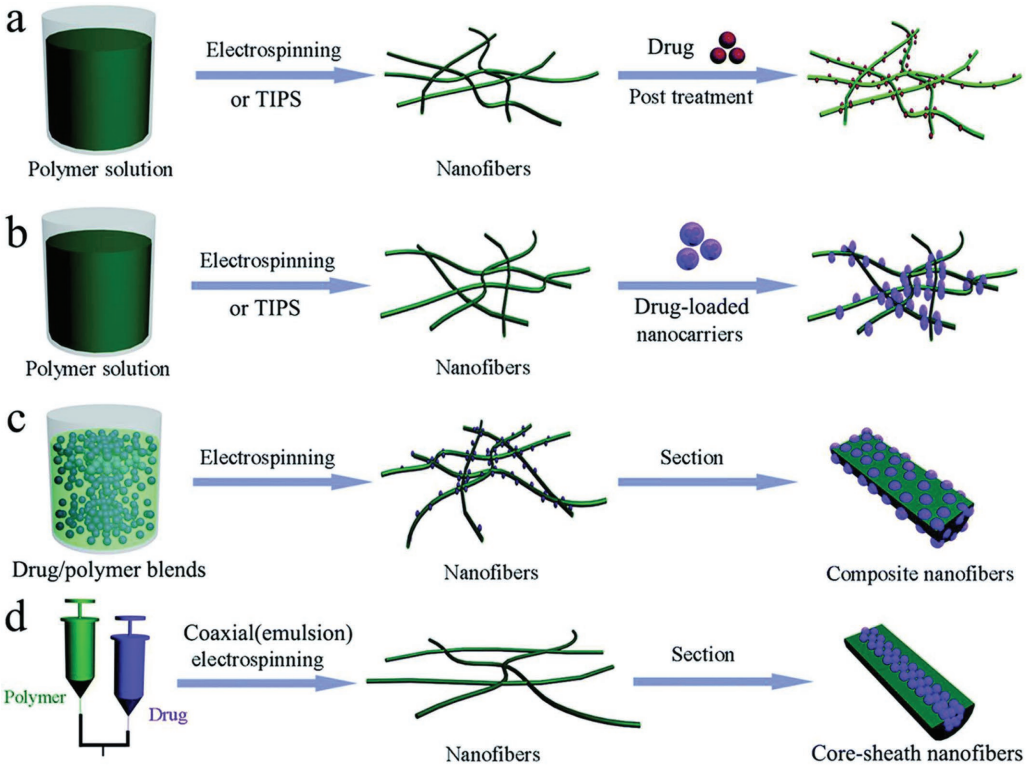

Figure 12. Schematic of possible methods of drug-loading methods in nanofibers: a) post-treatment; b) immobilization of drug-loaded nanocarriers into nanofibers. c) Co-electrospinning of drug-polymer blends; d) emulsion (coaxial) electrospinning. Reproduced with permission.[207] Copyright 2014, American Chemical Society.

applications for electrospun nanofibers as an ideal candidate vehicle for drug delivery in medicine. **Figures 12** and **13** show various drug incorporation techniques to load drugs in/on nanofibers using electrospinning.[207] Incorporation of the drug can be done easily into electrospun nanofibers by various techniques such as physical adsorption, chemical immobilization, blending, coaxial electrospinning, and emulsion electrospinning.[208–213]

Recent efforts in electrospinning via fabrication of micro- and nanofibers with tailored structure such as single, coaxial, hollow, porous, and triaxial fibers offer ability for encapsulating functional molecules or therapeutic agents, protecting the therapeutic agents from the surrounding environment, the possibility of modulating the release kinetics by altering the fiber thickness and localization, maintaining the blood level of the drug between minimum threshold concentration and the toxic concentration for an extended period, and modulate the mechanical and biological properties of the nanofiber. Electrospun fibers with various configurations are shown in **Figure 14**.[87] Coaxial and triaxial electrospinning techniques resolve the limitations of the traditional drug delivery methods. Medicated nanofibers made by coaxial/triaxial electrospinning provide altered release time profiles according to loading location and distribution of the drug into the nanofibers (Figure 14).[87]

Recently, considerable progress has been made in the fabrication of smart electrospun nanofibers for controlled drug release. In this method, physical and/or chemical stimuli such as pH value, ionic strength, temperature, light, electric or magnetic fields, or combinations of them cause drug release. Electrospun nanofibers are gaining considerable attention as smart materials for oral drug delivery,[221–223] transdermal drug delivery,[224–226] vaginal drug delivery,[227,228] and as a scaffold for tissue regeneration due to morphological similarities to the natural extracellular matrix, high surface-to-volume ratio, very high and tunable porosity, and good mechanical properties.[24,229–232] Future efforts may be focused on the development of multiple stimuli-responsive electrospun nanofibers and their biocompatibility with the human body. Niiyama et al.[233] have developed a smart anticancer fiber mesh to control tumor-killing activity against lung adenocarcinoma precisely. The mesh is loaded with chemotherapeutic drug as well as magnetic nanoparticles (MNPs). It can be activated and generate heat when the loaded MNPs exposed to an alternating magnetic field (AMF). The proposed system is a safe and effective cancer treatment[233] (**Figure 15**).

Drugs release from electrospun fibers can be controlled by various factors such as fiber composition, swelling, diameter, porosity, construct, geometry, and thickness.[234–240] A combination of diffusion, polymer degradation, drug partitioning in polymers, and drug dissolution are considered as a drug release mechanism from fibers. The drug release mechanism for the nonbiodegradable matrix is driven by the concentration gradient and osmotic pressure or matrix swelling, for biodegradable matrix or biodegradable matrix with the conjugated drug, the hydrolytic or enzymatic cleavage of the relevant chemical

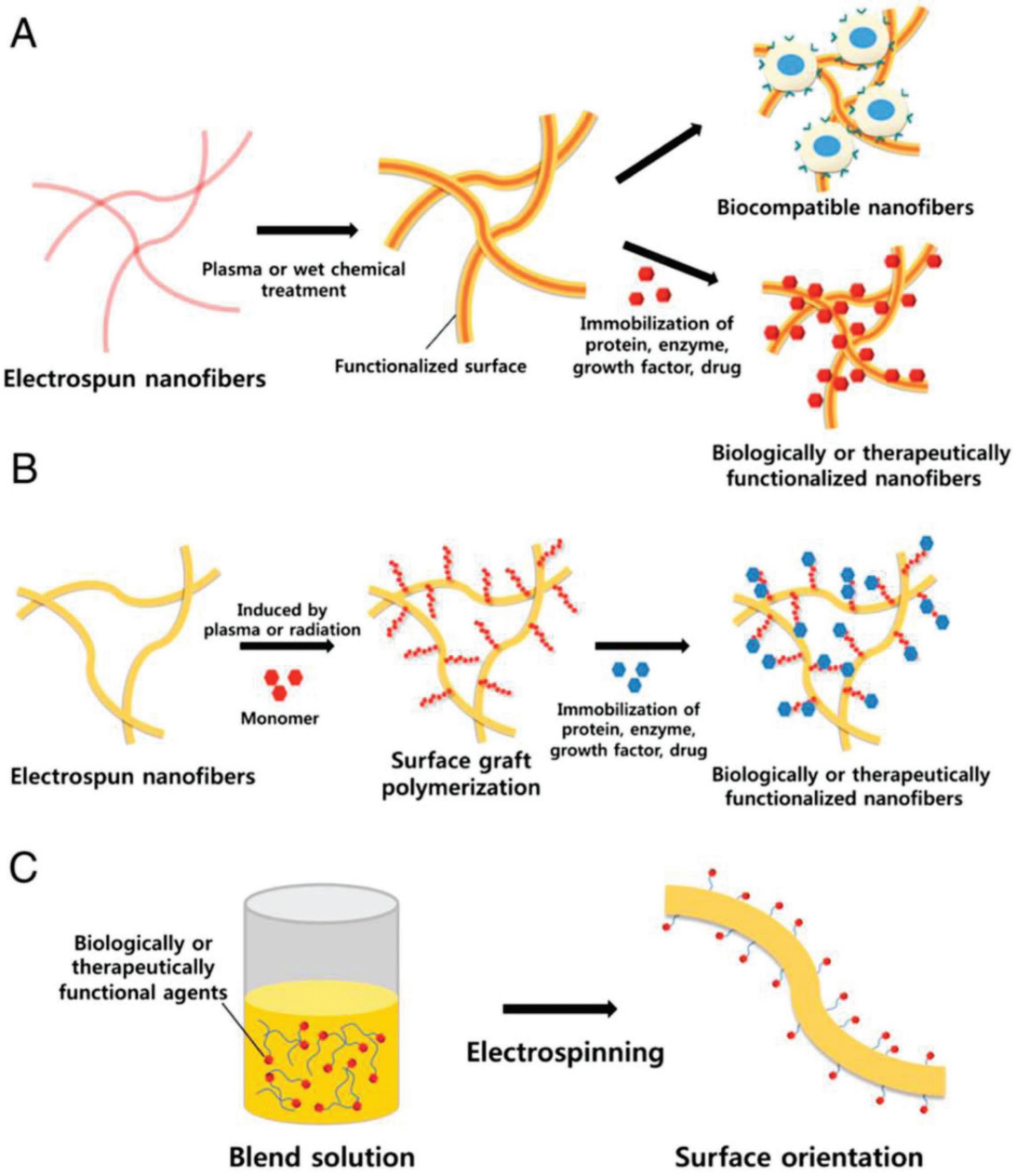

Figure 13. Different surface immobilization techniques for incorporating biologically active compounds (drugs) into nanofibers: A) Plasma treatment, B) surface graft polymerization, C) co-electrospinning. Reproduced with permission.[209] Copyright 2009, Elsevier.

bonds are involved.[240] Some studies of nanofibers in drug delivery are shown in **Table 4**.

6. Nanofibers for Wound Healing and Skin Care

Many researchers are currently conducting investigations to achieve proper wound dressing materials to simultaneously fight infection while improving tissue healing without the development of resistant bacteria. Electrospun nanofibers show immense potential in wound healing. Electrospun nanofiber mats provide a structure-like native extracellular matrix with high interconnected porosity (60–90%),[36] great absorbancies, water absorbance capacity of nanofiber is between 18–213% more than films fabricated from the same polymers,[212] balanced moisture and gas permeability bring an appropriate environment to protect the wound from exogenous infection, cell migration and proliferation, hemostasis, exudate absorption and cell respiration. Electrospun nanofibers can regulate skin cell responses including proliferation, migration, differentiation, and native extracellular matrix deposition. The wound healing ability of nanofibers

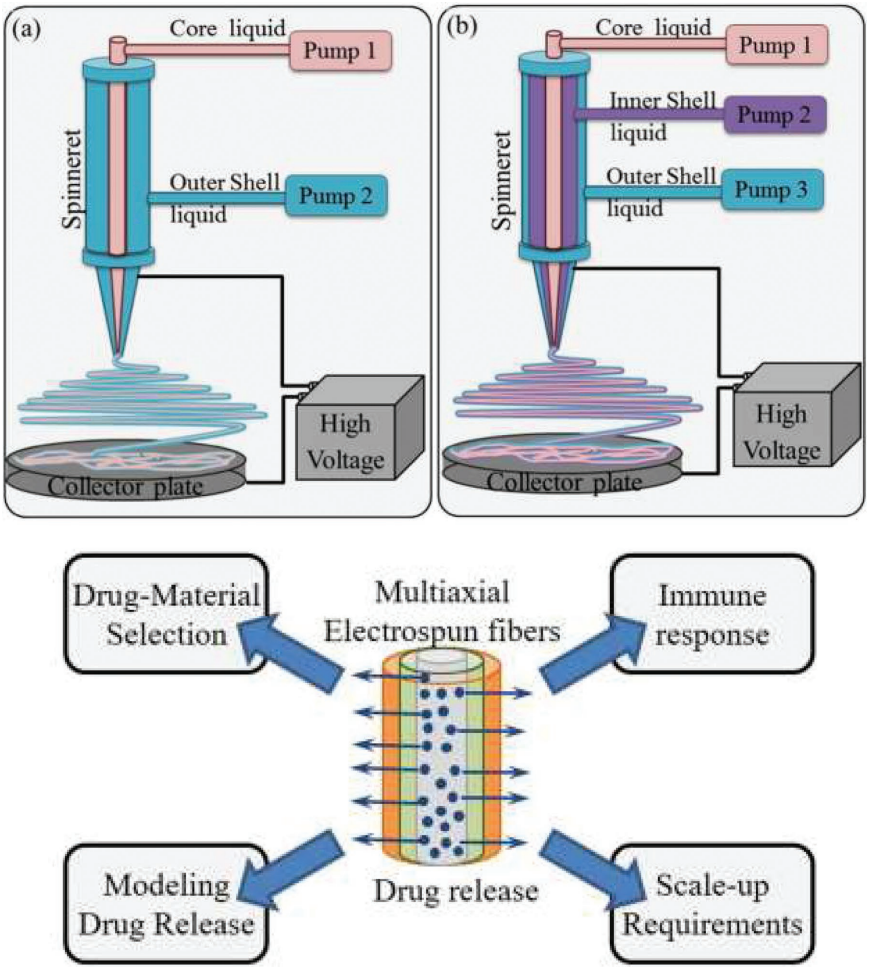

Figure 14. Schematics of a cross-sectional view of electrospun fibers with various configurations: a) Coaxial electrospinning and b) triaxial electrospinning with the loading of required agents. Reproduced with permission.[87] Copyright 2017, Elsevier.

is shown in **Figure 16**. The wound healing of the mouse was efficiently cured by electrospun nanofibers within 14 days.[275]

Loading antimicrobials agents, growth factors, vitamins, and drugs into nanofibers provides a great potential in the development of an effective antimicrobial system able to treat infections in the wound regions, prohibition of bacterial biofilm formation, prolonging drug release, and decreasing the time of wound healing process.[37–39,276–278] Collagen,[131,279] polyvinyl alcohol,[280] polyvinylpyrrolidone,[281,282] polyacrylic acid,[283,284] gelatin,[285] chitosan,[286] silk fibroin,[19] polyesters and polyurethane[39] have been used to fabricate nanofibrous materials as a wound dressing. There is need to attain smart nanofiber with the ability to provide optimal drug release profiles and rates of release according to the type of wound, the conditions of the wound and subsequently, start the release of drug agents with the optimum delivery profile only when needed to treat in the wound region. An initial burst effect is toxic to tissue cells.[24,136] However, up to now these systems are not available. Recently many researchers have focused to achieve these smart systems and translate them into an effective wound healing.[287–289] The effects of different layered nanofiber matrices are presented in **Figure 17**, and the ability of the scaffold was evaluated.[290] The new generation of smart electrospun nanofibers with electrical stimulation, mechanical stress, and pulsed magnetic field could enhance and accelerate wound healing.[291–293] Interestingly, the scaffolding application of electrospun nanofiber mats has already been applied at the industrial scale.

Electrospinning provides the great potential for various application in the cosmetic market such as for skin health and renewal such as skin healing, skin therapy, and facial masks for skin cleansing.[294–298] The nanofiber mat can be considered as a vehicle for incorporating active ingredients with the controlled release in some cases to cosmetic applications. Fathi-Azarbayjani et al.[299] have developed polymeric nanofiber face masks made of PVA and RMβ-CD that were incorporated with several skin nutrients such as ascorbic acid, retinoic acid, gold, and collagen. In comparison with commercially available facial cotton masks, the nanofiber mask provides high contact with the skin and helps to enhance the skin permeation to restore its healthy appearance. When moistened, the

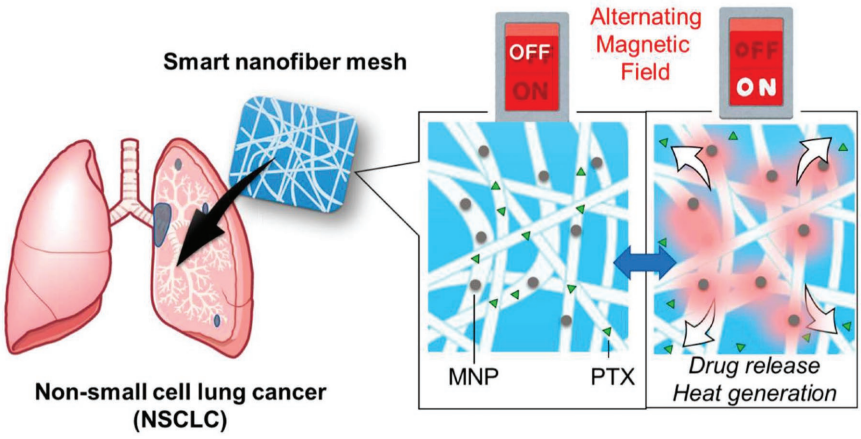

Figure 15. Alternating magnetic field-triggered switchable nanofiber mesh for cancer thermochemotherapy. Reproduced with permission.[233] Copyright 2018, MDPI.

Table 4. Therapeutic delivery applications of nanofibers.

Application	Nanofiber	Therapeutic agent	Result	Ref.
Antibacterial activity	PLA (MW = 100 000) and ciprofloxacin conjugated PLA	Ciprofloxacin	The ciprofloxacin released from the drug-conjugated nanofiber possesses antimicrobial activity against *S. aureus* bacteria	[241]
	Halloysite nanotubes/poly(lactic-*co*-glycolic acid)	Tetracycline hydrochloride (TCH)	The composite nanofibers display sustained release manner of the antibacterial drug for 42 days	[242]
	Poly(acrylic acid) (PAA)	DOXY-h	Streptococcus agalactiae and *S. aureus* as gram-positive bacteria were more sensitive to PAA/DOXY-h nanofiber mats than *Pseudomonas aeruginosa* as gram-negative bacteria	[243]
	Polyacrylonitrile (PAN)/agar	Ampicillin (AMC)	The agar/polyacrylonitrile nanofiber showed good biocompatibility and long-lasting antibacterial activity to gram-negative *E. coli*	[244]
	Laponite (LAP)-doped poly(lactic-*co*-glycolic acid) (PLGA)	Amoxicillin (AMX)	The antimicrobial activity of AMX against of *S. aureus* does not compromise after being loaded into the nanofiber	[245]
	Polyacrylonitrile (PAN)	Chitosan	Polyacrylonitrile–chitosan nanofibers exhibited a 5-log reduction toward *Micrococcus luteus*, *S. aureus* and *E. coli*	[246]
	Poly(methyl methacrylate) (PMMA)	Silver nanoparticles	PMMA nanofibers loaded Ag NPs showed excellent antibacterial activity against gram-negative and gram-positive bacteria	[247]
	Chitosan (CS)/poly(vinyl alcohol) (PVA)	Silver nanoparticles	CS/PVA nanofibers containing Ag NPs showed high antibacterial ability against *E. coli*	[248]
	Polyacrylonitrile (PAN)/*N,N* dimethylformamide	Silver nanoparticles	Nanofibers showed strong antibacterial activity against *Pseudomonas aeruginosa*	[249]
	Poly(vinylidene fluoride) (PVDF)	Silver nanoparticles	The PVDF nanofibrous mats containing silver nanoparticles showed good antibacterial activity against *S. aureus* (gram-positive) and Klebsiella pneumoniae (gram-negative) bacteria compared to the PVDF nanofiber control	[250]
	Poly(methyl methacrylate) (PMMA)	Silver nanoparticles	The silver/PMMA nanofiber had enhanced antimicrobial against both gram-negative (*E. coli*) and gram-positive (*S. aureus*) bacteria efficacy compared to that of silver nitrate and silver sulfadiazine at the same silver concentration	[251]
	-Poly(caprolactone)/poly(vinyl alcohol)	Thyme extract	Nanofiber showed antimicrobial activity against two bacteria—gram-positive Staphylococcus and gram-negative Escherichia	[252]
	Hydroxyapat/poly(lactic-*co*-glycolic acid) (PLGA)	Amoxicillin (AMX)	Nanofiber inhibited the growth of *S. aureus*	[253]
	Polyvinyl alcohol (PVA)	Allyl isothiocyanate (AITC)	Nanofiber has shown higher antibacterial activity against *E. coli* and *S. aureus*	[254]
	Chitosan	Gentamicin loaded liposome	Nanofiber showed bactericidal activity against *E. coli*, Pseudomonas aeruginosa, and *S. aureus*	[255]
	Polycaprolactone@chitosan	Silver nanoparticles	Gram-negative *E. coli* BH5α and gram-positive *S. aureus* were tested against modified coaxial nanofibers for antibacterial activity, 13 mm inhibition zones were measured against *E. coli* which were higher than *S. aureus*	[217]
	Poly(lactic acid) (PLA) and polyvinylpyrrolidone (PVP)	Copaiba (Copaifera sp.) oil	Nanofiber had a greater antimicrobial action against *S. aureus*	[256]
	Poly(vinyl alcohol) (PVA)	Benzyl triethylammonium chloride (BTEAC)	BTEAC-PVA nanofibers successfully inhibited the growth of gram-positive and gram-negative bacteria and bacteriophages MS2 and PhiX174	[257]
Antiviral activity	PLLA/PEO hydrophilic polyethylene oxide (PEO) and hydrophobic poly-L-lactic acid (PLLA)	Maraviroc (MVC),3′azido-3′ deoxythymidine (AZT), acyclovir	The fabricated nanofibers facilitate simultaneous release of multiple drug against sperm, HIV-1, and HSV-2	[258]
	Poly (L-lactide-*co*-glycolide) (PLGA)	Griffithsin	Nanofiber potently inhibits HIV infection in vitro	[259]
	Poly(lactic-*co*-glycolic acid) (PLGA) and poly(-D-L-lactide-*co*-ε-caprolactone) (PLCL)	Acyclovir (ACV)	PLGA/PLCL/ACV nanofibers provided complete and efficacious protection against HSV-2 infection in vitro	[260]

(Continued)

Table 4. Continued.

Application	Nanofiber	Therapeutic agent	Result	Ref.
	Poly(vinyl alcohol) (PVA)	Tenofovir (TFV)	The results support the potential for scale-up of TFV-loaded fibers against HIV-1	[261]
Antifungal activity	Poly(vinyl alcohol)/poly(methyl methacrylate) (PVP/PMMA)	cetylpyridinim chloride (CPC)	Nanofiber had antifungal action against *C. albicans*	[262]
	Polycaprolactone (PCL)	Egg lecithin and terbinafine hydrochloride (terbinafine)	Nanofiber showed antifungal efficacy against molds as well as dermatophytic fungus	[263]
	Polycaprolactone (PCL)	Ketoconazole	Functionalized nanofibers exhibited antifungal activity toward aspergillus flavus, Penicillium citrinum, and Fusarium oxysporum	[264]
	Polyethylene oxide (PEO) and polycaprolactone (PCL)	Clotrimazole	In vitro antifungal study suggested the PEO/PCL/clotrimazole shows therapeutic effectiveness in the treatment of oral candidiasis	[265]
	Polycaprolactone(PCL)/gelatin	terbinafine hydrochloride (TFH)	Nanofiber showed antifungal activity against Trichophyton mentagrophytes, Aspergillus fumigatus, and Candida albicans	[266]
Multi antimicrobial activity	Chitin	Silver nanoparticles	Chitin/Ag nanofiber showed much stronger antimicrobial properties against *E. coli*, *P. aeruginosa*, and influenza A virus	[267]
Orthopedic implant-related infection	Poly(D,L-lactic acid-*co*-glycolic acid) (PLGA)	Fusidic acid (FA) and rifampicin (RIF)	All dual-loaded formulations exhibited direct antimicrobial activity in vitro against two strains of methicillin-resistant *S. aureus* (MRSA) and *Staphylococcus epidermidis*	[21]
Treatment of bacteria-related biofilm	Poly(D,L-lactide-*co* glycolide)–poly(ε-caprolactone)	Quercetin	Nanofiber showed the antibiofilm activity against Candida albicans	[268]
	Polyethylene/silver nanofibers (Ag-Nfbs) ≈80 nm	–	Bacterial viability tests showed that the silver-nanofiber composites inhibited the growth of *E. coli* ATCC 25 923 by 88% and 56%	[269]
	Poly(acrylonitrile)	Commercial hydrolytic enzymes	No biofilm formation was observed on nanofibers that were coated with the enzymes	[270]
	Poly(ε-caprolactone) (PCL)/ polyethylene oxide (PEO)	Vancomycin	Nanofiber prevented MRSA biofilm formation on the surface of ossicular prostheses regardless of materials in vitro, and MRSA otitis media in vivo	[271]
	Poly(L-lactide-*co*-glycolide)/ PLGA/PCL)	Vancomycin (Van), linezolid (Lin) and daptomycin (Dap)	In a mouse model of biofilm-associated orthopedic-implant infection, three different combinations of antibiotic-loaded coatings were biocompatible with enhanced osseointegration and were highly effective implant biofilm formation and in preventing infection of the bone/joint tissue	[272]
Antibiofilm nanofiberScaffolds as a wound dressing material	Poly-D,L-lactide (PDLLA) and poly(ethylene oxide) (PEO)	Copper particles	After 48 h biofilm formation by *S. aureus* Xen 30 and *P. aeruginosa* PA01S. was reduced by 50% and 41%, respectively	[273]
Tissue engineering	Poly (L-lactide-*co*-glycolide)/ (PLGA/PLLA)	Doxycycline (DOXY)	In vitro antibacterial tests, scaffold confirmed its ability to prevent common bacterial growth (*E. coli* and *S. aureus*) for a prolonged duration	[17]
	Poly(1-caprolactone) (PCL/ gelatin)	Metronidazole	The controlled and sustained release manner of the drug from the membrane significantly prevented the anaerobic bacteria colonization. Until the drug content reached 30% cells could adhere to and proliferate on the membranes without cytotoxicity	[18]
Prevention of abdominal adhesions and antimicrobial activity	Caprolactone(PCL)	Biteral	Microscopical and histological evaluations exhibited that using these barriers reduces the extent, type, and tenacity of adhesion. The antibiotic embedded membranes significantly eradicated postsurgery abdominal adhesions, and also improved healing	[274]

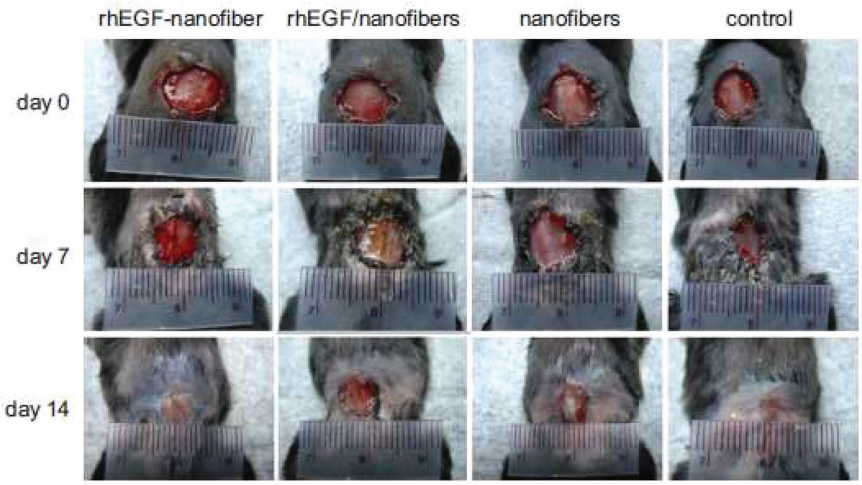

Figure 16. The extent of nanofiber wound healing ability in diabetic C57BL/6 mice treated with various formulations. Reproduced with permission.[275] Copyright 2008, Elsevier.

active content in the mask will gradually dissolve and release providing a maximum skin penetration.[299] It seems that nanofibers will get more attention due to their unique features in this specific application in the cosmetics market in the future.

7. Nanofiber for Air, Water, and Blood Purification

Nanofiber purification membranes represent the next generation of nonwoven ultrafiltration media due to their unique properties. Traffic and transportation and the manufacturing industry continuously release large amounts of fine particles (<2.5 μm) into the atmosphere, turns out to be a major cause of respiratory and cardiovascular illness. Commercial ultrafiltration (UF) membranes for air, water, and blood were therefore modified using polymeric nanofibers in order to gain additional treatment functionality.[300,301] The use of nanofibers in filtration membranes minimize the pressure drop and provides higher filtration efficiency than conventional fiber and increase its lifetime. The high surface area and the large porosity (over 80%) of nanofiber membranes improve the adsorption of contaminants for air, water, and blood purification. To use nanofiber in ultrafiltration, the nanofiber membrane should be used with a supporting substrate. The tapping of a particle in membrane pores in ultrafiltration or nanofiltration causes the degradation of the membrane performance. The supporting substrate is vital to prevent rupture of the film under high pressure while allowing high flux. In this case, membrane surface was modified using biocidal electrospun polyurethane nanofibers.[302] Nanofibrous membranes have an extremely high surface-to-volume ratio, small pore size, high porosity and permeability, and easy surface functionalization. Nanofibrous membranes with specific adsorptive chemistry to metal ions have shown higher efficiency for capturing these impurities than the conventional adsorptive membrane. The appropriate pore size, surface wettability, fiber diameter, and morphology led to the preparation of membranes with high water permeability in the ultrafiltration range and noticeable antifouling property. Nanofiber membranes bring effective solution related to quality and quantity problems for removing pollutants from air, water, and blood. Nanofibrous membranes have an extremely high surface-to-volume ratio, small pore size, high porosity and permeability, easy surface functionalization, and less toxicity with minimum health risks suggested as an appropriate technique to remove unwanted particles smaller

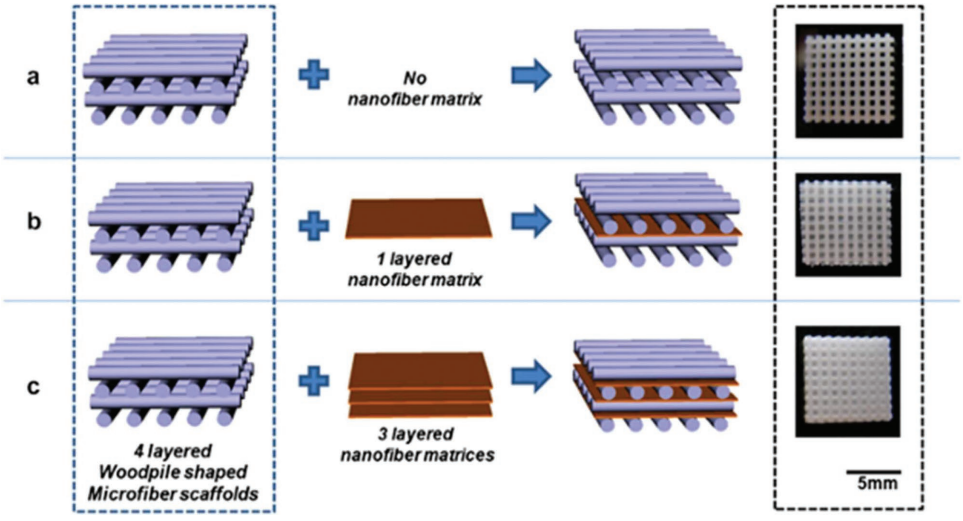

Figure 17. Different types of hybrid scaffolds employed in the cell culture tests. a) Scaffold matrix has no nanofiber matrix and only a PCL scaffold as a control specimen. b) Scaffold matrix made of a one-layer PCL/collagen nanofiber matrix, and c) scaffold matrix made of a three-layer PCL/collagen nanofiber matrix. Reproduced with permission.[290] Copyright 2008, Elsevier.

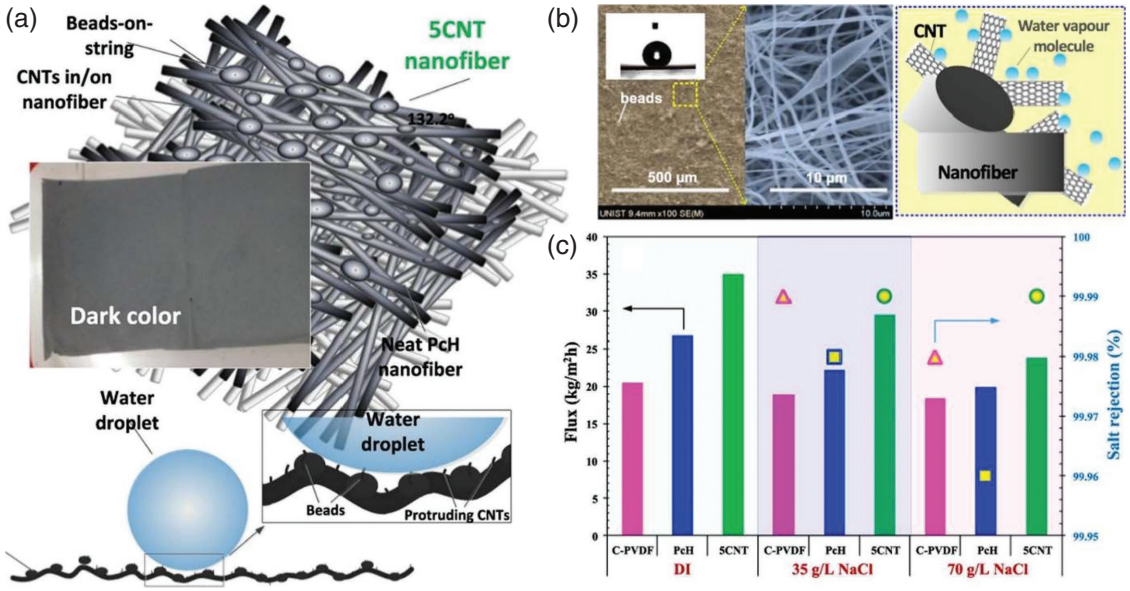

Figure 18. Super-hydrophobic nanofiber membrane containing carbon nanotubes for high-performance direct contact membrane distillation (DCMD): (a) Liquid entry pressure and contact angle measurements, (b) schematic representation of the structure of the neat and CNT-incorporated nanofiber structures and SEM images showing the beads and CNTs on the fiber. Reproduced with permission. (c) Effect of feed type on the DCMD performance of different membranes tested in the present study: deionised water (DI), 35 g/L NaCl and 70 g/L NaCl. Reproduced with permission.[320] Copyright 2016, Elsevier.

than 300 nm.[303] Current researches are focused on the surface membrane modification of existing industrially produced ultrafiltration membranes with different types of polymeric nanofibers, for the purpose of added functionality (e.g., catalysts, biodegradable particles, and substances).[304–307]

7.1. Nanofiber for Water Purification

According to WHO report, about 2.1 billion people lack safe drinking water at home.[308,309] Thus there is an essential need to a new technology to remove contaminants from the water. Environmental contaminants such as heavy metals (e.g., Hg^{2+}, Cu^{2+}, Pb^{2+}, Ni^{2+}, Cd^{2+}), soluble organic compounds (e.g., dyes, phenols, drugs) in industrial wastewater, and microorganisms have the carcinogenic effects on the human body. The nanofiber membranes bring effective solutions for removing these pollutants from water. Water membrane biofouling has a negative effect on membrane performance. To solve this problem, membrane surface was modified using biocidal agents.[302] Current researches are focused on the surface membrane modification with different types of polymeric nanofibers, photocatalysts, and biodegradable substances.[310–312]

Nanofiber membranes are very effective in removing viruses,[313] antibiotics, metal nanoparticles,[314–316] soluble organic compounds, bacteria, and microorganisms from water.[317,318] Functional compounds such as poly(quaternary ammonium) can be used to target pathogenic microorganisms[317] such as nanobiocides that can be entrapped in the nanofibers.[318] Singh et al.[319] fabricated CdS nanoparticles integrated mesoporous hollow TiO_2 nanofibers by a coaxial electrospinning technique for the photocatalytic degradation of para-nitrophenol (4-NP), a well-known model water pollutant dye. The presence of CdS nanoparticles on the nanofiber surface-enhanced light absorption in the visible region. The fabricated nanofibers are reusable, and their nanostructure does not change after repetitive usage. Tijing et al.[320] developed superhydrophobic, robust, mixed matrix polyvinylidene fluoride-*co*-hexafluoropropylene (PcH) nanofiber membranes containing CNTs as nanofiller to impart additional mechanical and hydrophobic properties (**Figure 18**). The resulting flux of the 5 wt% CNT-incorporated nanofiber membrane (29.5 L m^{-2} h) was consistently higher than the commercial membrane (18 L m^{-2} h) without compromising the salt rejection (>99%).[320]

7.2. Nanofibers for Air Purification

Due to the carcinogenic effect of air pollution (particulate matter) and toxic gases such as sulfur oxides (SO_2), nitrogen oxides (NOx), carbon monoxide (CO), and chlorofluorocarbons (CFCs) mainly derived from the manufacturing processes of various industries and cars, and pathogenic bioaerosols, many attempts have been conducted to solve this serious threat to public health globally. The penetration of particulates with a diameter below 2.5 μm (PM 2.5) and 10 μm (PM10) into the respiratory system in long-term exposure, can cause many serious health problems.[321] Several studies have proved the excellent ability of electrospun nanofibers in filtering heavy metal ions from polluted water and air due to their unique properties such as the large surface area to volume ratio, high and interconnected porosity in comparison with conventional materials.[322–324] It was suggested that the removal mechanism of heavy metal by electrospun nanofibers is based on electrostatic interactions between the metal ion and polymer.[325,326]

Pathogenic bioaerosols are the other health threat. The face mask fabricated from nanofiber membrane provides an

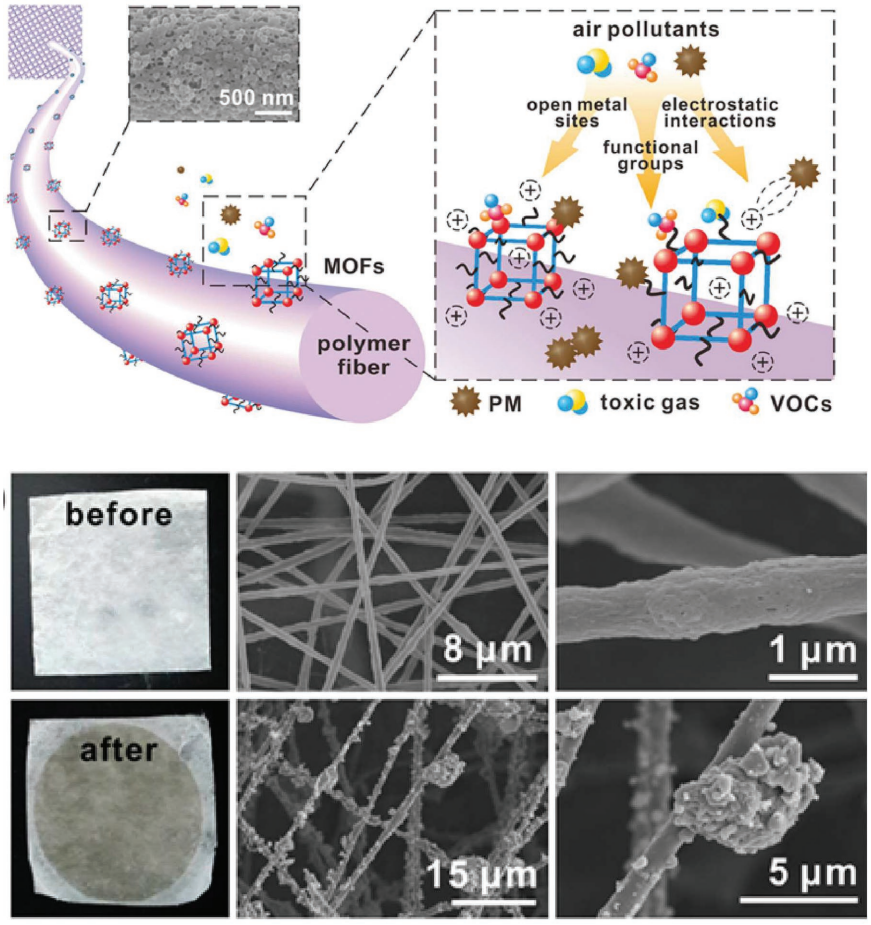

Figure 19. Proposed capture mechanism of the MO filter for air pollutants. Inset is the SEM image of the MOF/polymer composite fiber surface. Photos and SEM images of the ZIF-8/PAN MOFilter before and after PM capture. Suggested capture mechanism of the air pollutants by the MO filter can be done by three mechanisms: 1) Binding to the open metal sites on MOFs; 2) interacting with the functional groups on MOFs and/or polymers; 3) electrostatic interactions with MOF nanocrystals. Reproduced with permission.[323] Copyright 2016, American Chemical Society.

effective protection against various airborne pathogens. One of the nanofibrous face masks on the market is the RespiPro mask. This mask is made from the nanofiber fabric RESPILON consisting of several layers constituting a functional unit with complex filtering capabilities to capture all airborne biological threats. Zhang et al.[323] have designed polyacrylonitrile nanofiber/ZIF-8 as a metal–organic framework filter (PAN/ZIF-8) for air pollutants control. The nanofibrous filters (noted as MOFilter) showed high PM removal efficiencies up to 89.6% and 88.3% for PM10 and PM2.5, respectively, in the hazy environment, and the performance remains largely unchanged over 48 h of continuous use. **Figure 19** shows PAN MO Filter before and after long-term PM capture.[323]

Electrospun fibers as ideal protective clothings[327–330] with high surface area, porosity, and ease of functionalizing have shown high efficiency in comparison with conventional materials to protect against nanoparticulate aerosols, chemicals, and biological threats (which include chemicals like nerve agents, mustard gas, blood agents such as cyanides, and biological toxins such as bacterial spores, viruses, and rickettsiae).[331,332] Faccini et al. have developed nanofibrous mats of polyamide 6 (PA6) that were deposited onto a nonwoven viscose substrate as a protective clothing against nanoparticulate aerosols. A really thin coating of this nanofiber provided up to 80% retention of 20 nm size particles and over 50% retention of 200 nm size nanoparticles.[331] Agarwal et al. (2012) investigated the detoxicification performance of zeolite catalysts (Linde Type A and Mordenite) coated onto cellulose/polyethylene terephthalate (PET) electrospun nanofibers against paraxon, a nerve agent stimulant. The zeolite was incorporated onto nanofibers by simultaneous electrospraying. The results showed the detoxification ability of the functionalized fibers and their potential to be employed in textiles for protection and detoxifying the nerve agent stimulant.[333] Bedford and Steckl[334] created photocatalytic self-cleaning textile made of core-shell nanofibers with cellulose acetate as the core phase and a dispersion of nanocrystalline TiO_2, a well-known photocatalyst, as the sheath. Consequently, the photocatalytic property of nanofibers created from coaxial electrospinning coated with TiO_2 nanoparticles is better compared to the dispersion of TiO_2 nanoparticles on nanofiber by electrospraying.[334] Dhineshbabu et al. fabricated electrospun MgO/nylon6 hybrid nanofibers for providing antibacterial and fire retardancy properties. MgO/Nylon 6 nanofiber mat shows enhanced antibacterial activity (*Staphylococcus aureus* and *E. coli*) and the fire retardancy (burning time and ash count) comparing with the unmodified Nylon 6 nanofiber mat.[335]

7.3. Nanofiber for Blood Purification

Kidney failure is a debilitating condition in which the kidneys are no longer able to remove enough waste (i.e., urea, creatine, and uric acid) and excess fluid from the body.[336–338] Namekawa et al.[42] prepared a zeolite–poly(ethylene-*co*-vinyl alcohol) (EVOH) nanofiber membrane to remove uremic toxins from the blood. The EVOH membrane is compatible with the human body and zeolites are capable of selectively adsorbing uremic toxins (**Figure 20**). Wang et al.[339] fabricated a thermo-responsive chitosan nanofiber substrate to effectively capture, purify, and release the target cancer cells, assisted by poly(*N*-isopropylacrylamide) brushes and DNA hybridization. These brushes are designed to enable white blood cells to detach from aptamer-poly(*N*-isopropylacrylamide)/chitosan nanofiber surfaces during the conformational transition. Meanwhile, these

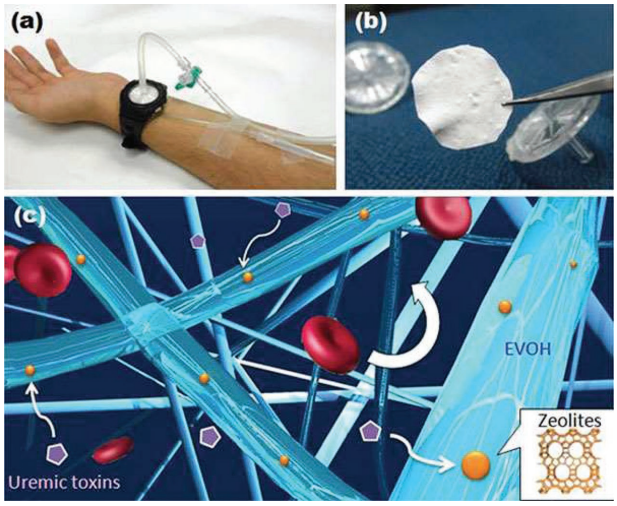

Figure 20. Nanofiber mesh filters blood of toxins allows for tiny hemodialysis machines: a) Photographs of a wearable blood purification system; (b) zeolite–poly(ethylene-*co*-vinyl alcohol) (EVOH) membrane; (c) nanofiber is composed of EVOH as the primary matrix polymer and zeolites for selectively adsorbing uremic toxins. Reproduced with permission.[42] Copyright 2014, Royal Society of Chemistry.

specific captured circulating tumor cells (CTCs) are retained at a high purity.[339]

8. Conclusions

Nanofibers are an important and versatile class of nanomaterials that are attracting increasing attention from academics as well as several industries in recent years. Novel fabrication techniques (i.e., physical, chemical, and biological methods) of nanofibers are being reported in the literature at an ever-increasing rate and there is no sign of slowing down. Electrospinning is the most common fabrication technique and it can produce a wide range of nanofiber materials (i.e., polymer, metal oxide, carbon, and composite) with high surface area, flexibility, high interconnected porosity, and surface functionality. Nanofibers have received a great deal of attention for the development of a new generation of drug delivery systems due to the unique features including high drug loading, encapsulation efficiency, enhanced therapeutic index, localized delivery, reduced drug side effects, ability to modulate drug release. The remarkable properties make nanofibers ideal candidates for a wide range of biomedical and healthcare applications, especially the antimicrobial treatment of bacteria-related biofilms, orthopedic implant-related infections, tissue scaffolds, and wound dressings. The nanofiber membranes can be used in air, water, and blood purification with high efficiency at low pressure. Although some successful and available examples of nanofiber-based products for biomedical nanofibrous materials have been reported, they have not yet been fully explored in biomedical and healthcare fields. Nanofibers have shown the most promising results as dressings for wound healing and tissue-engineered scaffolds with architectures and functions similar to those of native extracellular matrix. The nanofibrous scaffolds are currently being used in vasculature, skin, bone, cartilage, neural, and tendon/ligament. The future challenges of nanofibers can be summarized as follows: i) Novel nanofiber fabrication techniques are still needed to move from nanofiber production from laboratory scale to commercial and industrial settings, ii) Nanofibers are still being required more attempts to achieve the most ideal nanofiber properties (e.g., composition, diameter, morphology, pore size) for effective healthcare and biomedical applications in the market scale.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomedical, biosensor, cosmetics, drug delivery, medical filtration, nanofiber, protective textiles, tissue engineering

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