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Review Article

Advances in Latest Application Status, Challenges, and Future Development Direction of Electrospinning Technology in the Biomedical

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In recent years, nanotechnology has attracted much attention in the field of biomedicine and sensing technology. As one of the simplest and most effective methods to prepare nanofiber materials, electrospinning technology has a lot of application research in biomedical fields such as sensor detection, drug delivery, and tissue engineering because of its high porosity, large surface area to volume ratio, and uniform size. In this review, we summarized the latest application progress of electrospinning materials in biomedicine, sensing, and textile industry and discussed the challenges and future development direction of electrospinning technology.

1. Introduction

Nanotechnology has generated wide interest in biomedicine, sensing technology, and textile industry applications [1–3]. In particular, due to the excellent mechanical strength, high porosity, and ease of manufacture of nanofibers, much research has been conducted on the use of nanofiber technology for possible biomedical [4–7], technological sensing [8–10], and textile [11, 12] applications. It is widely known that electrospinning technology is one of the simplest and most effective methods of preparing nanofibrous materials [13]. High pressure is used to extract charged wires from a polymer solution at a preset rate, after which micro/nanofibers are produced by solvent evaporation [14]. During the preparation of electrospun fibers, a polymer solution was treated with a potential of 10-20 kV, and liquid droplets of the surface-aggregated charge were obtained. Subsequently, a polymer jet was formed under critical voltage, the solvent evaporated, and residual fibers were collected [14–16]. Electrostatic nanocrystalline materials can be either natural or synthetic, making them useful in the textile industry as well as in biomedical and other applications.

In biomedical applications, electrostatic spinning has been used primarily for drug delivery [17–21] and tissue engineering [22–26]. Electrospun fibers possess high porosity, large surface area-to-volume ratios, uniform size, and the potential for diverse compositions. They can function as bioactive molecules in drug delivery/release and in scaffold regeneration. For example, a number of therapeutic agents have been incorporated into an electrospun, fibrous matrix through encapsulation during the electrospinning process, including small molecular drugs and biological substances such as antibiotics, proteins, DNA, RNA, growth factors, and living cells [27]. Due to their superior performance,

nanospun fibrous materials also can play a key role in the field of sensing technology [8, 28]. For example, electrospun nanofibers have been used to prepare highly stable and sensitive electrodes for glucose detection [29]. Thus, due to these superior properties, nanospun materials play a central role in the field of sensing technology and the fabrication of blood glucose meters. The high porosity of electrospun materials has fostered their use in waterproof and breathable fabrics in the textile industry. Nanoscale fibers made by companies such as Finetextech are widely used in the textile and automobile industries.

The aim of this review is to briefly generalize the recent applications of electrospinning materials in the biomedical sensing. First, this review outlines electrospinning material technologies (*i.e.*, conventional assays, 2D electrospinning, and 3D electrospinning) and then summarizes recent advances in developing electrospun fibers for drug delivery and tissue engineering. We also highlight the value of electrospinning for biosensors and the greatly improved performance of sensing elements. Finally, the significance of electrospun materials in the preparation of breathable and hydrophobic membranes is briefly described. Challenges and future directions for electrospinning are discussed in the conclusion.

2. Electrospinning Technology

2.1. Traditional Electrospinning. Conventional electrospinning processes chiefly produce continuous ultrafine fibers using electrostatic forces [7]. A spinning solution is pumped through a syringe pump or forced through the tip of a needle or spinneret using pressurized gas. High surface tension forms hemispherical droplets. Then, as high-voltage power is applied, the droplets become charged and elongated into a conical shape (referred to as a "Taylor cone") between the needle and the grounded dust collector. Further increasing the pressure and voltage causes the jets of the spinning solution to tilt toward the collector, accelerate, and condense into solid fibers as the solvent evaporates [30, 31].

In recent years, nanofibers have attracted considerable attention due to their tensile strength, electrical conductivity, corrosion resistance, and heat tolerance [32–34]. Based on traditional electrospinning principles, current methods for manufacturing short electrospun nanofibers with different lengths include direct electrospinning, mortar grinding, cryogenic cutting, and ultrasonication. For example, Fathona and Yabuki utilized direct electrospinning to fabricate short nanofibers that established an electric spark in electrical discharge machining [35]. In their study, the length of the short nanofibers was varied by the flow rate of the polymer solution and the applied voltage. With an increase in flow rate, the fiber length increased. Conversely, as the voltage increased, the fiber length decreased. These adjustments can yield short nanofibers with lengths of 37–670 μm. An alternative method for producing short nanofibers is to pulverize the prepared electrospun nanofibers in mortar [36]. Using this method, PVP/TiO2 nanofibers were calcined to anatase TiO2 nanofibers and then crushed into short nanofibers (SNFs) a few microns in length. Finally, the TiO2-SNFs were dispersed in a polymer solution to obtain a nanofiber composite. This mortar grinding is a simple method for high-volume production. However, this method is suitable only for brittle polymers and not ductile polymers. Cryogenic methods are reliable for cutting both brittle and ductile polymer nanofibers [37].

The morphology and structure of single fiber is the most basic structure in electrospinning. Generally, fibers have a smooth surface, a circular cross section, and a uniform diameter. It benefits some applications but hinders the expansion of others. In recent studies, fibers have emerged with a variety of fascinating morphology and secondary structure.

2.2. Two-Dimensional (2D) Electrospinning. Compared with 1D electrospinning, 2D electrospinning can allow for the adjustment of drug release dynamics and the alteration of tissue scaffold properties. Electrospinning polymeric mixtures provides a means of preparing composite nanofibers. In addition, electrospinning technology has advanced the manufacturing of nuclear sheath structures, providing a method for prolonged drug release. Electrospinning can produce nanofibers using diverse polymers, and layered scaffolds can be prepared by depositing different polymers in different regions to form spatial scaffolds. Finally, multilayer electrospinning can be used to produce nanofiber scaffolding that can achieve programmed, stepwise drug delivery, or a drug-free nanofiber layer to delay the release of an additional drug. For example, Deniz et al. [36] developed a multilayer nanofiber that could be used for the step-by-step release of dichloroacetate (DCA) and oxaliplatin. Using this strategy to achieve drug release at different times, for example, could allow drugs to exert synergistic effects on cervical cancer *in vitro* and *in vivo*. In the work of Deniz et al. [36], DCA and oxaliplatin were electrospun into different layers of synthetic fabrics, and the fiber layers were loaded on oxaliplatin and sealed between a base film layer and two fiber layers. In this way, nontoxic DCA could regulate cell metabolism to selectively promote metabolism, while oxaliplatin subsequently killed residual cells at low concentrations. This study reported that, after implantation at the cervical cancer resection margin in a murine model, a dual drug-loaded multilayer fiber mat exhibited higher antirecurrence efficacy and reduced side effects over 30 days compared to a drug-loaded monolayer fiber mat. In addition to the applications in drug delivery, spinning of such multilayer structures can also be applied to tissue engineering. For example, a three-layer electrical nanofiber was manufactured as a corneal tissue engineering scaffold [38]. In this work, poly (d, l-lactide-glycolide; PLGA, 50 : 50) nanofibers were electrospun on the outer and inner layers of a scaffold, while type I collagen nanofibers were electrospun on the middle layer. This scaffold was cross-linked by 1-ethyl-3-(3 dimethylaminopropyl) carbodiimide hydrochloride and glutaraldehyde. Various material characterizations, such as Fourier transform infrared spectroscopy, tensile testing, and biodegradation testing, confirmed the possibility of applying this material in corneal tissue engineering. Meanwhile, multilayer electrospinning could modulate cell behavior through the

alteration of nanofiber characteristics. For instance, the behavior of bone mesenchymal stem cells (BMSCs) was studied by preparing two composite nanofibers with different arrangements (nested and disordered) using a mixed solution of poly-L-lactic acid (PLLA) and gelatine (1 : 1 weight) [39]. Mesenchymal stem cells cultured *in vitro* showed that nested nanofibers were more conducive to osteogenic differentiation than randomly arranged fibers, while there was no significant difference in cell proliferation. Therefore, it is feasible to enhance bone regeneration by multilayer nanofiber alignment.

2.3. Three-Dimensional (3D) Electrospinning. Although electrospinning has been widely utilized in tissue engineering, its application is limited by the small aperture of 2D fibers, which prevents cells from growing in 3D. Therefore, an increasing number of studies have been devoted to the research and development of 3D nanofibers for developing 3D nanofiber scaffolds that can achieve the uniform diffusion of oxygen, nutrients, and delivery substances. In the following section, we describe 3D nanofiber spinning methods (*i.e.,* direct fabrication, textile technology, ultrasonication, and 3D printing) and their characteristics.

2.3.1. 3D Nanofiber. A 3D nanofiber scaffold can be obtained by modifying the collector during the electrospinning preparation process. For example, developing a three-dimensional, cotton-ball-shaped electrospinning scaffold to obtain a porous, three-dimensional scaffold could allow the penetration of cells inside the scaffold [40]. A stent is similar in diameter to conventional nanofibers, but on a microscopic scale, the structural density is smaller. In addition, *in vitro* cell culture experiments have confirmed that cells grow 40% faster on a 3D scaffold than on conventional scaffolds. Recently, a programmed electrospun 3D nanofiber collector was developed, which produced the desired 3D nanofibers by precisely controlling the movement of the collector [41]. In this study, four different microstructured nanofibers were produced simultaneously on the collector surface, which was achieved by varying the forward collector speed. A quantitative analysis of microcomputed tomography (μ-CT), scanning electron microscopy (SEM), and confocal laser scanning microscopy (CLSM) demonstrated that the pore size and porosity increased regularly as the collector moved faster. Moreover, dynamic fibers improved the proliferation and differentiation of preosteoblastic MC3T3 cells compared with fibers prepared from static collectors.

2.3.2. Weaving Technology Combined with Electrospinning. Electrospinning can be combined with weaving technology to prepare 3D scaffolds. Textile technology is a powerful technique that can precisely control the mechanical properties and patterns of cells or living molecules to create three-dimensional structures. However, textile technology requires the presence of fibers with high mechanical strength. Tamayol et al. used a wet spinning technique combined with an alginate template to prepare a composite hydrogel fiber [42]. Alginate can be used in weaving because of its high mechanical strength. In this work, alginate containing fluorescent microbeads with a diameter of 600 μm (GelMA fibers; 2%: 10% w/v) were fabricated and woven into a structure as shown. In addition, three cells (NIH-3 T3 fibroblasts, HepG2 liver cells, and human umbilical vein endothelial cells (HUVECs)) were encapsulated in fibers with different fluorescent colors that indicated specific liver functions (*i.e.*, albumin and urea secretion). Thus, weaving technology not only allows for three-dimensional cell culture but is also expected to be applied to the construction of complex tissues.

2.3.3. Application in Textile. Recently, electrospinning technology is widely used in different polymers, with low cost and simple process. More importantly, electrospinning nanofiber membranes have high porosity, which was used to make waterproof and breathable membranes in the textile industry. For instance, electrospinning technology was used to prepare polyvinylidene fluoride (PVDF) nanofiber membranes for development of waterproof materials [43]. PVDF is a tough, stable fluoropolymer with low free energy, and it is easily soluble in conventional solvents compared with polypropylene (PP), polytetrafluoroethylene (PTFE), and other polymers. In addition, it has strong hydrophobicity, strong chemical resistance, and heat resistance.

However, in the PVDF manufacturing industry, although some researchers have produced pure electrospun PVDF hydrophobic and breathable membranes with coarse fibers and large holes, the waterproof properties of the materials obtained are limited, and the mechanical properties are poor. Therefore, optimizing the porous structure of PVDF membrane to improve its application performance is an important research point. For example, an effective method to improve the performance of PVDF membrane is thermal posttreatment. Li et al. utilized hot pressing to enhance the performance of electrospun PVDF membrane and adjust the membrane pore structure. In this study, the hydrostatic pressure of the obtained membrane was 102 kPa, and the water vapor transmission rate (WVTR) was 10.87 $kg\,m^{-2}\,d^{-1}$ [44]. Although hot pressing is an effective method to strengthen the bonding structure and reduce the pore size of the PVDF membrane, it consumed high energy and required high equipment. To solve this problem, Zhang et al. prepared PVDF nanofibers filled with polyvinyl butyral (PVB) and used a thermal baking method to adjust the pore structure of the membrane. Due to the low melting point of PVB (60-65°C), PVDF/PVB membranes can only form a large amount of bonding structure by thermal baking at 140°C, so that the pore size and porosity are rapidly reduced. The prepared film exhibited moderate water resistance and high air permeability.

Polystyrene (PS) nanofiber membrane is another common hydrophobic and breathable membrane. Inspired by lotus leaf and mugwort leaf, in order to imitate the hollow structure of polar bear hair with extremely high thermal insulation, Eykens et al. fabricated polyacrylonitrile (PAN)/PS core-shell nanofibers with unique groove structures through coaxial electrospinning technology [45]. This kind of membrane exhibited high porosity, which helps to reduce the conduction heat loss when water vapor passes through

the membrane. This membrane showed a high WVTR of 60.1 $kg\,m^{-2}\,h^{-1}$ at a temperature difference between both sides of 40°C and a good water inlet pressure of 86 kPa.

At present, the protective clothing made of nanofiber membrane has reached the industry level. For example, Finetex has manufactured PU hydrophobic and breathable nanofiber membranes with the "Nexture nanomembrane" trademark and successively produced breathable and waterproof composite fabrics with a hydrostatic pressure of 70 kPa and a WVTR of 9 $kg\,m^{-2}\,d^{-1}$. In addition to protective clothing, nanofiber membranes hold great promise for the next generation of fast dry sportswear [46]. Conventional waterborne fabrics deliver water and moisture to the body in one direction, rapidly pulling sweat from the skin into the atmosphere. However, they usually lack effective water resistance in the opposite direction, resulting in poor protection. To solve this problem, a trifoliated W&B nanofiber membrane with progressive wettability was constructed, which could deliver rapid evaporation of human sweat while preventing infiltration of external liquid water. Another study developed an environment-friendly nonfluorinated polyurethane nanofiber film without coating [47]. This membrane showed high water contact angle of 137.1°, robust hydrostatic pressure of 35.9 kPa, desirable water vapor transmission rate of 4885 $g\,m^{-2}\,d^{-1}$, excellent air permeability of 19.9 $mm\,s^{-1}$, good tensile elongation of 372.4%, and remarkable elasticity of 56.9%. Thus, this work offered a potential for protective textiles and leaving no toxic solvent residues.

2.3.4. Gas-Foaming Technology Combined with Electrospinning. Gas-foaming technology has been used to achieve the orderly arrangement of 3D fibrous structures for nerve and muscle tissue engineering applications. Recently, in treating peripheral nerve injury to restore nerve function around the central nerve conduit, researchers prepared directional 3D nanofibers by combining electrospinning and gas-foaming techniques [48]. Polylactic acid (PLA)/silk fibroin nanofiber sponge scaffolds were prepared as fillers to construct 3D nanofiber sponges containing NGC (SNGC). It was confirmed by *in vitro* cell experiments that SNGC can promote the proliferation of Schwann cells. Moreover, animal experiments have found that SNGC significantly promotes the recovery of peripheral nerve function and is of great value for peripheral nerve repair.

2.3.5. Ultrasound or 3D Printing Technology Combined with Electrospinning. Ultrasonic vibration can increase the pore size and decrease the density of nanofibers by mechanically separating densely packed nanofiber-based materials. The porosity of electrospun nanofibers can be greatly improved by ultrasonic treatment in an aqueous solution. The size of nanofiber pores is related to the duration and intensity of ultrasonic treatment [49–51]. By adjusting these two parameters, specific electrospun fiber densities can be produced.

As an emerging technology, 3D printing offers precise controllability to yield a desired structural scaffold shape. For example, amorphous morphologies of electrospun loratadine nanofibers were prepared using low-cost 3D-printed, electrostatic nanofibers using counterflow air for the rapid production of nanofibers [52]. In this study, leaching studies showed that 66% of the drug was released from nanofiber pads within 10 min, which was significantly higher than the highest drug release (4%) of the reference samples.

3. Biomedical Applications

Electrospinning provides an advantageous nanotechnology methodology for producing a variety of novel structural materials with many potential biomedical applications, such as drug delivery, biosensing, and regenerative medicine. The following sections describe these applications.

3.1. Drug Delivery. Drug delivery is an important application for electrospinning. Due to the high surface area-to-volume ratio of electrospun substrates, drug loading efficiency has been improved (Table 1). In addition, changing nanofiber surface properties, such as temperature, pH, ultrasound, light, and magnetic field, can alter drug release efficiency.

Utilizing changes in pH to alter drug release is currently widely used in the treatment of various diseases. For example, xanthan–chitosan (X-Ch) polysaccharide nanofibers (Figure 1(a)(i)) were fabricated for the oral delivery of gastrointestinal drugs [53]. In this study, uniform and homogeneous xanthan gum–chitosan nanofibers were prepared by electrospinning to allow study of a curcumin encapsulation and delivery system. The results showed that x-CH-Cu nanofibers remained stable in aqueous HBSS media with different pH values (6.5 and 7.4). In addition, x-CH-Cu nanofibers were incubated with Caco-2 cells, and it was found that X-CH nanofibers interacted with Caco-2 cells in the intestine, resulting in the opening of tight connections, which promoted an increase in the cross-epithelial permeability of curcumin but did not impair cell viability (Figure 1(a)(ii)). Therefore, the interaction between electrospun fibers and epithelial cells can be used to promote the absorption of bioactive substances. Thus, X-CH nanofibers can be utilized in the oral delivery of compounds of low solubility in water for gastrointestinal treatment.

In addition to oral drug delivery, electrospinning triggered to release drugs at a specific pH could be used to treat tumors. Owing to the difference in pH between normal tissue and tumor tissue, pH-responsive drug release materials can be designed to achieve drug release precisely at tumor sites. For example, Xi and Zhao prepared silk fibroin smooth, beaded, and coaxial beaded nanofiber materials to compare their drug release properties at different pH values [54]. Drug release experiments showed that the electrospun materials exhibited a pH-sensitive release of more drug faster into an acid buffer. In addition, compared with smooth fiber and beaded fiber, the electrospun coaxial beaded fiber had a slower rate of drug release. Therefore, coaxial beaded fiber materials are effective and have the potential to be used as a continuous drug delivery system for the treatment of cancer. In another study, pH-dependent material properties were used for the treatment of external wounds [55]. In this work, three nanofiber materials (*i.e.*, silk fibroin smooth fiber, coaxial bead-on-string fiber, and bead-on-string fiber materials) were fabricated, and their drug release efficacy

Table 1: Drug delivery.

Application	Drug	Polymer	Ref
pH-responsive drug delivery systems	Antibacterial agent ciprofloxacin	Hydrophobic (poly(lactide-co-ε-caprolactone); PLCL) and hydrophilic (gelatine) polymers	[77]
Drug-release behavior	Ibuprofen (IBU)	Gliadin	[78]
	Doxycycline monohydrate (DCMH)	Silk fibroin (SF) and gelatine (GT) polymers	[79]
pH-responsive drug delivery systems	Anesthetic benzocaine (BZC)	Cellulose acetate (CA)-based nanofibers	[55]
Modified coaxial process regardless (enhance solution)	Quercetin or tamoxifen citrate (TC)	Polyvinylpyrrolidone (PVP) K90 or Polycaprolactone (PCL)	[80]
Ecofriendly drug delivery system	Ciprofloxacin (Cipro)	PVA/Dex (dextran sulfate) nanofibers	[81]
Treatment of colorectal cancer (CRC)	Curcumin (CUR) and 5-fluorouracil (5-FU)	Silk fibroin (SF)-based nanofibrous membrane, polydioxanone (PDO) stent	[82]
pH-responsive drug delivery systems	Curcumin (Cu)	Xanthan-chitosan (X-Ch) polysaccharides nanofibers	[53]
Long-term continuous drug delivery	Paclitaxel (PTX)	Polydioxanone (PDS) nanoyarns	[83]

was tested at different pH values. Moreover, the tested drugs were released faster in an acid buffer. In addition, the electrospun coaxial bead-on-string fiber material had a slower release rate than the other two fiber materials. Based on these characteristics, coaxial bead-on-string fiber material seems to be an efficient and potentially durable drug delivery system for diseases such as cancer.

The spinning of heat-sensitive materials as drug carriers has been widely studied. For example, a stable PNIPAM–gelatine nanofibrous structure (Figure 1(b)(i)), which can withstand multiple swelling and deswelling cycles and release drugs in thermal response, was prepared by in situ cross-linkage electrospinning [56]. In this study, based on the use of NHS/EDC cross-linking agents, gels were combined with pNIPAM-NHS and cross-connected. When loaded with DOX, nanofibers can release it in response to a temperature increase, and the released DOX can effectively reduce the vitality of *in vitro* human cervical cancer HeLa cells (Figure 1(b)(ii)). Other thermoresponsive materials, such as polylactic acid and hydroxypropyl cellulose (PLA-HPC), have also been incorporated into nanofiber drug release studies, providing a more effective strategy for developing materials with predictable drug delivery capabilities (Figure 1(c)). [57].

Recently, poly(N-isopropylacrylamide-N-methylolacrylamide-acrylamide) (PNIPAm-NMA-Am) was electrospun into nanofibers and used as a drug carrier after heat treatment [58]. In this study, the results of thermogravimetric analysis, scanning electron microscopy (SEM), and atomic force microscopy (AFM) showed that the pNIPAM-NMA-AM nanofibers are uniform, thermally stable, and retain excellent integrity in a water environment. Additionally, the properties of the PNIPAM-NMA-AM nanofiber can be adjusted when the temperature of the critical solution is lower than 48°C. Following 60 minutes of 6 cycles of heating and cooling, 80% of the drugs were released. The most important property was that this nanofiber had no cytotoxicity and showed great potential as a precise biomedical drug delivery system.

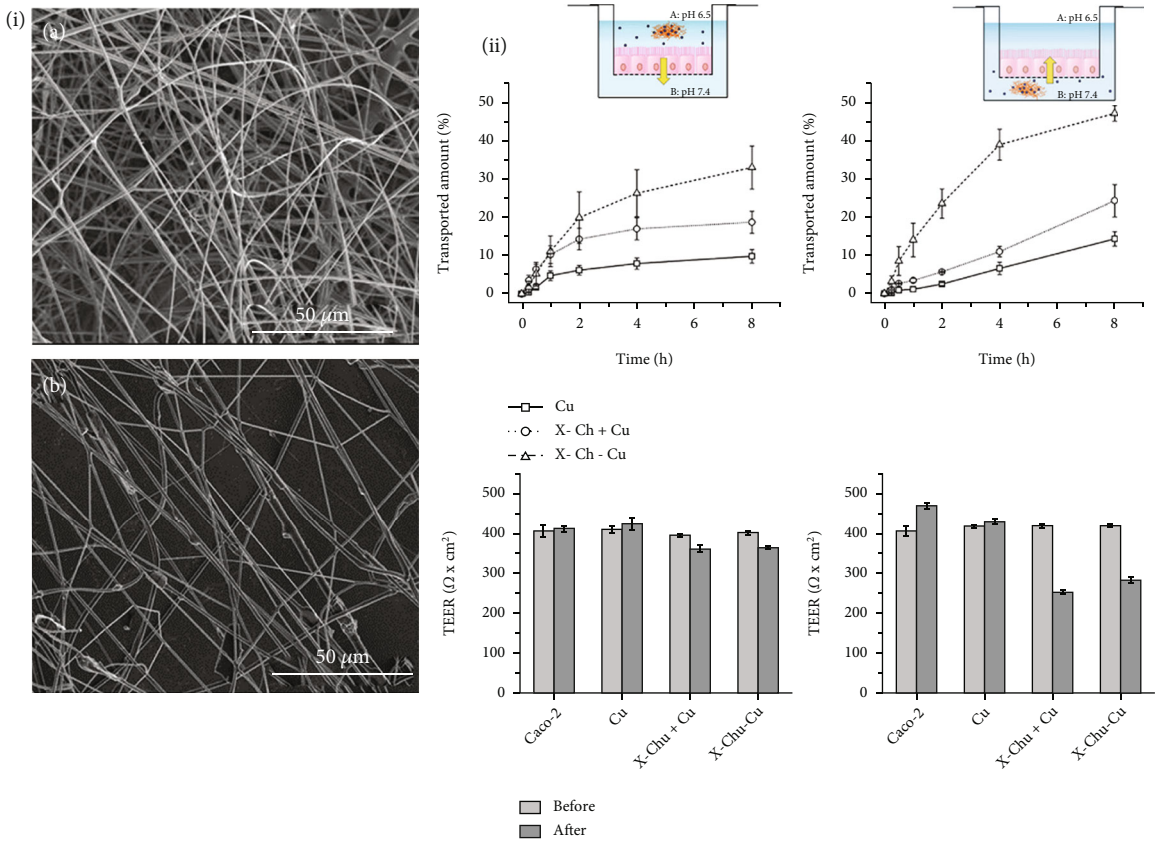
Another study demonstrated that ultrasound irradiation can achieve on-demand drug release. For example, ultrasonic irradiation can trigger the on-demand release of nanoparticles (rhodamine B-loaded mesoporous silica nanoparticles (MSNs)) in a two-drug PLGA composite fiber loaded with fluorescein (FLU) and rhodamine B mesoporous silica [59]. Drugs released from PLGA fibers and MSNs can be released by ultrasound stimulation to control a temperature rise. By selectively controlling the ultrasonic power and pulse cycles, drug delivery can occur on demand.

Magnetic response characteristics can be introduced by magnetic nanoparticles such as iron oxide nanoparticles (IONPS). Wang et al. prepared drug-loaded magnetic nanofibers by injecting ions into a PCL shell and confining ketoconazole to the PCL hollow core through coaxial electrostatic spinning [60]. The release study showed that due to ion activation molecular motion, the introduction of an auxiliary magnetic field accelerates the release of ketoconazole.

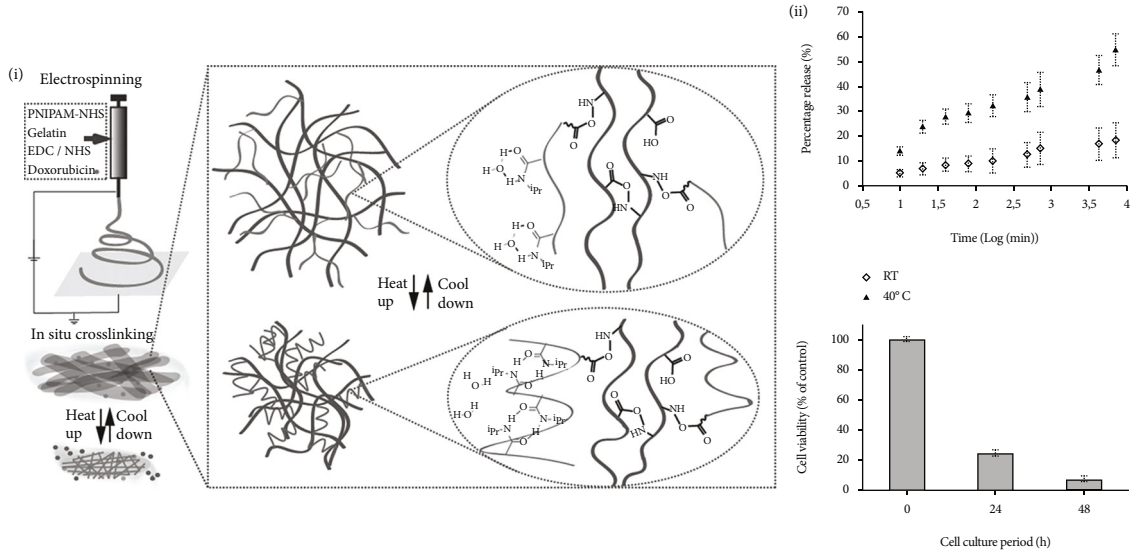
3.2. Tissue Engineering Applications. Tissue engineering is one of the most interesting interdisciplinary areas of research applying life science and engineering principles. Electrospun nanofiber scaffolds resemble the nanoscale characteristics of the natural extracellular matrix (ECM), which guide many aspects of cellular organization and survival. Because of their controllable properties, electrospun nanofiber scaffolds have been widely utilized in tissue engineering, such as the liver, kidney, skin, vessel, cardiac, and bone engineering (Table 2).

3.2.1. Skin. The skin is the body's first barrier and largest organ protecting human health. Thus, repairing damaged skin by tissue engineering plays an important role in treating various body conditions. Skin tissue repair by electrostatic spinning is a trending topic in current research.

For example, a multilayer electrospinning fiber membrane consisting of an external layer of polycaprolactone (PCL) and an internal layer of physically cross-linked

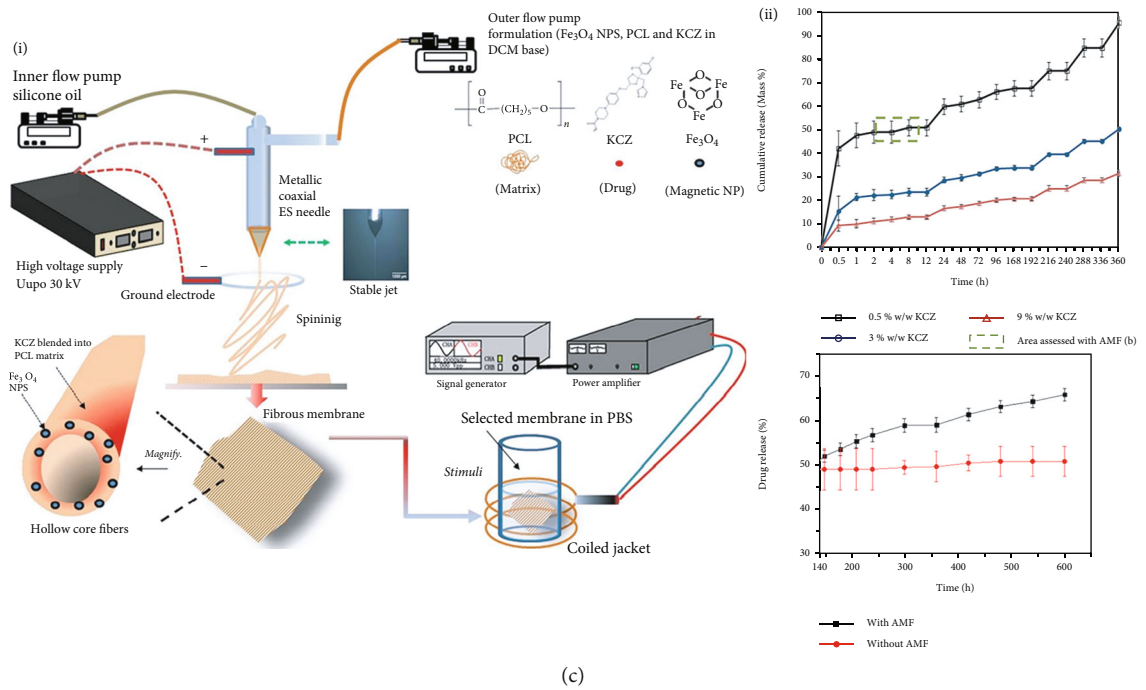


(a)



(b)

Figure 1: Continued.



(c)

Figure 1: Application of electrospinning technique in drug delivery. (a) (i) SEM images of nanofibers of (A) xanthan-chitosan (0.75–3%w/v) and (B) xanthan-chitosan-curcumin (0.75-3-2% w/v). (ii) Study of the transepithelial transport across Caco-2 cell monolayers of free curcumin, free curcumin (150 μM) + 3.0 mg xanthan-chitosan nanofibers (X-Ch + Cu), and 9.0 mg curcumin-loaded xanthan-chitosan nanofibers (X-Ch-Cu, fibers amount that corresponded to 150 μM released curcumin) at the donor chamber [10] (b) (i) Schematic of thermos-responsive PNIPAM–gelatin nanofibers. (ii) (A) Accumulative release of doxorubicin at different temperatures; (B) Hela cell viability after treating with the release doxorubicin [11] (c) (i) Schematic of fabrication of the hollow polycaprolactone composite fibers; (ii) (A) Release curves of KCZ-loaded fibrous membranes; (B) drug release curves of magnetic hollow fibers with 0.5% w/w KCZ loading with and without AMF [12].

sodium alginate (SA) embedding ZnO-NPs was prepared as wound healing patches (Figure 2(a)) [61]. This membrane demonstrated a highly porous structure, suitable mechanical properties, and good manageability. Moreover, the external PCL layer is hydrophobic and repels fluid, while the internal alginate layer prevents bacterial proliferation by removing wound exudates and allowing gas exchange, providing an ideal environment for cells, and promoting tissue regeneration. Additionally, the membrane exhibits drug delivery capabilities and can be easily adjusted to achieve controlled drug release properties. In another study, PCL combined with α-lactalbumin was utilized to fabricate electrospun nanofibrous mats (ENMs) for wound healing [62]. ENMs possess negligible cytotoxicity, adhere well, and promote the proliferation of fibroblasts. In this study, the composite stent promoted wound healing and showed comparable results within 16 days when compared other to wound dressings. In addition, ENM increased type I collagen synthesis and reduced scar formation, making it a promising biomaterial for burned skin.

Recently, a novel curcumin-loaded sandwich-like nanofibrous membrane (CSNM), using sequential electrospinning, were prepared for skin wound healing [63]. The study introduced that CSNM has excellent hemostatic properties, high antioxidant activity, and antibacterial activity. In the mechanism, this trilayer nanofibrous membrane can accelerate the wound healing by promoting the expression of CD31 and TGF-β in the early stage of wound and enhancing epidermal regeneration.

3.2.2. Bone. Although bone tissue is naturally regenerative enough to heal small lesions, such as cracks and certain types of fractures, defects above the critical size threshold (typically >2 cm, depending on the anatomical site) do not heal by themselves. Surgical excision of traumatic injury, degenerative disease, congenital defects, or tumors can result in large bone defects or leaks that require clinical intervention to achieve functional recovery and complete healing. Bone fixation with bioinert metal devices, autografts, and allografts is the current gold standard for the treatment of large bone defects. However, metal implants usually require subsequent surgical removal, the use of allografts carries the risk of disease transmission from donor material, and the use of autografts can lead to additional morbidity associated with donor healing. At present, the results show that defects from the above methods can be avoided, and bone tissue repair can be accelerated by using biomaterial electrospinning technology. For instance, a bioinspired osteoid composite structure prepared by electrospinning catecholamines and Ca^{2+}-containing collagen was utilized for repairing and regenerating bone defects and injuries [64]. In this study, the presence of divalent cations led to the local oxidative polymerization of catecholamines and the cross-linking of collagen nanofibers, resulting in a mat with mechanical

Table 2: Tissue engineering.

Application	Polymer	Cell	Ref
Bone	Collagen, catecholamines and Ca^{2+}	Human fetal osteoblasts	[64]
	PCL/PLA	Human mesenchymal stem cells (hMSCs) derived osteoblast	[84]
	Nanoclay (nanosilicate, NS)-functionalized 3D gelatine nanofibrous scaffold (GF/NS)	Human mesenchymal stem cells (hMSCs) derived osteoblast	[85]
	Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx)	HUVECs	[86]
	Bone-like extracellular matrix (ECM) and PCL	MLOA5 cells	[65]
	3D-printed PCL scaffolds with PLLA electrospun microfibrous (3D-M-EF) and nanofibrous (3D-N-EF) composites	M2 macrophages	[66]
Cardiac	Polyvinylidene fluoride (PVDF)	Human-induced pluripotent stem cell-derived cardiomyocytes	[71]
	PCL and gelatine	Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs)	[87]
	Carbon nanotube/silk fibroin	Neonatal rat cardiomyocytes	[72]
	Collagen, hyaluronic acid, and polyaniline (PANi)		[71]
	Poly (glycerol sebacate) elastomer and poly (lactic acid)	Newborn rat cardiomyocytes	[88]
	Poly (l-lactic acid) (PLLA), different ECM derived proteins such as collagen, gelatine, fibronectin, and poly-L-lysine	Adult human cardiac fibroblasts (AHCF)	[89]
Nerve	Poly(c-caprolactone) (PCL), chitosan and polypyrrole (PPy)	PC12 cells	[90]
	PLGA-PEG	SH-SY5Y human neural cell	[91]
	Poly (lactic-co-glycolic acid) (PLGA), laminin	Human adipose-derived stem cells (h-ADSCs) derived Schwann like cell	[92]
	Poly (lactic-co-glycolic acid) (PLGA), sphingolipid ceramide N-deacylase (SCDase)-hydrolyzed monosialotetrahexosylganglioside (LysoGM1)	Embryonic Sprague–Dawley rat primary neurons	[69]
	Poly(ε-caprolactone) (PCL) and carbon nanotubes (CNTs) with optimized matrix alignment	Neural cells	[70]
	Nimodipine; PLGA	Schwann cells	[93]
Skin	Poly(lactic-co-glycolic) acid (PLGA)/fibrin polymers	Fibroblasts	[94]
	Polycaprolactone; sodium alginate	Fibroblasts	[61]
	Sulfonated polyether ether ketone (SPEEK) nanofibrous	HaCaT keratinocytes and fibroblasts	[95]
	α-Lactalbumin (ALA), polycaprolactone (PCL)	Fibroblasts	[62]
	Cellulose acetate (CA)-Manuka honey (MH) composite	NIH 3 T3 cell	[96]
	Liraglutide-loaded PLGA/gelatine	Endothelial cells	[97]
	Curcumin-loaded sandwich-like nanofibrous membrane (CSNM)	Blood cells, fibroblasts and myofibroblasts	[63]
Vessel	Hyaluronic acid oligosaccharides (oHAs), collagen	Vascular endothelial cell (EC)	[98]
	Poly (ε-caprolactone) (PCL), poly (D, L-lactide-co-glycolide) (PLGA) and gelatine	Smooth muscle cells (SMCs) and endothelial cells (ECs)	[99]
	Matrix metallopeptidase 2 (MMP2), vascular endothelial growth factor (VEGF), heparin, PCL	HUVECs	[100]
	Polyglycolic acid (PGA)	Human dermal fibroblasts	[67]
	Bacterial cellulose (BC) and submicrofibrous cellulose acetate (CA)	HUVECs	[101]
	PELCL-REDV, microRNA-126, microRNA-145	Vascular smooth muscle cells (SMCs)	[68]

PCL: polycaprolactone.

strength and luminescence properties. In addition, ammonium carbonate can also mineralize cushions, polymerize catecholamines, and precipitate amorphous calcium carbonate $CaCO_3$. Due to the participation of collagen material, the composite scaffolds possess good mechanical properties, and the Young's modulus results show that they are close to the limit of cancellous bone. Biological studies have demonstrated that human fetal osteoblasts inoculated on this composite scaffold possess higher bone protein expression and cell adhesion than original collagen or tissue culture plates.

In another study, a biomimetic scaffold was prepared for osteogenesis and angiogenesis [65]. In this study, a

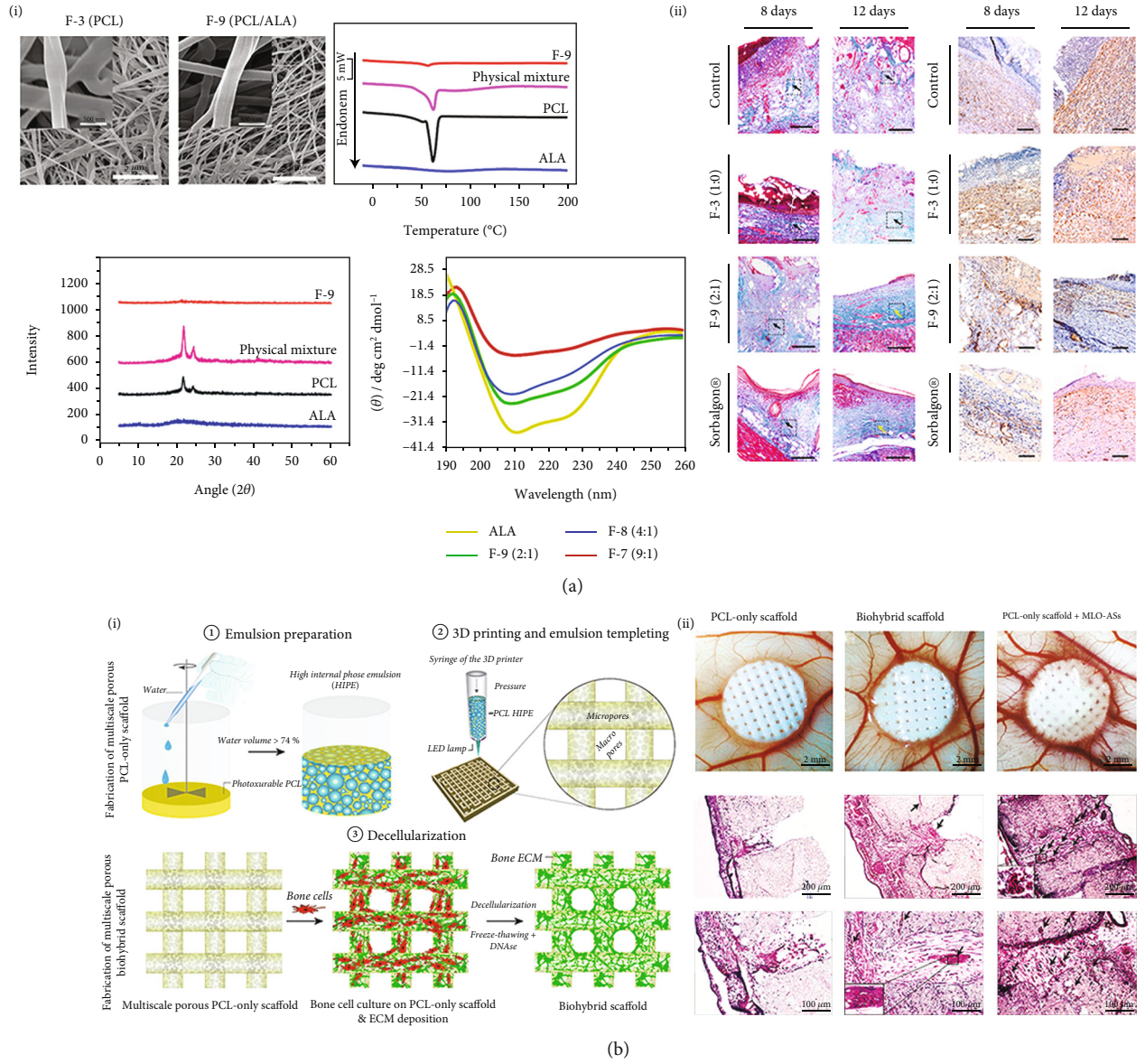


Figure 2: Application of electrospinning technique in skin and bone regeneration. (a) (i) Characterization of F-3 and F-9; (ii) the images of Masson-stained histological sections after 8 days and 12 days of treatment with F-3 and F-9 [1]. (b) (i) Schematic of preparation of multiscale porous photocurable polycaprolactone (PCL) scaffolds and multiscale porous biohybrid scaffolds; (ii) evaluation of the angiogenic potential of PCL-only, PCL-only populated with murine long bone osteocyte cells (MLO-A5s), and biohybrid scaffolds using chick chorioallantoic membrane (CAM) assay [2].

multilayer porous PCL matrix scaffold was successfully prepared by the combination of emulsion template technology and 3D printing technology (Figure 2(b)). After bone cells were cultured on these scaffolds for bone ECM deposition, the acellular process successfully removed 95% of the DNA and retained most of the collagen and minerals on the scaffolds. Due to ECM deposition, cell adhesion and proliferation were enhanced, and thus, angiogenesis activity was enhanced. Therefore, these ECM-decorated multiscale porous scaffolds have potential as a bone graft substitute. More recently, 3D printing and electrospinning technology were utilized to combined PCL scaffolds with PLLA fibers for bone regeneration [66]. In this study, 3D-printed PCL scaffolds with PLLA electrospun microfibrous (3D-M-EF) and nanofibrous (3D-N-EF) composites were constructed using layer-by-layer deposition and electrospinning techniques, and their immunomodulatory and subsequent osteogenic effects were explored. The results showed that 3D-MEF scaffolds polarized more RAW264.7 cells toward alternative activated macrophages (m2). Furthermore, 3D-MEF scaffolds transferred RAW264.7 cells to the M2 phenotype via PI3K/AKT signaling and enhanced VEGF and BMP-2 expression. Conditioned media from RAW264.7 cells in 3D-M-EF scaffolds promoted osteogenesis of MC3T3-E1 cells. Furthermore, in an in vivo study of repairing calcium-calcium defects in rats, 3D-MEF scaffolds increased polarization of M2 macrophages, enhanced angiogenesis, and accelerated new bone formation.

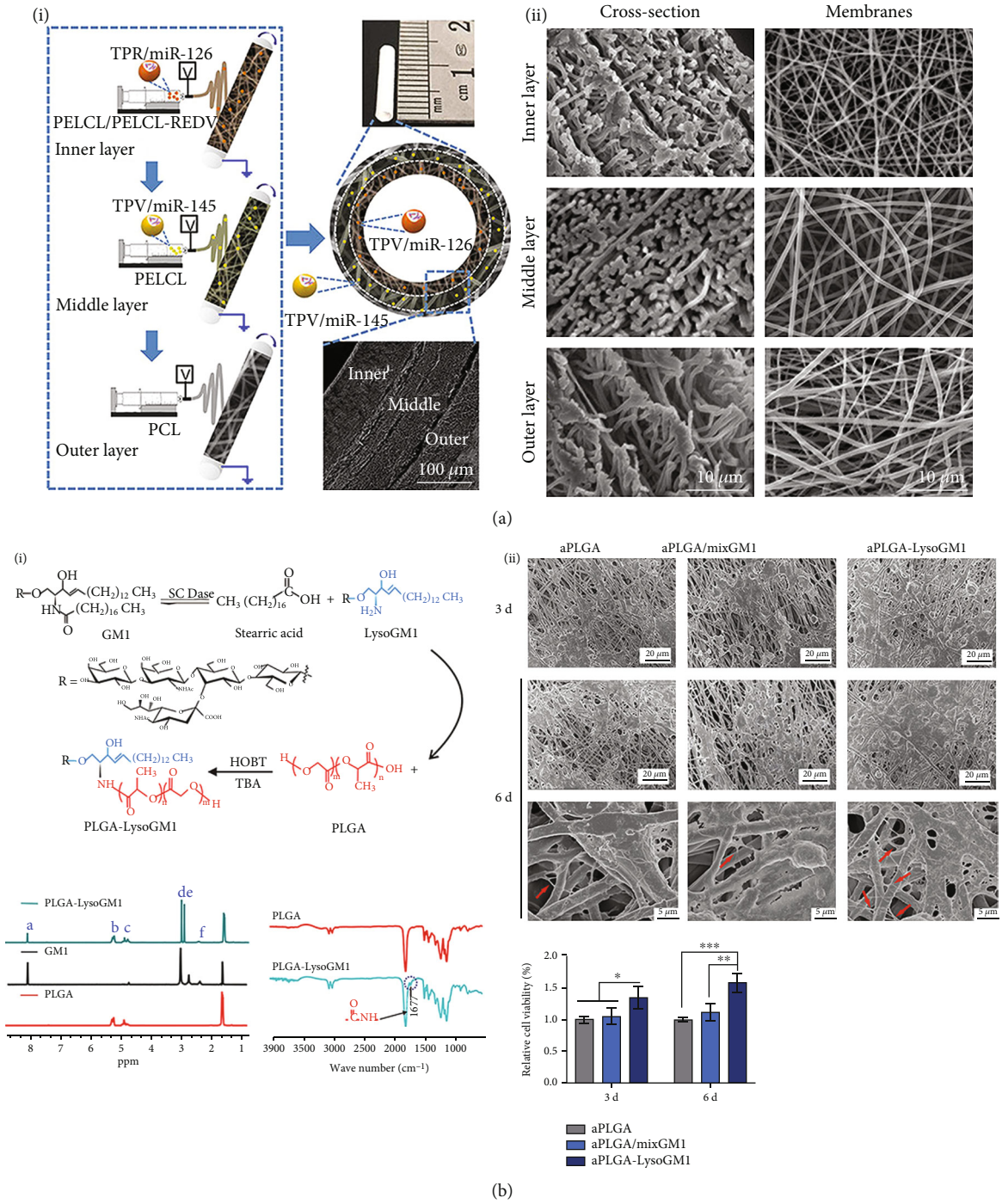


Figure 3: Application of electrospinning technique in vascular and brain regeneration. (a) (i) Schematic preparation of the Trilayered Vascular Grafts Encapsulating miR-126 and miR-145; (ii) SEM images of cross-sectional grafts and surfaces of electrospun membranes [3] (b) (i) Chemical synthesis route of PLGA-LysoGM1. (ii) SEM images of aPLGA, aPLGA/mixGM1 and aPLGA-LysoGM1, and neuronal cells' viability on these scaffolds [4].

3.2.3. Vessels. Electrospinning nanofibers mimic the extracellular matrix, providing a three-dimensional microenvironment in which cells can easily obtain clear functional morphology, maintain connections between cells, and promote cell bioactivity, dynamic growth, and differentiation. Based on the characteristics of electrospun fibers, the application of electrospun nanofibers as biomaterials to promote angiogenesis and neovascularization in engineered vascular transplantation has also attracted attention. For example, human skin fibroblasts were cultured on polyglycolic acid (PGA) electrospun scaffolds and subjected to circumferential mechanical tensile stimulation through a pulsed perfusion system [67]. In this study, a PGA scaffold was fabricated by electrospinning, and the pore size and bulkiness were

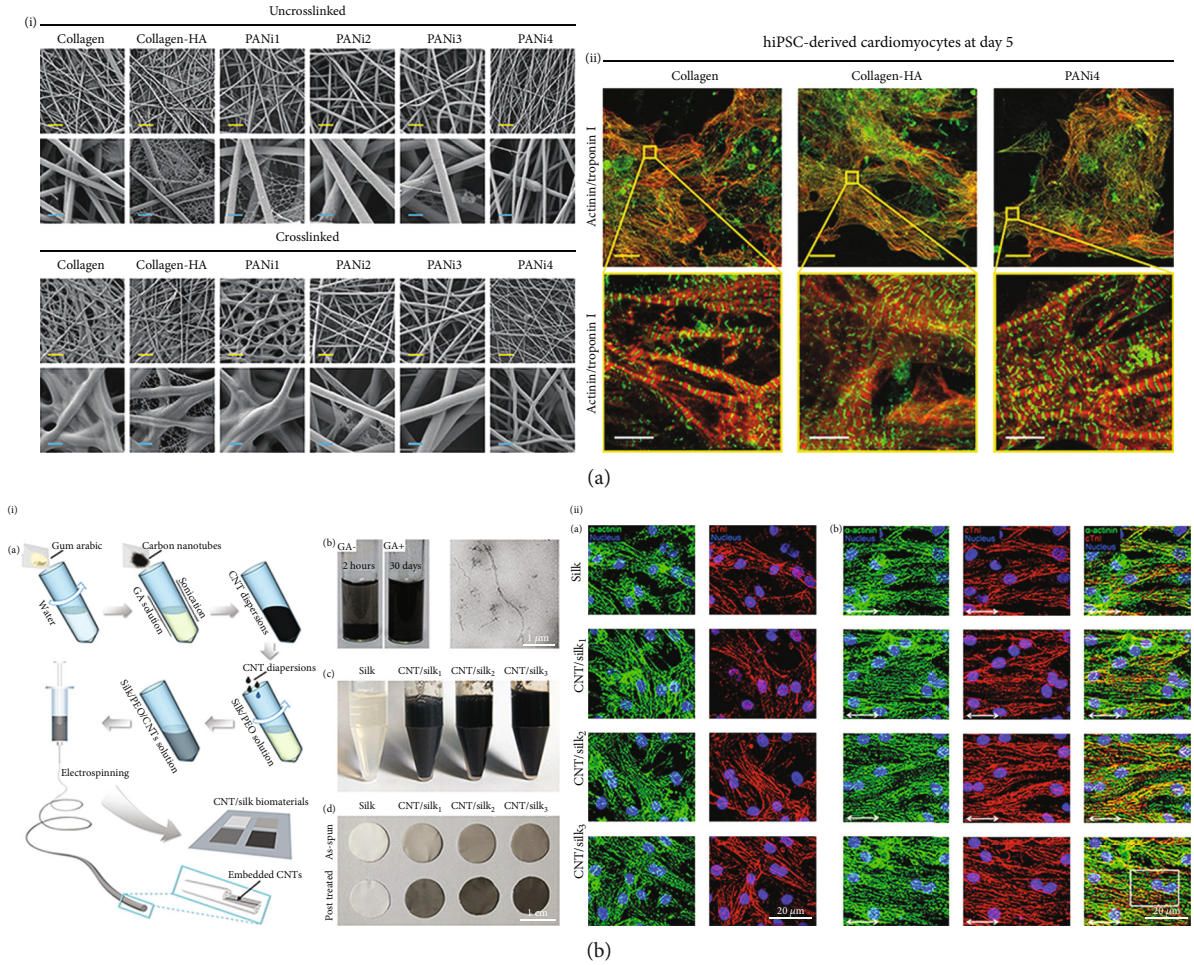


Figure 4: Application of electrospinning technique in cardiac tissue regeneration. (a) (i) SEM images of electrospun collagen, collagen/HA, and collagen/HA/PANi blends before and after crosslinking with glutaraldehyde vapor; (ii) confocal images of hiPSC-derived cardiomyocytes cultured on electrospun fiber mats at day 5 [5] (b) (i) Schematic fabrication of CNT/silk electrospun scaffolds. (ii) Immunofluorescence images costaining α-actinin and cTnI show the formation of sarcomere structures in cardiomyocytes cultured on (A) random and (B) aligned scaffolds [6].

increased by coelectrospraying sacrificial polyethylene oxide particles. Compared with an engineered blood vessel cultured under static conditions, the collagen of this engineered blood vessel with a pulsatile perfusion system was twice that of the statically cultured blood vessel. In addition, the stress–strain curve of tissue-engineered vessels after mechanical stretching showed that the ultimate tensile strength and elastic modulus of tissue-engineered vessels were significantly increased. The combination of the versatile characteristics of the electrospinning gallows and the bionic culture system can produce suitable tissue-engineered blood vessels composed of extracellular matrix as vascular grafts. In another study, to regulate angiogenesis, a small-diameter three-layer tissue engineering vascular graft with biological activity was prepared to inhibit intimal hyperplasia and prevent calcification [68]. In this study, microRNA-126 and microRNA-145 were wrapped in the inner and middle layers of the fibers to quickly complete endothelialization and inhibit calcium deposition (Figure 3(a)(i)). At the same time, the local biological activities of microRNA-126 and microRNA-145 in the three-layer vascular graft may regulate inflammation and inhibit calcification by promoting the conversion of macrophages to the anti-inflammatory M2 phenotype (Figure 3(a)(ii)). These findings showed that a three-layer electrospun graft that delivers dual microRNAs locally can be used as a bioactive alternative to artificial small-caliber blood vessels.

3.2.4. Nerve Tissue. The irreversibility of nerve function injury makes the repair of brain injury an especially difficult problem. At present, studies have found that electrospinning materials can be used for the repair of nerve units and provide a treatment strategy for brain tissue regeneration. For instance, a directional biofunctional scaffold (aPLGA-LysoGM1) was developed and used for electrospinning to form a neatly arranged fiber grid for nerve repair (Figure 3(b)) [69]. Among them, polylactic acid-glycolic acid (PLGA) was hydrolyzed by sphingolipid ceramide N-deacylase (SCDase) to hydrolyze monosialotetrahexose ganglioside (LysoGM1) and modified by electrospinning

Table 3: Biosensors (no microfluidic-based and microfluidic-based).

Polymer	Analyte	Sensitivity	LOD	Range	REF
Fe3O4 NPs), polyacrylonitrile nanofibers (PANnFs)	Vitamin-D3	0.90 μA ng^{-1} mL cm^{-2}	0.12 ng mL^{-1}	10–100 ng mL^{-1}	[102]
Poly (acrylic acid) (PAA), poly(3,4-ethylenedioxythiophene) (PEDOT), NBR rubber	Non-Hodgkin lymphoma gene	1aM (1 × 10(−18) mol/L)	NR	NR	[103]
Alpha-Fe2O3, gamma-Fe2O3	Small biomolecules				[104]
Carboxylated multiwalled carbon nanotubes (MWCNTs)-doped polycaprolactam 6 (PA6) electrospun nanofibers (PA6-MWCNTs)	Antioncogene		0.5fM	1.0 × 10(−15) ~1.0 × 10(−12) M	[105]
Polycaprolactone (PCL)	Zika viral cDNA		0.5 nM		[106]
Polycaprolactone (PCL)	Zika virus DNA		0.5 nM		[107]
Au-Ag/Co3O4 nanofibers	Hydrogen peroxide released from human cancer cells	1241.1muAmM (-1) cm (-2)	0.01 μM	0.05-5000 μM	[108]
Graphene-doped Mn2O3 nanofibers (GMnO) and polyaniline/polyethylene oxide (PANi/PEO) nanofibers	DNA hybridization		1.9fM	10fM-1microM	[109]
Polyimide (PI)	Pressure response	2.204 kPa 1 at 3.5–4.1 pa	3.5 pa	0–1.388 MPa	[9]

to form a neatly arranged fiber network. As the ganglioside of the neuron membrane, functionalized LysoGM1 gives the scaffold unique biological characteristics, which are beneficial to the growth of neurons and the regeneration of damaged brain tissue. In addition, arrayed PLga-Lysogm1 fibers serve as a topographical cue to guide neurite elongation, which is essential for the formation of tissue synaptic networks (neural networks). *In vitro* studies showed that directional biofunctional scaffolds promoted neuronal activity, neurite outgrowth, and synapse formation and protected neurons from stress-related damage. In addition, in a rat brain trauma model, more endogenous neurons migrated and infiltrated into the defect area in the rat brain of the implanted aPLGA-LysoGM1 scaffold compared with an alternative scaffold. These results indicated that the directed biofunctional APLga-LysoGM1 stent is a promising treatment strategy for brain tissue regeneration after traumatic brain injury.

More recently, a novel conductive composite fiber, prepared by poly(ε-caprolactone) (PCL) and carbon nanotubes (CNTs) with different orientation degrees by electrospinning at various rotational speed, showing highly sensitive to the fiber anisotropy and electrical conductivity [70]. Consequently, the conductive PCL/CNTs composite fiber were demonstrated to have a great potential as instructive candidates for physical nerve injury.

3.2.5. Parenchymal Organ. Electrospinning is not only used for the tissue reconstruction of skin, blood vessels, and bone but also as an ideal material for the tissue engineering of parenchymal organs. The most frequently used organ is the repair of heart tissue. For example, an electrospun pad containing conductive polyaniline, collagen, and/or hyaluronic acid has been attached to cardiomyocytes for myocardial tissue regeneration (Figure 4) [71]. These fiber pads contained collagen (9.89%), hyaluronic acid (1.1%), and polyaniline (PANi, 1.34%), which enabled cardiomyocytes to have longer contraction times, higher contraction amplitudes, and lower beating rates (Figure 4(a)). Moreover, fibrous pads exhibited good cytotoxicity and adhesion properties. In another study, a fully aqueous process was used to fabricate conductive carbon nanotube/silk protein (CNT/silk) electrospun scaffolds in a rat cardiomyocyte culture (Figure 4(b)) [72]. In this study, carbon nanotubes were well dispersed in the nanofibers and provided scaffolds with enhanced conductivity and biocompatibility, which could be used for the culture of neonatal rat cardiomyocytes and to enhance the expression of heart-specific proteins. Additionally, the aligned CNT/silk fibroin composite scaffolds exhibited the ability to guide the oriented organization of cardiac tissues and the bio mimic distribution of sarcomeres and gap junctions. These findings demonstrated the great potential of CNT/silk scaffolds prepared using this water treatment method to support the formation of enhanced heart tissue.

4. Application in Biosensors

Nanofiber membranes possess a high surface-to-volume ratio and porous structure, making them excellent candidate materials for chemical detection and biosensor applications (Table 3). The blood glucose meter is the earliest developed biosensor for diagnosis. Currently, electrospinning technology provides a feasible technical route for optimizing the performance of glucose meters [73]. Electrospun metal oxide nanofibers and noble metal nanofibers can form high-porosity three-dimensional networks that provide high electrical conductivity, minimum diffusion resistance of analyte, and enhanced electron transfer, which is of great significance in glucose detection. One of the simplest methods in the preparation of a glucometer is to mix glucose oxidase into a solution and then electrospun it. After immersing the electrospinning-coated electrode in a glucose solution,

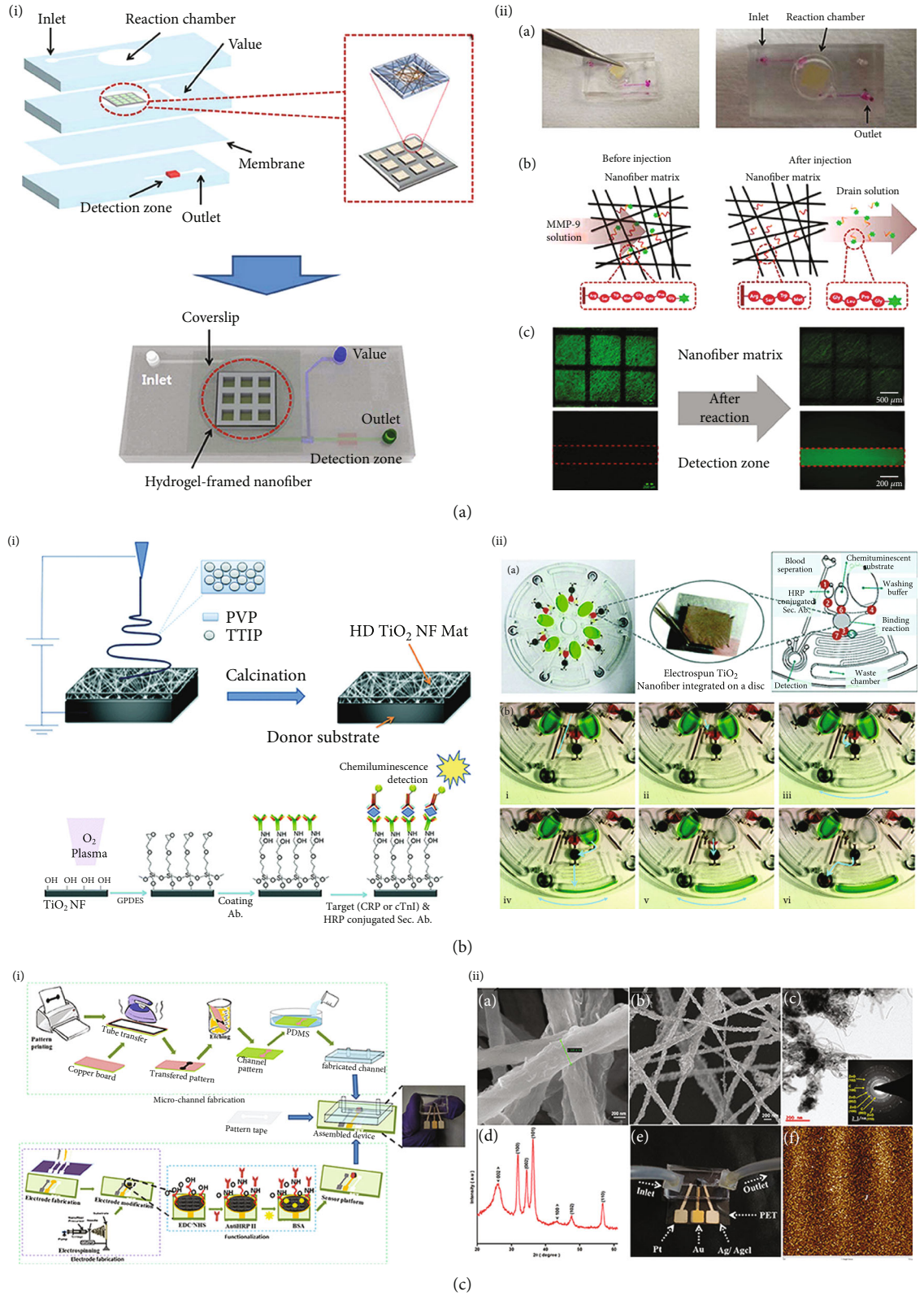


Figure 5: Application of electrospinning technique in biosensors. (a) (i) Schematic of the MMP-9 detecting microfluidic device. (ii) The microfluidic device with inserted hydrogel-framed nanofiber matrix immobilizing MMP-9-specific peptides [7] (b) (i) Schematic diagram of the TiO2 NF mat on a donor substrate by electrospinning and calcination. (ii) Microfluidic device design and operation images of the device integrated with a TiO2 NF mat [8] (c) (i) Schematic of fabrication of the biochip with inserted C-ZnONFs fibers for infectious detection. (ii) (A-B) SEM image of C-ZnONFs; (C) TEM image of nanofiber mat; (D) XRD results of C-ZnONFs; (E) Optical image of the fabricated device connected with inlet and outlet tubing; (F) 2D AFM image of the C-ZnONFs modified sensing electrode [9].

a subsequent change in current can be detected. However, the sensor fails due to loss of enzyme activity due to changes in environmental parameters (such as temperature and pH). However, electrospinning nanofibers and their composites overcomes the shortcomings of previous studies and improves the overall sensing performance of glucose measurement devices. Functionalized electrospinning materials have a high surface-to-volume ratio, electrical conductivity, and unique optoelectronic properties. They also have been widely used in the preparation of biosensor applications. Therefore, electrospinning biosensors based on microfluidics offer a unique advantage in the detection field. For instance, an electrospun nanofiber matrix was utilized to fix FITC-labeled MMP-9 to prepare a sensing platform for MMP detection (Figure 5(a)) [74]. In this biosensor, FITC-labeled MMP-9-specific peptides were covalently fixed to the electrospinning nanofiber matrix and inserted into a microfluidic device to form a reaction chamber and a detection area (Figure 5(a)(i)). In this platform, a fixed peptide reacted with a solution containing MMP-9 in the reaction chamber, resulting in cleavage of the FITC-containing peptide fragment and a subsequent fluorescence flow in the detection area (Figure 5(a)(ii)). The concentration of MMP-9 is directly proportional to the generated fluorescence signal, so its content can be detected. Due to the large surface area of the nanofibers and the small size of the microsystems, this biosensor showed a faster response time (30 minutes) and lower detection limits (10 pM).

In another study, a microfluidic platform-based biosensor composed of TiO_2 nanofiber pads was prepared for the detection of cardiac biomarkers (C-reactive protein and troponin I) [75]. This platform was sensitive for detecting serum proteins with a wide dynamic range within 30 minutes (Figure 5(b)(i)). TiO_2 nanofibers provided a high specific surface area and active functional groups that captured a considerable number of antibodies on the surface. In addition, the equipment provided effective mixing and cleaning functions to improve the signal-to-noise ratio, resulting in improved overall detection sensitivity (Figure 5(b)(ii)). This biosensor exhibited a wide dynamic range of six orders of magnitude from $1\,pg\,mL^{(-1)}$ (~8 fM) to $100\,ng\,mL^{(-1)}$ (~0.8 pM), a low detection limit of $0.8\,pg\,mL^{(-1)}$ (~6 fM) for CRP spiked in CRP-free serum, and a dynamic range of $10\,pg\,mL^{(-1)}$ (~0.4 pM) to $100\,ng\,mL^{(-1)}$ (~4 nM) with a detection limit of $37\,pg\,mL^{(-1)}$ (~1.5 pM) for cTnI spiked in whole blood.

In another study, an electrospun-based microfluidic platform was utilized for an infectious marker for a malaria-specific antigen [76]. In this platform, the microfluidic channel was fabricated by the tune transfer method and integrated with a sensing component, which comprised antibody-immobilized carbon nanotube-zinc oxide (C-ZnO) nanofibers (Figure 5(c)(i)). Here, C-ZnO nanofibers were fabricated by the electrospun technique and conjugated with histidine-rich protein II antibodies (AntiHRP II) for the detection of infectious malaria-specific antigens. The analyte was evaluated using the pulse voltammetry method. This chip showed a high sensitivity of $1.19\,mA/((g\,mL^{-1})/cm^2)$ over a wide detection range ($10\,fg/mL$ to $100\,\mu g/mL$) with a low detection limit of $7.5\,fg/mL$ towards the malaria-specific antigen (Figure 5(c)(ii)). Thus, this integrated electrospinning technology biochip provides a promising cost-effective method for detecting biomarkers of several other infectious diseases.

5. Conclusion

The unique properties of electrospinning (including ECM structure, large surface area, and high porosity) have been driving the development of new strategies in biomedical, textile, and electrode sensor design research. By designing the surface chemistry, morphological structure, and other electrochemical elements of the scaffold, electrospun materials can be applied to the delivery of various drugs and the growth and differentiation of cells. Meanwhile, they can be used to improve the performance of electrodes and improve the functions of sensors. They can even be widely used in the textile industry to develop technologically emerging materials.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Yimin Wang and Liguo Liang designed the study; Yimin Wang and Siming Lu contributed to the writing—original draft preparation; supervision was performed by Liguo Liang and Jiayong Zheng.; funding acquisition was contributed by Liguo Liang. All authors have read and agreed to the published version of the manuscript. Yimin Wang and Siming Lu are the co-first authors.

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Supplementary Materials

Applications of electrospinning include drug delivery, biosensors, textile, and tissue engineering (Skin, Bone, Vessels, Nerve, and Parenchymal), etc. *(Supplementary Materials)*

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