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Keywords: electrospinning, microfiber, electrospinning improvement, biomedical application, electrospinning principle, nanofiber

Biomedical Applications and Research Progress of Electrospinning Technology and Electrospinning Nanofibers

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Abstract

Electrospinning technology is one of the most popular technologies in nanoscience and nanotechnology, there are a variety of polymers can be used to spin (natural materials, composite materials and inorganic materials) into micro/nanofibers, obtained micro/nanofibers usually have special structures or special functions with excellent flexibility and adjustability. In recent years, electrospinning has attracted more and more attention of researchers, showing great application potentials in the field of biomedicine or biomedical engineering. In this review, we will introduce the working principle and types of electrospinning, the improvements of electrospinning devices, the properties and property applications of electrospinning micro/nanofibers in recent years, and emphasis on the applications of electrospinning micro/nanofibers in biomedical or biomedical engineering. At the end of this review, the prospective and challenges of application of electrospinning technology and micro/nanofibers was also discussed, We hoped this review may provide some ideas and inspirations for the applications of electrospinning technology in biomedical or biomedical engineering.

Keywords: electrospinning, micro/nanofiber, electrospinning principle, electrospinning improvement, biomedical application.

1. Introduction

Electrospinning technology is one of the main technologies of nanoscience and nanotechnology. Because it can spin a variety of polymers into uniform micro/nanofibers in a continuous and large-scale manner, it is becoming more and more popular in drug delivery[1, 2], tissue engineering[3, 4, 5, 6], wound dressings[7, 8], food packaging[9, 10], sewage treatment[11], energy conversion and storage[12, 13], electronics[14, 15], etc. At present, there are many treatment methods for modifying or functionalizing micro/nanofibers prepared by electrospinning technology, including coaxial electrospinning technology[16, 17], core-shell electrospinning technology[18, 19], coating technology[20, 21, 22], drug delivery technology and surface chemical modification[23, 24, 25, 26] and other methods. These methods can obtain a variety of special structures or micro/nanofibers or micro/nanofiber scaffolds with special functions. The obtained micro/nanofibers or micro/nanofiber scaffolds have excellent flexibility and porosity and can simulate cells or organ tissue structure to a large extent to promote cell growth, proliferation and differentiation. Therefore,

the biomedical applications of electrospinning technology have attracted more and more attention from researchers. For example, Masoudi Rad M, et al. [27] found that the double-layer nanofiber membrane had a good promotion effect on bone tissue regeneration; Babitha S, et al.[28] prepared zein polydopamine (ZeinPDA) nanofibers by electrospinning technology, This kind of nanofibers are coated with TiO₂ nanoparticles conjugated with BMP-2 peptide, and played an important role in the treatment of orthopedic diseases; Zhang S, et al.[29] used electrospinning technology to prepare a novel bone tissue repair scaffold consisting of poly-3-hydroxybutyrate-co-3-hydroxyvalerate (PHBV)/polyaspartic acid (PAA) and nano-hydroxyapatite(nHA). Experimental results showed that the PHBV/PAA-nHA nanofiber scaffolds can be used as a good biomimetic material for bone tissue repair.

Due to the diverse processing technology and abundant resources of electrospinning technology and the obtained electrospinning micro/nano fibers have large surface area and porosity, more and more scientists apply electrospinning technology into biomedical engineering, especially in the treatment of neurodegenerative diseases, bone diseases, trauma, and tumors. In this paper, we will review the working principle, main applications, challenges and prospective of electrospinning, and highlights the applications of electrospinning technology in biomedical engineering in recent years.

2 The working principle and types of electrospinning technology

Typically, electrospinning systems consist of a high voltage power supply, a syringe pump with a metal nozzle, and a collecting device (a plate or a rotating drum). In the electrospinning process, a polymer solution or a molten polymer with a certain viscosity and conductivity is extruded through a syringe pump while an electric field is applied between the metal nozzle and the collecting device, a Taylor cone is formed at the metal nozzle because polymer droplets are caused by electrostatic action, and when the applied electric field overcomes the critical surface tension of the polymer liquid, the polymer-charged jet is ejected from the tip of the Taylor cone, stretched, and finally deposited on the collecting device to form a oriented or non-oriented fibers ranging from micrometer to nanometer in diameter.

Electrospinning is the process of polymer solution to overcome surface tension by higher electrostatic pressure. The electrospinning process mainly includes the following important parameters: (1) Electrospinning process (voltage, flow rate and metal nozzle-receiver distance), (2) Electrospinning solution (polymer concentration, polymer viscosity, and polymer conductivity), (3) Electrospinning environment (temperature and humidity). These parameters play an important role in the morphology and performance of electrospun nanofibers (fiber diameter, porosity and orientation), which can regulate cell behaviors and determine electrospinning nanofibers in biomedical applications.

At present, electrospinning technology has developed many kinds of types according to the preparation methods of the spinning solution, mainly including melt electrospinning technology [30], solution electrospinning technology[31], near-field electrospinning technology[32, 33] and near-field melt electrospinning technology[34]. In order to meet special requirements and uses, there are many different improvements in electrospinning technology. (1) Improvements of metal nozzle. For example, coaxial metal nozzle or three-axis concentric nozzle[35, 36, 37, 38, 39] can be used to obtain hollow nanofibers, porous nanofibers, or special structure nanofiber membranes[40]. On this basis, two or more different kinds of polymer solution are simultaneously electrospun using a coaxial metal nozzle[41] or a multi-axis concentric nozzle[42, 43, 44]; or mixed polymer solution and

nanoparticles into a syringe pump to obtain the nanofiber membrane with a special structure or with special functions because of nanoparticles. In order to overcome the limitations of conventional nozzle-based electrospinning devices, some scientists have developed some kinds of nozzle-free electrospinning device. For example, Seongjun Moon et al. [45] used a spiral probe-containing rotating cylinder instead of a conventional metal nozzle, compared with the traditional metal nozzles, this kind of nozzle-free electrospinning device has higher productivity and good processability. Heikki J. Nieminen et al. [46] reported a orifice-free electrospinning technique using high-intensity focused ultrasound, called ultrasound-enhanced electrospinning. In this technique, droplet liquid protrusion with Taylor cone is generated by ultrasound bursts in the surface of the polyethylene oxide polymer solution. When the polymer was charged with a high negative voltage, nanofibers ejected from protrusion and falled down the collector. (2) improvements of collecting device. For example, set grounded collector with a hemispherical bowl shape, which could obtain the typical cotton-ball like scaffold of fibers[47], and Jeong In Kim, et al.[48] developed a hemispherical nonconductive collector with a metal pin in the center and copper wire forming a circle around at the edge, which could fabricated a kind of 3D hemispherical transparent scaffold with radially aligned nanofibers. (3) Improvements of power supplies. A conventional melt electrospinning setup needs a large, heavy high-voltage power supply, so there are much limitations for application of melt electrospinning. Recently, some scientists change the huge power supply with a portable hand-operated generator, which demonstrated a great potential application in tissue engineering[49, 50]. Need to point out is, because of toxic solvents and low output of the traditional electrospinning technology, with increasing need for nanofibers, some scientists developed a new electrospinning method, called centrifugal electrospinning with a combination of centrifuge, electrostation, gravity, and auxiliary forces acting on the initial jet, which has the advantage of enabling the production of high-performance nanofibers with high yield[51, 52].

Figure 1. Several types of electrospinning technologies and their working principles or working system structures. a and b: a schematic of melt electrospinning and solution electrospinning[30] ; c: a apparatus of near-field electrospinning[31]; d: a apparatus of near-field melt electrospinning[34]; e: a schematic of co-axial electrospinning[35]; f: a schematic of tri-axial electrospinning process[37]; g: Self-powered melt electrospinning apparatus based on a handoperated Wimshurst generator[50]; h: Design of the solar cell and hand generator-powered portable e-spinning (SHPE) device: (a) 3D schematic drawing, (b) exploded drawing of the SHPE device assembly[49]; i: Schematic depicting the electrospinning parameters implemented in generating PCL (red), PEO (green), and PCL/PEO composite scaffold[41]; j: a schematic of electrospinning with grounded collector with a hemispherical bowl shape[47]; k: (A) Electrospinning setup of the fabrication of 3D radially oriented nanofibrous scaffolds, (B) copper wires, and metal pin in the hemispherical device designed to be electrically connected to each other[48]; l: Schematic diagram and realistic electrospinning machine of rotating probed cylinder[45].

3 Material source of electrospinning

Electrospinning has a large of source materials, including natural materials, composites and inorganic materials. It is reported that more than 200 natural materials or synthetic materials have been electrospun into nano-scale or micro-scale fibers. Here, we summarized polymers used for electrospinning and their applications in this review in Table 1.

Table 1 polymers used for electrospinning and their applications

Polymers	Solvents	Concentration	Fiber diameter	Advantages	Ref.
PCL/PGS/ β -TCP	chloroform: methanol (80:20)	15% (w/v)	513.6 $\pm$ 114.3 nm	osteoconductivity and degradation	[27]
PCL/PGS/chitosan	TFA	15% (w/v)	204 $\pm$ 8 nm	osteoconductivity, and degradation	[27]
PHBV/PAA/nHA	HFIP	8% (w/v)	368 $\pm$ 120 nm	bone tissue regeneration	[29]
PCL/Curcumin	/	/	4250 $\pm$ 1170nm	/	[30]
Ethyl cellulose/KET	ethanol	23% (w/v)	740 $\pm$ 60nm	sophisticated structural features	[37]
PCL/PVP	TFE, water	15% (w/v, PVP), 10% (w/v, PVP)	702 $\pm$ 327nm	drug release	[38]
PLA/PCL	/	/	/	wound healing	[44]
PDO/Curcumin	HFIP	9% (w/v)	1800 $\pm$ 700nm	tissue repair conjunctival	[53]
collagen/PLCL	HFIP	9% (w/w)	248.83 $\pm$ 26.44 nm	epithelial coloboma repair	[55]
calcined FeZnO/ PVA	distilled water	8% (w/v)	200-300 nm	catalytic applications	[56]
PAN/GCN	DMF	8% (w/v)	262 $\pm$ 6nm	purification of OPW	[57]
ZnO/ γ -Al ₂ O ₃	DMF	16% (w/v)	200 $\pm$ 20 nm	photocatalytic water treatment	[58]
silk fibroin/gelatin	formic acid	10% (w/v)	380.16 $\pm$ 49 nm	drug delivery	[59]

pectin/alginate/chitosan	DMSO/DMF	/	256.3 ± 21.5 nm	antibacterial activity, wound dressing	[60]
PLLA/PET	HFIP	15% (w/v)	/	biomolecule distribution and functions	[65]
PNIPAAm/EL100-55	ethanol	20% (w/v)	1116 ± 290 nm	drug delivery and tissue engineering	[84]
PCL	chloroform/ methanol	8% (w/v)	810 ± 420 nm	drug delivery	[68]
PLGA/PCL	THF, HFIP	12.5% (w/v, PCL), 5% (w/v, PLGA)	900 ± 200 nm	pH-sensitive for monitoring the cellular environment	[80]

NOTE: PGS: poly glycerol sebacate; PCL: polycaprolactone; β -TCP: Beta tri-calcium phosphate; PDO: Poly dioxanone; PHBV: poly-3-hydroxybutyrate-co-3-hydroxyvalerate; PAA: poly aspartic acid; HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol; nHA: Nano-hydroxyapatite; KET: ketoprofen; DMF: N,N-Dimethylformamide; THF: Tetrahydrofuran; PLCL: poly(L-lactic acid-co- ϵ -caprolactone); PVA: Polyvinyl alcohol; GCN: graphitic carbon nitride; PVP: Polyvinylpyrrolidone; OPW: oilfield produced water; PNIPAAm: polymer poly(N-isopropylacrylamide).

4 Properties of micro/nanofibers produced by electrospinning

4.1 Degradation characteristics

Some natural biomaterials or synthetic materials, such as poly lactic acid (PLA), poly (lactide-co-glycolide) (PLGA), poly(D,L-lactic acid) (PDLLA), polycaprolactone (PCL), collagen, hyaluronic acid, Sodium alginate, chitosan, polydioxanone (PDO), PGA and so on, because of their molecular structures or special properties, they can degrade naturally or in special conditions. Because of the favorable property, those degradable materials have a great potential application in drug delivery, tissue regeneration and biomedical engineering. For example, Mouthuy PA et al. [53] prepared PDO filaments containing various amounts of curcumin for soft tissue repair applications, found that low amounts of curcumin are more promising for stimulating tissue repair. Qinke Yao et al. [54] prepared nanofibrous scaffold by using collagen and poly(L-lactic acid-co- ϵ -caprolactone) (PLCL) for repairing conjunctival epithelial coloboma, found the nanofibrous scaffold had a high cell viability.

Generally, natural biomaterials or synthetic materials exist several different degradation ways, including water degradation, enzyme degradation, photocatalytic degradation and biodegradation. Degradation is a phenomenon including irregular breakage of polymer chains, elimination reaction of side group and low molecule, resulting in the decrease of polymerization degree and the loss of relative molecular mass under the external factors such as heat, light, mechanical force, chemical reagents, microorganism and so on. Need to point out is, water degradation as a kind of common and important degradation ways, is a process of interaction between water and functional groups in the molecule structure, which will result in breaking up of the chemical bonds. Water degradation can be catalyzed by acids, bases, salts or enzymes, and its sensitivity to hydrolysis is related to its chemical structure, morphology, size and body environment. Recently, due to the special properties of iron-doped ZnO nanoparticles[55], graphite carbonitride[55], or Ag/ZnO/ γ -Al₂O₃ nanofibers[57], they exhibit good photocatalytic degradation under visible or ultraviolet light irradiation, which

attracts more and more scientists to pay more attention to the field of renewable energy. For example, Sekar AD et al.[56] incorporated green mediated synthesis Fe-doped ZnO nanoparticles into PVA nanofibers through electrospinning, found that the calcined Fe-doped ZnO nanofibers had a good photocatalytic degradation activity; and Alias NH et al. [58] prepared a liquid-permeable self-supporting photocatalytic nanofiber mat by incorporated graphitic carbon nitride into polyacrylonitrile nanofibers using electrospinning, the photocatalytic nanofiber demonstrated 85.4% degradation of OPW under visible light irradiation, and improved the degradation to 96.6% under UV light.

4.2 Antibacterial characteristics

Antibacterial characteristics of nanofibers produced by electrospinning technology is one of important and popular characteristics for food packaging and biomedical applications. Usually, antibacterial or sterility is necessary in food packaging and biomedical engineering, electrospinning technology not only spin some materials with antimicrobial properties to obtain nanofibers with porous porosity and large surface area, but also maintain their antimicrobial properties; for some high-stability polymer materials, such as polypropylene, polyvinyl chloride, they also can obtain antibacterial micro- or nanofibers by encapsulating natural or synthetic antibacterial drugs through electrospinning technology. more and more scientists focus on developing new antibacterial agents or new antibacterial materials. For example, Dadras Chomachayi M et al. [59] prepared the nanofibrous membrane based on the silk fibroin and gelatin polymers, and added the thyme essential oil and doxycycline monohydrate as the antibacterial agents, found that TEO-loaded nanofibrous membrane and DCMH-loaded nanofibrous membrane both have the better cell compatibility and antibacterial effect of *Staphylococcus aureus* and *Klebsiella pneumoniae* bacteria. Chen S et al. [60] compared the properties of three different electrospun nanofibrous dressings of pectin, alginate and chitosan, found that pectinate nanofiber had the better exudates absorption, higher antibacterial activity than the alginate nanofiber and chitosan nanofiber. Sarhan WA et al.[61] developed green wound dressings fabricated by honey, polyvinyl alcohol and chitosan nanofibers loaded with bee venom, propolis and/or bacteriophage, which exhibited the most potent antibacterial activity.

Generally, there are three types of antibacterial agents applied in electrospinning: natural antibacterial agents, metallic nanoparticles and synthetic agents. Metallic nanoparticles, especially Ag, Cu and Zn nanoparticles, because of their superior antibacterial property, often used as antibacterial agents alone or combined with other kinds of antibacterial agents. For example, Zhou Y et al.[62] prepared colorful and multifunctional silk fabric modified by biogenic AgNPs and honeysuckle extract, this special silk fabric had excellent antibacterial activities against *E. coli* and *S. aureus*, and certain antioxidant activity. Ma K et al. [63] reported an environmentally benign Ag-containing nanocomposite coating with efficient antibacterial property fabricated on the metal implant via electrophoretic deposition. Wang Z et al[64] deposited ZnO on polyamide 6 nanofiber surface by atomic layer deposition and hydrothermal techniques, found that the ZnO/PA6 core-shell composite have a good efficiency in suppressing bacteria survivorship.

At present, the natural antibacterial agents commonly used in electrospinning technology are thyme essential oil[59], honey[61], bee venom[61], honeysuckle extract[62], caffeic acid[119], clove oil[121], and so on. They often have good antibacterial effect and they are also environmental-friendly. There is a great application limitation that it is difficult to quantify the

antibacterial components and the drug release is also slow or difficult because of the complexity of antibacterial components; there is another great application limitation in biomedical engineering that drug distribution in obtained natural antibiotics-loaded micro- or nanofibers is uneven. A summary of the antimicrobial agents involved in this review is given in Table 2.

So far, precise manipulation of biomolecular distribution and functions via biomolecule–matrix interaction is very important and challenging for tissue engineering and regenerative medicine. As a well-known biomimetic matrix, microfibers or nanofibers often lack the unique spatial complexity compared to their natural counterparts in vivo and thus cannot deliver fully the regulatory cues to biomolecules. For this purpose, Wenwu Xiao et al. [39] invented a facile and reliable method to fabricate micro- and nanostructured poly(L-lactic acid) (PLLA) fibrous matrices with spatial complexity by a combination of advanced electrospinning and agarose hydrogel stamp-based micropatterning. By using this kind of electrospinning, they fabricated three types of PLLA fibrous matrices including patterned nano-Ag/PLLA hybrid fibers, patterned bicompartiment polyethylene terephthalate/PLLA fibers, and patterned hollow PLLA fibers, those electrospinning fibers had an excellent performance for bacterial distribution and antibacterial performance, cell patterning and adhesion/spreading behaviors, and protein adsorption and delivery.

Figure 2. Patterning Multi-Nanostructured PLLA Fibrous Matrices via Solvent-Loaded Agarose Hydrogel Stamps: (a) Electrospinning Multi-Nanostructured Fibrous Matrices (i.e., Nano-Ag/PLLA Hybrid Fibers Using Conventional Electrospinning, Bicompartiment PET/PLLA Fibers Using Side-By-Side Electrospinning, Hollow PLLA Fibers Using Coaxial Electrospinning); (b) Fabricating Agarose Hydrogel Stamps via Soft Lithography; (c) Microcontacting Multi-Nanostructured Fibrous Matrices with Solvent-Loaded Agarose Hydrogel Stamps; (d) Immersing Coaxial Electrospun Fibrous Matrices into n-Hexane Solution to Extract Inner Castor Oil; and (e) Patterned Multi-Nanostructured Fibrous Matrices and Refreshable Agarose Hydrogel Stamps[65].

Figure 3. SEM images of three types of PLLA fibrous matrices and their applications of biomolecule distribution and functions[65].

Table 2. Antibacterial materials in this review

Materials Type	Antibacterial materials	Ref.
Metallic nanoparticles	Ag	[58], [62], [105]
	Cu/CuO	[126]
	Zn/ZnO	[55], [107], [120]
	thyme essential oil	[59]
	doxycycline monohydrate	[59]
Natural antibacterial agents	Pectin	[60]
	Chitosan	[60]
	bee venom	[61]
	Propolis	[61]
	clove oil	[121]
	Bacteriophage	[61]
	caffeic acid phenethyl ester	[119]
Synthetic agents	Chlorhexidine	[122]
	β -tricalcium phosphate	[122]
	poly(catechol)	[123]
	polyhydroxy antibiotics	[125]

4.3 Drug delivery

Drug delivery is one of main advantages of electrospinning technology. On one hand, Micro/nanofibers fabricated by electrospinning have larger porosity and larger surface area, porous nanofibers or bead nanofibers can also be obtained by adjusting the parameters of electrospinning process(different reagents or different reagent ratios, voltage and so on), which greatly improves the application of microfibers or nanofibers in drug delivery, on the other hand, electrospinning has a large of source materials and environmentally friendly technological process, have being attracting more and more scientists' attentions.

So far, drug blending with polymer solution is main way for drug delivery of electrospinning, another way is drugs chemically grafted onto the molecular structure of polymers by chemical bonding. For example, Li H et al.[66] prepared a kind of temperature and pH dual-responsive drug delivery systems including the thermosensitive polymer poly(N-isopropylacrylamide) and Ketoprofen by using electrospinning, which may lead to the development of multi-responsive fibers for drug delivery and tissue engineering; and Marek Rychter et al.[67] developed electrospun cilostazol-loaded (CIL) nanomembranes, which have an efficient delivery system for vascular implant applications. de Cassan D et al.[68] modified poly(ϵ -caprolactone) electrospinning membrane by using a chitosan grafted with PCL, which allow adsorption of oppositely charged nanoparticulate drug-delivery systems, this special drug-delivery system is possible to attach different polymeric and inorganic nanoparticulate drug-release systems of cationic or anionic nature. And recently, Lancina MG 3rd et al. [69] developed a kind of fast dissolving dendrimer-based nanofibers (DNF) as a topical delivery system, in vitro and in vivo experiments indicate electrospun dendrimer nanofibers are safe, effective and non-toxic. For wound healing applications to simultaneously mitigate bacterial colonization and to stimulate wound closure of infected wounds, Albright V et al.[70] reported a dual-releasing, multiscale system of biodegradable electrospun nanofibers coated with biocompatible micellar nanocarriers. In this system, transforming growth factor- β 1 is incorporated into polycaprolactone/collagen (PCL/Coll) nanofibers via electrospinning. For wound healing, and biocompatible nanocarriers of polypeptide-based block copolymer micelles are deposited onto the surfaces of PCL/Coll nanofibers using tannic acid as a binding partner for prevent infection. Xiaoming Lu et al. [71] developed a micelle-generating depot by blend electrospinning of PEG-poly (lactide) (PELA) copolymers, PMCPT and polyethylene oxide (PEO), this kind of micelle-generating depot had stronger tumor inhibitory efficacy, and could reduce systemic toxicity and more effective inhibition of tumor metastasis, demonstrating great potential for targeted cancer therapy with sustained efficacy.

Figure 4. Schematic representation of a modular system to simultaneously stimulate wound healing and mitigate infection. TGF- β 1 was incorporated into PCL/Coll nanofibers to stimulate fibroblast-to-myofibroblast differentiation. Micellar nanocarriers were deposited on the surface of PCL/Coll nanofibers and loaded with antibiotics to prevent infection[70].

Figure 5. Schematic illustration of the implantable micelle-generating depot for targeted and on demand drug delivery [70].

4.4 Conductivity

Another great application of electrospinning is electricity and photoelectricity area. Generally, the reason for the electrical conductivity of the electrospun membrane or electrospun fiber is that the conductive materials or the conductive material is added during the electrospinning process or in the electrospinning mixture. For example, Chuan Fan et al. [46] synthesized a supercapacitor electrodes systems including a flexible film electrode of NiCo_2O_4 and Co/C hybrid nanofibers through electrospinning combining with carbonization and hydrothermal reaction, which has a high specific capacitance of up to 1710 F g^{-1} at 5 mV s^{-1} . Jingxin Zhao et al. [47] developed a facile and cost-effective method to fabricate a highly capacitive positive electrode based on hierarchical ferric-cobalt-nickel ternary oxide nanowire arrays/graphene fibers and a negative electrode based on polyaniline-derived carbon nanorods/graphene fibers, this supercapacitor device has an operating voltage of 1.4 V , a specific capacitance up to 61.58 mF cm^{-2} , and an energy density reaching $16.76 \text{ } \mu\text{W} \cdot \text{h cm}^{-2}$. Sobolčiak P et al. [48] fabricated a novel 2D $\text{Ti}_3\text{C}_2\text{Tx}$ (MXene)-reinforced polyvinyl alcohol (PVA) nanofibers by electrospinning technique, and PVA nanofibers containing $0.14 \text{ wt. \%}$ $\text{Ti}_3\text{C}_2\text{Tx}$ exhibited dc conductivity of 0.8 mS/cm conductivity, improved mechanical and electrical characteristics. For better application of bone regeneration, Khorshidi S et al. [49] prepared a hydrogel/fiber scaffold possessing electrical conductivity, which possessed electrical conductivity due to the presence of polyaniline (PANI) and graphene nanoparticles. For rapid production of large-area, stretchable and transparent electrodes, Jiuk Jang, et al. [50] prepared a kind of ultra-long Ag nanofibers (AgNFs) as a large-area continuous network for transparent, stretchable electrodes and heaters by simple and low-cost electrospinning process, These nanofiber networks provide excellent optoelectronic properties (sheet resistance of $\sim 1.3 \text{ } \Omega \text{ per sq}$ with an optical transmittance of $\sim 90\%$) and mechanical reliability (90% stretchability).

For multi-element oxides and binary-metal oxides fabrication, Chaojiang Niu, et al. [51] designed a gradient electrospinning and controlled pyrolysis method to synthesize various

controllable 1D nanostructures, including mesoporous nanotubes, pea-like nanotubes and continuous nanowires, this simple technique is extended to various inorganic multi-element oxides, binary-metal oxides and single-metal oxides, and the nanotubes or nanowires exhibit ultrastable electrochemical performance when used in lithium-ion batteries, sodium-ion batteries and supercapacitors, respectively.

Figure 6. Fabrication and characterization of the Fe-Co-Ni ternary oxide nanowire arrays/GF. (a) Schematic illustration of the process to fabricate the Fe-Co-Ni ternary oxide nanowire arrays/GF; (b) and (c) SEM images of bare GF at low and high magnification, respectively; (d) and (e) SEM images of Fe-Co-Ni ternary oxide nanowire arrays coated on GF at low and high magnification, respectively; (f) XRD pattern of the FCNO nanowire array; and (g) N₂ adsorption/desorption isotherms of the FCNO nanowire arrays/GF, inset image shows the pore size distribution calculated using the nonlocal density functional theory (NLDFT) model[73].

Figure 7. Schematics of the gradient electrospinning and controlled pyrolysis method. (a) Preparation process of mesoporous nanotubes. (1) After the electrospinning process, the low-, middle- and high-molecular-weight PVA tend to be distributed into three layers in the radial direction of composite nanowires. (2) As the temperature is slowly increased, the inner low-weight PVA first pyrolyses and moves towards the boundary of the low-/middleweight PVA, carrying the inorganic materials. Then the middle-weight PVA pyrolyses and moves towards the high-weight PVA as well. (3) All of the preliminary pyrolysed PVA and inorganic materials converge together in the tube walls. (4) After sintering in air, all of the PVA pyrolyse and uniform mesoporous nanotubes are obtained, which are composed of tiny inorganic nanoparticles. On the other hand, after high-temperature sintering under argon, PVA carbonize, uniform mesoporous nanotubes are also obtained, which consists of inorganic nanoparticles and carbon nanotubes. The mesopores result from the decomposition of the inorganic materials and a part of PVA polymers. (b) Preparation process of pea-like nanotubes. (1) After the electrospinning process, the composite nanowires are directly and immediately placed into a furnace in air, which is preheated to and maintained at 300 C. (2, 3) All of the PVA decompose at the same time and rapidly move towards the outer high-weight PVA layer without carrying the inorganic materials, leaving them in the centre. (4) After high-temperature sintering under argon, the outer PVA carbonize and the inner inorganic materials develop into nanoparticles, forming pea-like nanotubes[77].

Figure 8. Expansion of the gradient electrospinning and controlled pyrolysis method. (a–o) SEM and TEM images of multi-element oxides ($\text{Li}_3\text{V}_2(\text{PO}_4)_3$, $\text{Na}_3\text{V}_2(\text{PO}_4)_3$, $\text{Na}_{0.7}\text{Fe}_{0.7}\text{Mn}_{0.3}\text{O}_2$ and $\text{LiNi}_{1/3}\text{Co}_{1/3}\text{Mn}_{1/3}\text{O}_2$), binary-metal oxides (LiMn_2O_4 , LiCoO_2 , NiCo_2O_4 and LiV_3O_8) and single-metal oxides (CuO , Co_3O_4 , SnO_2 and MnO_2) mesoporous nanotubes, respectively, scale bars, 100 nm. (p–t) SEM and TEM images of pea-like nanotubes (Co , LiCoO_2 , $\text{Li}_3\text{V}_2(\text{PO}_4)_3$ and $\text{Na}_{0.7}\text{Fe}_{0.7}\text{Mn}_{0.3}\text{O}_2$) from different species with scale bars at 200 nm. The scale bars for the inset TEM images (e, j, o, t) are 100 nm[77].

4.5 pH sensitivity and thermo-sensitivity

For smart or effective controlling the drug release behavior, pH-responsive polymers or pH-sensitive groups usually be used as an additive. For example, Sang Q et al. [52] prepared a dual-drug-loaded pH-responsive fiber scaffolds by coaxial electrospinning, The shell was made up of a mixture of gelatin and sodium bicarbonate (added to provide pH-sensitivity), and was loaded with the anti-inflammatory drug ciprofloxacin; the core comprised poly (lactide-co- ϵ -caprolactone) with the chemotherapeutic doxorubicin hydrochloride. Jia D et al. [53] prepared a core/shell fibers containing the active pharmaceutical ingredients indomethacin (IMC) or mebeverine hydrochloride (MB-HCl), the shell of the fibers was fabricated from the pH sensitive Eudragit S100 polymer, while the drug-loaded core was based on the mucoadhesive poly(ethylene oxide) (PEO). For monitoring

pH within microenvironments of cultured cells in real-time, Di W, et al. [54] developed biodegradable and biocompatible polymer-based nanofibers, Sensors to monitor pH were created by directly electrospinning the sensor components within a polymeric matrix, which will provide a scaffold for tissue growth while simultaneously monitoring the extracellular environment. Interestingly, Daewoo Han et al. [55] produced a kind of core-sheath fiber with controlled multi-pH responses. In detail, the Core-sheath fibers made of Eudragit L 100 (EL100) core and Eudragit S 100 (ES100) sheath provide protection and/or controlled release of core material at pH 6 by adjusting the sheath thickness (controlled by the flow rate of source polymer solution). The thickest sheath (~250 nm) provides the least core release~1.25%/h, while the thinnest sheath (~140 nm) provides much quicker release ~16.75%/h. Furthermore, switching core and sheath material dramatically altered the pH response.

For thermoresponsive controlled release, Lv Y et al. [56] prepared core-sheath nanofibers by blending thermoresponsive poly-(N-isopropylacrylamide) (as core) and hydrophobic ethyl cellulose (as sheath) through coaxial electrospinning, in vitro drug-release study of nanofibers with KET displayed that the coaxial nanofibers were able to synergistically combine the characteristics of the 2 polymers producing a temperature-sensitive drug delivery system with sustained-release properties. Need to point out is, some scientists for more effectively regulating the drug release process, they design the a smart drug release system with the function of pH-response and thermo-response. For example, Yuan H et al. [57] synthesized chitosan-graft-poly (N-isopropylacrylamide) (CTS-g-PNIPAAm) copolymer by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxy succinimide (NHS) as grafting agents to graft carboxyl-terminated PNIPAAm (PNIPAAm-COOH) chains onto the CTS biomacromolecules, and then CTS-g-PNIPAAm with or without bovine serum albumin (BSA) was fabricated into nanofibers through electrospinning using poly(ethylene oxide) (PEO, 10 wt%) as a fiber-forming facilitating additive, the release of BSA could be well modulated by altering the environmental pH and temperature of the hydrogel nanofibers, and CTS-g-PNIPAAm possessed a temperature-induced phase transition and lower critical solution temperature (LCST) at 32°C in aqueous solutions. And for preparing temperature and pH dual-responsive drug delivery systems, Li H et al. [58] synthesized firstly the thermosensitive polymer poly(N-isopropylacrylamide) (PNIPAAm) by free-radical polymerization. and then co-dissolved with the pH-sensitive polymer Eudragit®L 100-55 (EL100-55) and processed into fibers using electrospinning.

Figure 9. Diagram of coaxial electrospinning and resulting core-sheath fibers[81].

Figure 10. Cross-sectional diagrams of Eudragit core-sheath fibers made of (a) EL100 core and ES100 sheath or (b) ES100 core and EL100 sheath, and their evolution in consecutive pH changes[81].

4.6 Magnetic property

Usually, micro/nanofibers with special magnetic functions can be obtained by blending magnetic materials or magnetic nanoparticles into electrospinning solution through electrospinning technology. This kind of micro/nanofibers are widely used in the fields of electronics[85, 86], environmental pollution control[87, 88], tissue regeneration and biomedical engineering[89, 90, 91, 92]. For example, Wu F et al. [85] prepared a self-powered composite nanofibers coated by modified MWNTs through electrospinning technology, and developed an electric stimulation power generation system based on electromagnetic induction effect under external rotating magnetic field. Because of the presence of magnetic nanoparticles in the external magnetic field, the self-powered composite nanofibers could generate electrical signals, and the output current of the nanocomposites

can be increased easily. Similarly, Im JS, et al.[86] prepared a kind of PVDF nanofiber membrane blended with magnetic Fe₃O₄ nanoparticles by electrospinning technology, and developed a friction generator using this special nanofiber membrane. For tissue regeneration application, Hao S, et al.[89] developed a superparamagnetic nanofiber scaffold, which can stimulate fibroblasts to secrete collagen type I protein, vascular endothelial growth factor A (VEGFA), TGF- β 1, and does not produce IL-1 β , monocyte chemoattractant protein-1(MCP1) and other pro-inflammatory factors. significantly this kind of nanofiber scaffold could promote osteogenic differentiation of pre-osteoblasts, superparamagnetic nanofiber scaffolds have been proved to be a promising candidate for tissue regeneration. In order to apply magnetic nanofibers to skin tissue engineering, Heng Zhang et al. [93] designed a PCL-PEG-PCL three-dimensional composite nanofibers membrane encapsulated with Fe₃O₄ nanoparticles by electrospinning technology. Results showed that the PCL-PEG-PCL 3D composite nanofibers membrane encapsulated with 5% Fe₃O₄ nanoparticles had a diameter of 250 nm, excellent cell adhesion and low cytotoxicity. Recently, Chen H et al. [94] designed a PLGA/PCL magnetic nanofiber membrane with bioactive surface and layer-by-layer assembly of superparamagnetic nanoparticles. this kind of PLGA/PCL magnetic nanofiber membrane could improve the hydrophilicity and elastic modulus of the surface of the fibrous membrane, and promote the osteogenic differentiation of stem cells.

5 Biomedical applications of electrospinning

5.1 Nerve repair and regeneration

Neural diseases such as spinal cord injury and peripheral nerve injury, usually result in permanent changes in strength and sensation functions below the site of the injury and affects thousands of people each year[95]. Micro/nanofibers produced by electrospinning can simulate the topography, mechanical, biological and extracellular matrix morphology of native tissue, which provides a promising strategy for nerve tissue regeneration. So far, there several ways to apply the electrospinning technology in nerve regeneration: provide a 3D scaffold for cell growth or tissue regeneration, mimic extracellular matrix, blend neurotherapeutic drugs or neurotrophic factors into micro/nanofibers. For example, Zhou X, et al.[96] prepared a conductive fiber-film (CFF) with core-sheath structure by electrospinning, include aligned PLLA micro/nanofibers electrochemical deposition of polypyrrole (PPy) nanoparticles, and the multiple components of ECM, including laminin, fibronectin and collagen, and then culturing and lysing L929 cells to fabricate the bioactive scaffold of ECM-linked CFF, the results indicated that the special ECM-linked CFF can could improve the nerve regeneration by encouraging neural-cell adhesion, neurite growth and extension. Roman JA et al.[97] prepared a kind of electrospun PLA micro/nanofibers blended with paclitaxel, a drug has been reported can promote axonal extension and attenuate the upregulation of inhibitory molecules after a spinal cord injury at a low concentration administration, found that the paclitaxel loaded PLA microfibers could improve the axonal extension. Lee SJ et al.[98] fabricated a novel 3D biomimetic neural scaffold with a tunable porous structure and embedded aligned fibers by stereolithography and electrospinning techniques, and the results showed that 3D printed scaffolds with electrospun fibers significantly improve neural stem cell adhesion and proliferation. Lee SJ, et al.[64] fabricated a novel 3D biomimetic neural scaffold with a tunable porous structure and embedded aligned fibers, and they utilized both synthetic and natural materials with varying chemical composition as bioink to enhance biocompatibilities and mechanical properties of the scaffold. And Huang L, et al. [99] constructed a O-CCH/PCL compound scaffold using a stage-wise strategy, including collagen-chitosan (O-CCH) filler prepared by orientated freezing technology, PCL sheaths prepared by electrospinning technology, found that the O-CCH/PCL scaffold with uniform longitudinal guidance filler and a porous sheath exhibits favorable properties for clinical use and promotes nerve regeneration and functional recovery. This maybe provide a promising new path for developing an optimal therapeutic alternative for peripheral nerve reconstruction. And Liu YT et al. [100] designed Schwann cell-seeded nerve guidance channels by genipin crosslinking of chitosan nanofibers, demonstrated that genipin treatment improves upon the

physical and biological properties of chitosan nanofibers towards their utility in nerve guidance channel design.

Figure 11. (A) The fabrication schematic illustration of NS-containing NGC by electrospinning. Digital photos of (B) PLCL/SF 3D nanofiber sponges and (C) NS-containing NGC. Cross-section SEM images of NS-containing NGC in (D) low and (E) high resolution; and (F) hollow NGC[101].

Figure 12. (A) Schematic illustration of transplanting NS-containing NGC into SD rat sciatic nerve defect model. (B) The gross observation of sciatic nerve after surgical procedures at week 0, and the regenerated sciatic nerve after implantation for 4 and 12 weeks (the scale bar = 10 mm, which marked the nerve defect site) [101].

Figure 13. (A) TEM images of the generated nerves at the middle segment of the NGCs (or autograft) after implanted 4 and 12 weeks. (B) The axon diameter and (C) the myelin thickness which calculated by TEM[101].

5.2 Cardiac repair and regeneration

There are many articles have been reported that electrospinning membrane or electrospinning scaffold plays a great role in cardiac repair and regeneration. For example, Liu Y et al. [102] fabricated fibrous scaffolds with different ratios of PLA and chitosan were by conventional electrospinning, found that scaffolds with aligned micro/nanofibers (PLA: chitosan ratios is 7:1) supported cardiomyocyte viability, elicited cell elongation, and enhanced production of sarcomeric α -actinin and troponin I. For 3D scaffold with physical, chemical, and electrical signal properties, Liu Y et al. [103] fabricated a special aligned and conductive scaffold to improve the function of cardiomyocytes through the synthetic microenvironments. In this scaffold, highly aligned nanofibers were fabricated with loaded up to 6% of carbon nanotubes (CNTs) to modulate the electrical conductivity. For mimicking morphology of the cardiac extracellular matrix, Xu Y et al. [104] builded an in vitro model based on ECM-mimicking nanofibers and a type of cardiac progenitor cell, cardiosphere-derived cells by electrospinning and electrospraying technique, and provided the evidence that the scaffold can directed the cardiosphere-derived cells differentiation into mature cardiomyocytes at gene expression level and protein expression level. For screening the superior substrate for cardiac repair, Castellano D et al. [105] compared PHB, PCL, silk, PLA, and polyamide (PA) nanofiber scaffolds in cardia repair application, found that PHB had the greatest adhesion/growth of cells and had a better performance in epicardial surface of healthy rats and infarcted rat heart experiments. In cardiac tissue engineering, cells are seeded within porous

biomaterial scaffolds to create functional cardiac patches is a good strategy for cardiac repair. For example, Sharon Fleischer. et al. [106] prepared a modular tissue consisting of multiple layers with distinct structures and functions. Albumin electrospun nanofiber scaffolds were laser-patterned to create microgrooves for engineering aligned cardiac tissues exhibiting anisotropic electrical signal propagation. Microchannels were patterned within the scaffolds and seeded with endothelial cells to form closed lumens. Moreover, cage-like structures were patterned within the scaffolds and accommodated PLGA microparticulate systems that controlled the release of VEGF, which promotes vascularization, or dexamethasone, an anti-inflammatory agent.

5.3 Bone repair and regeneration

So far, there are many therapy methods for bone repair and regeneration. As one promising methods, electrospinning can produce the huge porous nanostructures, which can mimic the biologic extracellular matrix and provide the drug delivery system for bone regeneration. There are many articles have been reported bone regeneration application of electrospinning. For example, Guo Z et al.[107] evaluated fiber scaffold loaded with naringin via electrospinning to guide bone regeneration. Khorshidi S, et al. [108] prepared hydrogel/fiber scaffold possessing electrical conductivity for bone regeneration. Masoudi Rad M et al. [109] developed a two-layered bioactive membrane fabricated by electrospinning whereas one layer provides guided bone regeneration (GBR) and fabricated using poly glycerol sebacate (PGS)/ PCL and β -tri-calcium phosphate (β -TCP) (5, 10 and 15%) and another one layer containing PCL/PGS and chitosan acts as guided tissue regeneration (GTR). There are some scientists focusing on the bone regeneration application of electrospinning in vivo. For example, Rampichová M, et al. [110] prepared fibrous scaffolds from PCL using three different fabrication methods (electrospinning, electro-blowing technology and melt-blown technology combined with electrospinning), rabbits experiments showed that PCL fibrous scaffold prepared using a combination of melt-blown and ES technology seems to be promising for bone regeneration. And Wei S, et al. [111] provided that resorbable electrospun vancomycin-impregnated PCL membrane was effective at controlling bone infection, and in the regeneration of bone in a critical bone defect animal model. Currently, combining biomaterial scaffolds with living stem cells for tissue regeneration is a main approach for tissue engineering. Mesenchymal stem cells (MSCs) are promising candidates for musculoskeletal tissue repair through differentiating into specific tissues, such as bone. For example, Luo Y, et al. [76] fabricated a kind of graphene oxide (GO)-doped PLGA nanofiber scaffold via electrospinning technique for the enhancement of osteogenic differentiation of MSCs, found that the scaffold had the excellent hydrophilic performance, and protein- and inducer-adsorption ability of the nanofibers. and the incorporated GO could accelerate the human MSCs (hMSCs) adhesion and proliferation versus pure PLGA nanofiber and induces the osteogenic differentiation.

5.4 Cartilage repair and regeneration

Electrospinning scaffold also has a great application on cartilage repair and regeneration. For example, Levorson EJ et al. [113] generated electrospun scaffolds containing two differently scaled fibers interspersed evenly throughout the entire construct as well as scaffolds containing fibers composed of two discrete materials using a dual extrusion electrospinning setup with a rotating mandrel, revealed that nanofibers within a microfiber mesh function to maintain scaffold cellularity under serum-free conditions as well as aid the deposition of glycosaminoglycan. For mimicking the structural organization and mechanical properties of cartilage's collagen fibrillar network,

McCullen SD, et al. [114] fabricated trilaminar scaffolds by sequential electrospinning and varying fiber size and orientation in a continuous construct, the trilaminar scaffolds could support cartilage formation in vitro, and had superior mechanical properties to homogenous scaffolds. And Formica FA et al. [115] mimicked the glycosaminoglycan component of the native ECM by using a polyanionic functionalized alginate added dexamethasone in electrospun component. For 3D tissue engineering scaffold application in Cartilage repair and regeneration, Chen W et al. [116] prepared a porous 3D scaffold based on electrospun gelatin/PLA nanofibers and a modified scaffold (3DS-2) cross-linked with hyaluronic acid (HA), the results indicated that two kind of 3D scaffolds exhibited superabsorbent property and excellent cytocompatibility. For exploring the potential of the combination of electrospinning technology and cell sheet engineering to create cartilage tissue, Mouthuy PA et al. [117] created a kind of PLGA electrospun membranes, collagen type I and HA were also added to the scaffolds to increase the histological biocompatibility, they found that that layering electrospun scaffolds and cell sheets is an efficient approach for the engineering of tissue transitions, and in particular the cartilage-bone transition.

6 Prospective and challenges of electrospinning

There are many types of electrospinning technologies, which can produce micro/nanofibers with different shapes or functions, such as hollow nanofibers, porous nanofibers and thin films[40]. But there are still exist many limitations about Biomedical application of micro/nanofibers.

How to continually obtain a large number of micro/nanofibers with uniform quality and performance, in other words, how to realize the industrialization of micro/nanofibers or scaffolds is a major technical issue. In recent years, many scientists have replaced the traditional single nozzle of multi-nozzles, which has largely solved the problem of low output of electrospinning, but it is still difficult to continually produce uniform nanofibers for a long time. At the same time, electrostatic action generated by nozzles also become one of the limitation factors to influence the quality of micro/nanofibers. There are many factors determine the quality of micro/nanofibers, including electrospinning process (voltage, flow rate and distance between metal nozzle and collecting device), electrospinning solution (polymer concentration, viscosity, conductivity), environment (temperature and humidity), to keep the uniformity and stability of polymer concentration, viscosity and conductivity in a long time in a highly homogeneous temperature, humidity and electrostatic-free clean space is the key to obtain high quality uniform micro/nanofibers. Flexible and timely adjustment of voltage, flow rate and distance between metal nozzle-collecting device in electrospinning process is the guarantee of achieving uniform and stable micro/nanofibers. Computer-assisted electrospinning (CAD) may be a excellent solution to the problem.

Some materials, such as PLGA, PLA, PCL, collagen, hyaluronic acid, sodium alginate, chitosan, PDO, PGA, can be degraded naturally or under special conditions due to their molecular structure or special properties, and have great application prospects in the field of biomedicine. There are many kind of degradable products made of degradable natural materials on the market, such as PGA, PCL or PDO sutures, hyaluronic acid or chitosan wound dressings. Because of its excellent degradation performance, it is becoming more and more popular in clinical application. But the biodegradability of these products is uncontrollable or cannot be accurately controlled. In clinical application, especially in medical instruments transplantation, there are strict safety requirements for degradable products. How to accurately regulate the degradation time and degradation rate of

degradable products in vivo to ensure that the degradable products maintain ideal functional status is an important problem to be solved necessarily and urgently.

In recent years, some scientists have prepared a series of responsive micro/nanofibers, such as temperature-sensitive micro/nanofibers[82, 83, 84], pH-sensitive micro/nanofibers[78, 79, 80], magnetic micro/nanofibers[128, 129], conductive micro/nanofibers[130, 131]. How to combine electrospinning with computer chip technology, It will be better way to accurately regulate and timely control the programmable and controllable degradation in vivo.

There is a very important and challenging task for tissue engineering and regenerative medicine that accurately regulate the interaction between biomolecules and matrix. As a well-known biomimetic matrix, micro/nanofibers often lack unique spatial complexity, and cannot completely transmit physiological signals to biological molecules. Many literatures have reported that the micro/nanofiber scaffolds prepared by electrospinning technology have good performance in regenerative medicine such as nerve repair, heart repair, bone repair or cartilage repair. Some articles provide evidence that micro/nanofiber scaffolds can play a good role in animal disease models or clinical trials. Here, we want to explain how to maximize the simulation of human microenvironment (such as skin structure, organ structure or body fluid components) or extracellular matrix, which is a very challenging and necessary subject.

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