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Multi-material electrospinning: from methods to biomedical applications

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ABSTRACT

Electrospinning as a versatile, simple, and cost-effective method to engineer a variety of micro or nanofibrous materials, has contributed to significant developments in the biomedical field. However, the traditional electrospinning of single material only can produce homogeneous fibrous assemblies with limited functional properties, which oftentimes fails to meet the ever-increasing requirements of biomedical applications. Thus, multi-material electrospinning referring to engineering two or more kinds of materials, has been recently developed to enable the fabrication of diversified complex fibrous structures with advanced performance for greatly promoting biomedical development. This review firstly gives an overview of multi-material electrospinning modalities, with a highlight on their features and accessibility for constructing different complex fibrous structures. A perspective of how multi-material electrospinning opens up new opportunities for specific biomedical applications, i.e., tissue engineering and drug delivery, is also offered.

1. Introduction

A biomaterial is defined as a substance that has been engineered to interface with biological systems, aiming to augment tissue function and treat diseases or injuries. The past few decades have witnessed the development of numerous new biomaterials for advanced applications, which have brought about enormous breakthroughs in various biomedical fields, such as tissue engineering, drug delivery, and medical imaging. It is widely recognized that a single-component biomaterial with structurally and chemically homogeneous architectures becomes inadequate to meet the requirements of ever-growing biomedical applications. Therefore, multi-material strategies have been proposed to obtain complex biomaterials with advanced functionalities by combining different materials to take full advantage of their merits.

Biomaterial blending is a direct and convenient physical modification technique that integrates several functions into one biomaterial by combining different material ingredients in specific proportions and mixing them together [1–3]. One of the most notable examples is the combination of naturally derived and synthetic polymers to create hybrid biomaterials. Typically, natural biomaterials possess satisfactory biodegradability, biocompatibility, and promote cell attachment and growth. However, they often exhibit weak mechanical properties and are challenging to process. On the other hand, synthetic bioresorbable polymers offer tailored mechanical properties and excellent processability but may lack certain biological characteristics. Therefore, the development of natural-synthetic biocomposites has gained significant attention. These composites are extensively utilized for constructing scaffolds with desirable mechanical and biological properties in tissue engineering [4,5]. In addition, the biocompatibility, biodegradability and low immunogenicity of chitosan, make it routinely used in tissue engineering and regenerative medicine. However, it lacks appropriate conductivity to mimic the extracellular matrix (ECM) of neural tissue. To address this limitation, blending chitosan with some conductive materials such as carbon nanofibers/tubes [6,7], gold nanowires/particles [8,9] and aniline oligomers [10,11], offers a simple yet effective solution to compensate for its inferior conductivity, making the conductor-based

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chitosan scaffolds an excellent candidate for nerve regeneration.

Electrospinning refers to the formation of continuous micro/nanofibers from a polymer-based fluid relying on a strong electric field [12,13]. Electrospinning has a long history of research and development, and its concept was put forward as early as in 1600. After 2000, it started to receive increasing attention, probably because the invention of electron microscopes provides a characterized means with resolving features down to the nanometer scale for electrospun nanofibers. The typical equipment for this technique includes a high-voltage power supply, a spinneret (a metallic needle), and a grounded collector. To date, various types of electrospinning techniques with unique fiber-making capabilities have emerged for engineering nanofibers to suit or enable various applications, such as solution electrospinning and melt electrospinning, far-field electrospinning and near-field electrospinning, as well as needle electrospinning and needleless electrospinning. The accessibility and versatility of electrospinning enable the production of various functional nanofibrous structures with high surface-to-volume ratio, porosity, and mechanical properties, from plenty of synthetic or natural materials. Thus, electrospinning as a powerful material engineering tool has been widely used in various fields, including catalysis, separation membranes, energy storage, sensors and biomedicine. Compared to other fields, the applications of electrospinning in biomedicine have received much attention, which takes up about one-third of all articles with the topic of "electrospinning", as shown in Fig. 1.

As mentioned above, the blending strategy provides an effective way to prepare biomaterial with novel properties. Therefore, electrospinning of multiple biomaterials contained solutions, termed blending electrospinning, was widely applied to create advanced heterogeneous nanofiber-based biomaterials with various compositions, which nearly accounts for half of the biomedical applications of electrospinning in the last six years (Fig. 1) [14–16]. For example, blending electrospun nanofibers as drug carriers, which incorporates therapeutic agents by co-dissolution of drugs and polymers in one solvent, has become one of the most promising drug delivery systems to treat different pathologies. This is because of the high surface area of electrospun nanofibers, excellent breathability, ease of incorporation of a drug, fast-drying process preventing phase separation, great flexibility in material choice, and cost-effectiveness of operation [17,18].

Although electrospinning of a blending of different materials can form nanocomposite fibers that can simultaneously inherit some merits of the distinct constituents, to a certain extent [19], it has an incapacity for the functionally-demanded spatial organization of these materials, which limits bioengineers to significantly tailor the properties of fibrous structures for an array of applications. Recently, multi-material electrospinning techniques, as an innovative extension of electrospinning, have been developed to tackle this bottleneck, through the controlled positioning of varying materials nanofibers at the macroscale or construction of well-defined hybrid nanostructures made from diverse materials, which particularly spark the development in terms of biomedical applications. In this review, we, therefore, focus on the application of multi-material electrospinning techniques to engineer complex nanofibrous structures for tissue engineering and drug delivery.

2. Multi-material electrospinning techniques

In this review, we focus on the recent progress in a subset of electrospinning, i.e., multi-material electrospinning. It designates electrospinning of two or more kinds of materials from distinct needles, in an independently site-controlled manner to gain region-specific features and performances. It is needful to clarify some definitions similar with multi-material electrospinning. Blending electrospinning refers to the electrospinning of one mixture of two or more different materials, making up one single-phase homogenous working liquid, using a single needle. Emulsion electrospinning utilizes emulsion-based solutions to fabricate electrospun fibers with distinct phases through the chemical separation principle [20]. Although, both electrospinning techniques have the advantage of simplicity to inherit the merits of all materials to some extent, they are insufficient to precisely control over the spatial organization of these materials for functional demands, which they are not therefore covered in the present review. Notably, the multi-material electrospinning process may involve the blending or emulsion electrospinning to implement one of its steps.

The development of multi-material electrospinning techniques has led to significant advancements toward on-demand fabrications of heterogeneous fibrous structures to meet the requirements of tissue engineering and drug delivery. These modalities of multi-material electrospinning mainly include sequential electrospinning, simultaneous electrospinning, coaxial electrospinning and side-by-side electrospinning, which are further discussed and compared (Table 1). The first two allow for flexible deposition of distinct-materials nanofibers into macroscopically heterogeneous structures. While the latter two are able to control the internal structure of nanofibers by the defined spatial arrangement of distinct materials for targeting certain functional features.

2.1. Sequential electrospinning

Sequential electrospinning refers to one-by-one electrospinning of

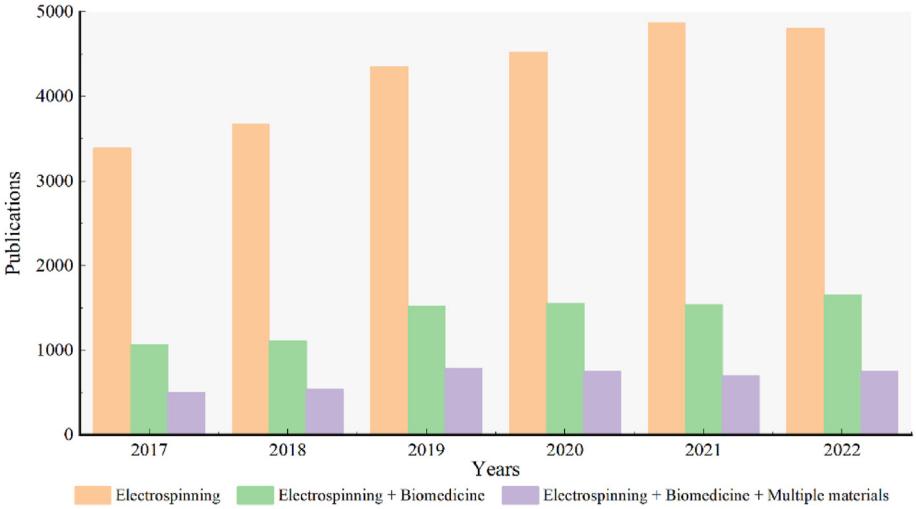


Fig. 1. The annual number of publications from 2017 to 2022 with the topic of "electrospinning" "electrospinning + biomedical or tissue engineering or drug delivery" and "electrospinning + biomedical or tissue engineering or drug delivery + blend or hybrid or composite" provided by the search engine of Web of Science.

Table 1
Comparison and applications of (A) sequential electrospinning, (B) simultaneous electrospinning, (C) coaxial electrospinning, and (D) side-by-side electrospinning.

Methods	(A) Sequential electrospinning	(B) Simultaneous electrospinning	(C) Coaxial electrospinning	(D) Side-by-side electrospinning
Illustration				
Advantages	• Suitable for building multilayered fibrous architecture • Ability to create graded mats • Adapt to a broad variety of materials • Without modified equipment	• Easy to build mixed fibrous architectures • Ability to construct graded architectures • Irrespective of the compatibility of different materials	• Ability to construct fibers with diverse morphologies • Making unelectrospinnable materials into fibrous structures	• Ability to construct Janus fibers • making unelectrospinnable materials into fibrous structures
limitations	• Potentially poor layer interface bonding	• Requiring special collectors to avoid the interplay	• Limited material pairs selection	• Difficult to obtain high-quality Janus structures
Applications	• Building multifunctional scaffolds • Biomimicking the heterogeneity of natural tissue • Regulation of single drug release profile • Controlled co-delivery of multiple agents • Creating a novel functionality	• Endowing the scaffolds with multiple characteristics • Increasing scaffold porosity • Mimicking *in vivo*-like gradients • Creating a novel functionality • Multidrug delivery	• Building scaffolds with multiple characteristics • Regulation of single drug release • Controlled multi-drug co-delivery	• Giving the scaffolds with multiple characteristics • Regulation of single drug release profile • Controlled multi-drug co-delivery

different-material solutions or melts through one single spinneret at one time, which could be considered as multiple replications of single-material electrospinning (Table 1 (A)). Thus, one can easily implement sequential electrospinning from a wide variety of materials, using the same experimental setup and process parameters as conventional electrospinning.

Sequential electrospinning is typically utilized to create a multilayered fibrous architecture with layer-specific materials (Fig. 2 (C_1)). Every layer thickness and layer number can be regulated easily by tuning electrospinning time and repetition number, respectively. Aside from controlling the material in each layer, it is possible to design the geometrical characteristics of electrospun fibers (such as diameter and orientation) in each layer through modulating the electrospinning process conditions, which further improves the heterogeneous diversity of the multilayered architectures [27–30]. For example, when collected onto a mandrel, different material nanofibers can independently be deposited into random or aligned states by adjusting the rotation speed of the mandrel [27]. To date, multilayered fibrous structures made from various materials have been developed to perform specific functions for biomedical applications, such as integrating multiple functionalities into a scaffold [31,32], biomimicking in vivo multilayer structures [33,34], unidirectional drainages of biofluid [35,36], regulating single drug release [37,38], and co-delivery of multiple agents [39,40].

In addition to the longitudinal heterogeneity, some easy-to-implement strategies also have been exploited to endow the sequential electrospinning with capabilities to produce either stratified or continuous gradations along the lateral direction, through regulating or tailoring the deposition area of the electrospun fiber in a layer-specific fashion, for tissue-to-tissue interfaces engineering. For example, multizone membranes with a gradual transition can be obtained by modulating relative motion between the spinnerets and the collectors [41,42]. First A material nanofibrous layer was electrospun onto the whole surface of a rotating collector, then another B material layer with a thickness gradient was formed on the first layer, by controlling the spinnerets to move back and forth along the axis of the rotating collector. The cause of the thickness gradient is the change in the distance between the spinneret tip and the cylindrical surface. Moreover, a selective-covered strategy can be employed to prepare a two-segment nanofibrous mat with a sharp boundary [43,44]. After the bottom layers were electrospun onto an aluminum foil collector, a plastic plate was half-covered on the as-electrospun layers to ensure that the top fibers only adhere to half of the foil.

A major challenge for sequential electrospun multilayered constructs is poor interface bonding between the varying-material layers, especially for the hydrophilic and hydrophobic ones, normally resulting in a tendency to delamination.

2.2. *Simultaneous electrospinning*

Simultaneous electrospinning, sometimes referred to as co-electrospinning, means concomitant electrospinning using two or more spinnerets onto one collector, to achieve an integrated fibrous architecture that different material nanofibers would interlay one another [45] (Table 1 (B)). Like sequential electrospinning, simultaneous electrospinning accommodates a great versatility for material systems as same as single-material electrospinning.

However, it requires extra work in this modality to carefully configure the electrospinning set-up to mitigate the interplay of multiple jets. This is because when multiple jets are simultaneously ejected from different spinnerets, the interplay of the external electric field and Coulombic repulsion among the jets usually results in instability and irregular paths of the jets, thereby it is difficult to achieve desired fibrous constructs [46]. In general, a movable collector is usually utilized to enable the constructure of integrated structures, such as rotating mandrels and reciprocating flat plates. Among these collectors, a rotating mandrel is widely used, where all spinnerets are evenly distributed along the axis of

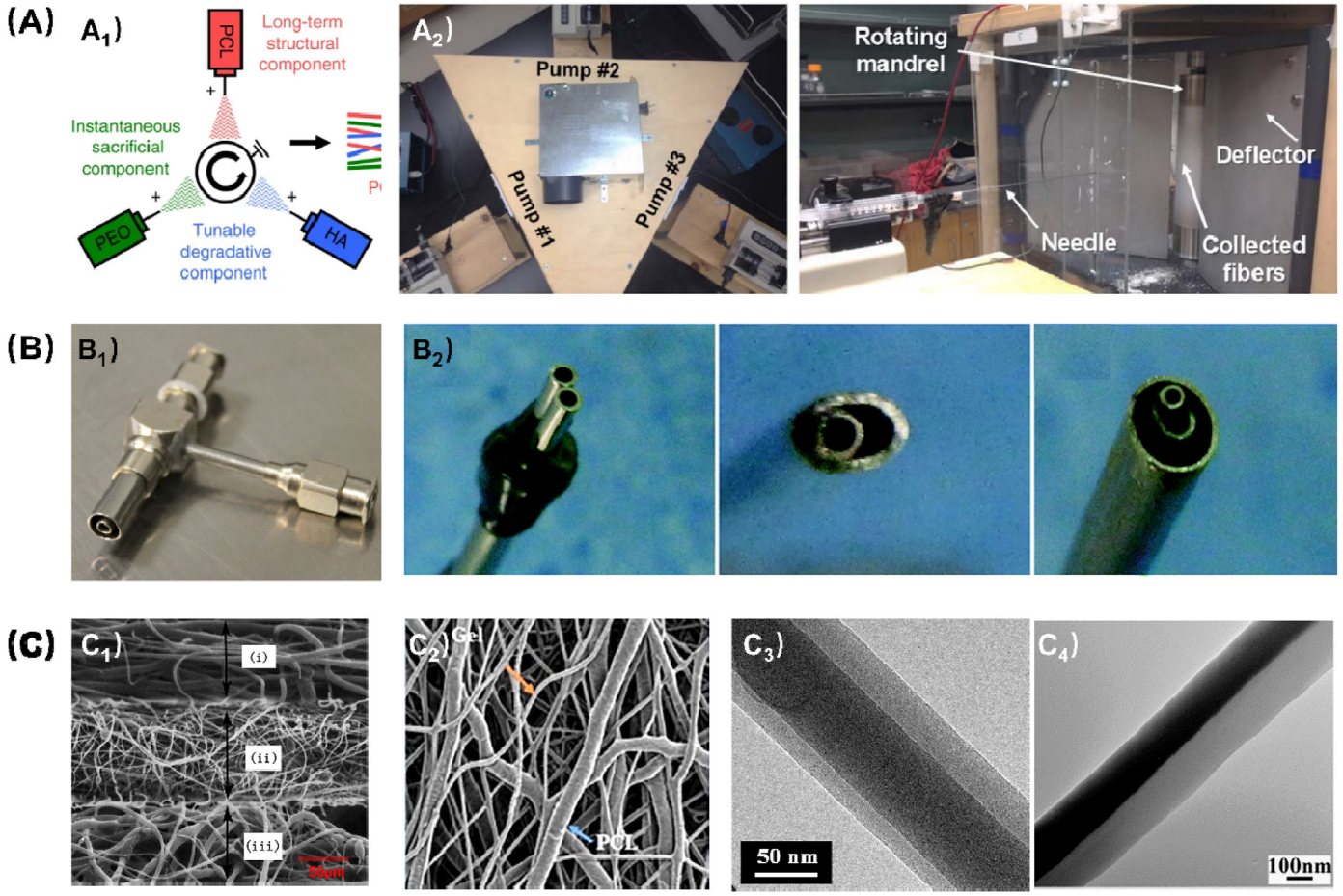


Fig. 2. (A) Schematic (A_1) and images (A_2) of tri-jet simultaneous electrospinning setup. Reproduced with permission [21]. Copyright 2017, Nature Publishing Group. (B) Photographs of the coaxial spinneret for coaxial electrospinning (B_1), and parallel and acentric, and structured spinnerets for side-by-side electrospinning (B_2). Reproduced with permission [22]. Copyright 2017, Royal Society of Chemistry. (C) SEM images of the sandwich-like nanofibrous membrane by sequential electrospinning (C_1), hybrid nanofibrous composites by simultaneous electrospinning (C_2), core-shell nanofibers by coaxial electrospinning(C_3), and Janus nanofibers by side-by-side electrospinning (C_4). C_1 Reproduced with permission [23]. Copyright 2012, Elsevier. C_2 Reproduced with permission [24]. Copyright 2017, Elsevier. C_3 Reproduced with permission [25]. Copyright 2016, Elsevier. C_4 Reproduced with permission [26]. Copyright 2017, Royal Society of Chemistry.

the mandrel to greatly alleviate the interplay of jets in most cases. For instance, a specific arrangement often employed involves the positioning of three needles around the collecting drum, with each needle placed at intervals of 180° from one another, as shown in Fig. 2 (A). The additional advantage of the rotating mandrel-based electrospinning is easily controlling the fiber orientation (aligned or nonaligned) by tuning the rotating speed of the mandrel.

When all varying-material spinnerets are placed at the middle position of the rotating mandrel, a homogeneously mixed fibrous mesh is produced (Fig. 2 (C_2)), which provides a simple and versatile strategy for integrating different materials to obtain desirable overall characteristics, such as mechanical tensile strength [47] and degradation rate [48]. More importantly, compared with blending electrospinning, simultaneous electrospinning is adaptable to more widely selective material systems, owing to its no need for a good solvent for simultaneously dissolving various materials to prepare a blending solution. Another advantage is that the different material components still maintain their individual physical and chemical properties at fiber-size scales. Therefore, these well-mixed fibrous constructs have found applications for producing more biomimetic scaffolds through mimicking multiple characteristics of native extracellular matrix (ECM) [49,50], and integrating multiple drug-loaded fibers together for their co-delivery [51,52]. Additionally, it can be developed to optimize the fibrous structure to obtain electrospun scaffolds with loose architecture and large pores, aiming to enhance cell infiltration [53,54].

Besides, simultaneous electrospinning is capable of fabricating fibrous architectures with the graded composition that can further determine structural or mechanical properties, which offers a simple way to recapitulate functionally heterogeneous natural gradients. A simple misplaced deposition strategy that offsets syringes loaded with different material solutions a certain distance along the length of the mandrel, could easily create a multi-region mesh consisting of a middle transition area from one material nanofibers to another. Appropriate regulation of the transition area width by adjusting electrospun parameters, such as voltage and distance between the syringes, could reasonable mimic various in vivo-like gradients [55,56]. In addition, continuous composition gradients in depth also could be obtained by programmed tuning relative feed rate of different materials solutions. For instance, it can add an intermixed interlayer between different material layers to make sure of keeping the integral structure and stability of the overall performance [57,58]. Recently, tandem electrospinning utilizing a planar collector was proposed to create heterogeneous nanofiber patterns. It provides more versatility to create an array of micro and nano-scale fibrous constructs with complex, ordered patterns [59].

2.3. Coaxial electrospinning

Among these modalities, coaxial electrospinning technologies have been the most extensively studied to fabricate novel nanostructures with advanced performance, which are indeed discussed in several excellent

reviews [60–62]. Coaxial electrospinning employs a coaxial spinneret (a typical setup is shown in Fig. 2 (B_1)), consisting of two or more concentrically nested needles supplied by different materials solutions or melts, to synthesize multiple fluids into 1D nanostructures with diverse morphologies, such as core-shell fibers (Fig. 2 (C_3)), beads-on-a-string structured fibers, and triple/quadruple-layered fibers (Table 1 (C)). More importantly, it has the capacity of forcing materials without filament-forming properties into 1D structure or generation of high-quality nanofibers from poorly spinnable polymers, through a spinnable shell solution encapsulating an unspinnable core material or core solutions surrounded by unspinnable sheath materials. This capability opens an exciting avenue to making naturally-derived biomaterials, such as collagen, gelatin, and alginate, into hydrogel nanofibers with excellent mechanical properties. The main disadvantage of coaxial electrospinning is the limited choice of material pairs available in preparing high-quality core-shell fibers. This is because the material selection is dominated by some extra parameters relative to traditional electrospinning, such as immiscibility or semimiscibility between the solutions, appropriate viscosity ratio of the solutions, and higher shell solution conductivity.

Compared with the nanocomposite of nanofibers with irregular constituent distribution produced by simultaneous electrospinning, the coaxial electrospun fibers can provide greater potential for tissue engineering and drug delivery applications, through precise structuralization of these materials for making the best of each material characteristics. These applications mainly include enhancing the biological property of scaffolds using a more biocompatible shell [63,64], construction of drug-loaded fibers from unspinnanble materials [65,66], fine tailoring the drug release profiles by a shell that served as a buffer [67,68], and co-delivery of multiple drugs with independent controlled release behaviors [69,70].

2.4. Side-by-side electrospinning

In side-by-side electrospinning, a spinneret with two or more paralleled needles arrangement is used to create Janus fibers (Fig. 2 (C_4)) [45,71], where each side of the structure can be individually designed with regard to both chemical compositions and functionalities (Table 1 (D)). Like core-shell fiber, the relative location of different chemical compositions can be rightly controlled at a fiber scale. However, both sides of the Janus structure are able to be directly exposed to their surrounding environment, which can be explored for a synergetic effect on the desired functional performances. Thus, the Janus fibers to date have found wide applications in tunable single drug release profiles [72] or controlled multidrug delivery [73] by incorporating pharmaceutical active ingredients into both sides of the Janus structure. Additionally, they also show great potential in producing multi-functional tissue-engineering scaffolds with maximized performance [74]. The Janus fibers made from two different recombinant spider silk, in which one of their sides can be selectively deposited with a conductive gold layer, were designed to synergistically provide biological and electrical cues. Moreover, side-by-side electrospinning also enables the treatment of an unspinnable fluid with an electrospinnable fluid to construct Janus structural nanocomposites [75].

The biphasic Janus fibers can be obtained either using one type of polymer as a template while doping different functional materials on each side, or using two distinct polymers. When using one polymer as a Janus template, it ensures good interfacial contact between the biphasic system, facilitating the formation of integral Janus structures, while the electrospinning solutions easily intermingle with each other, resulting in failing to create well-defined Janus fibers. The side-by-side electrospinning utilizing two distinct polymers offers the advantage of providing richer functionality from the two polymers. However, the successful creation of Janus fibers from two distinct polymers faces a great challenge, i.e., making sure the two working fluids with very different properties create integrated Janus structures without departure from each other during the electrospinning.

Recently, some elaborate spinneret designs have been reported for partly effective production of integrated Janus nanostructure. For example, a section of Teflon tube is coated onto the outlets of the parallel nozzles and projected slightly over their nozzles, ensuring the two working fluids converge before they were ejected from the spinneret [76]. Moreover, an eccentric spinneret, where a small round nozzle is not symmetrically inserted in a big elliptical nozzle, was applied to provide a larger contact surface area for the two side fluids, resulting in maintaining a robust and continuous preparation process [22], as shown in Fig. 2 (B_2).

3. Applications in tissue engineering and drug delivery

3.1. Tissue engineering

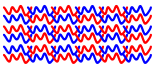
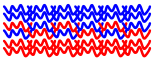
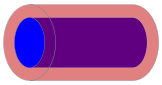
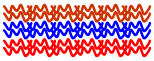
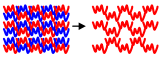
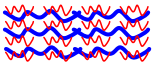
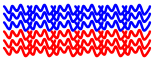
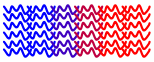
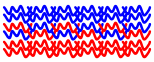
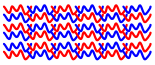
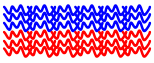
Tissue engineering aiming to replace, repair, and regenerate damaged or degenerated tissues, typically involves scaffold, cell, and growth factors [77]. Scaffolds made from various biomaterials come into direct contact with endogenous cells, when it gets into the body. Therefore, the physicochemical and biophysical properties of the scaffolds can influence and modify the functions and/or morphology of cells. An ideal tissue-engineered scaffolds should mimic the behavior of targeted tissue ECM, thereby providing a proper microenvironment for facilitating cellular activity, growth, adhesion, differentiation, and proliferation [3]. Besides, the selection of biomaterials based on target tissue plays a significant role in tissue engineering, an appropriate biomaterial engineering method is also important to recapitulate the native form and function of tissue organization for tissue regeneration. Electrospinning provides an attractive way to fabricate scaffolds, owing to its simplicity and flexibility, easily controlling their porosity, surface area, mechanical strength, and more importantly perfectly recapitulating nanofibrillar of native ECM because of their similarity in the aspect ratio (over 1:20) and size-scale (hundreds of nanometers) [78,79]. Compared to other electrospinning techniques, multi-material electrospinning can fabricate complex micro/nanofibrous architectures, endowing scaffolds with advanced performances for various tissue regeneration. Specifically, these advantages include integrating multiple characteristics into a scaffold, tuning the pore size of the scaffolds, endowing the scaffolds with in vivo-like gradients and creating novel functionality, as shown in Table 2, which will be introduced in the following subsections respectively.

3.1.1. Combining multiple characteristics in one scaffold

Due to complex compositions and diversity of native tissues, the single-material scaffolds usually fail to recapitulate the properties of native tissue. Multi-material electrospinning offers a feasible approach to organize varying materials in a controlled manner for better structural and functional restoration of defected tissues.

3.1.1.1. Mechanical and biological properties. A composite scaffold with interlaced synthetic and natural nanofibers can be easily achieved by simultaneous electrospinning, aiming to render it with hybrid properties for closely mimicking native ECM [137,138]. More importantly, these hybrid properties can be finely regulated by adjusting the synthetic and natural ratio, to address the specific requirements of the tissue to be regenerated. To date, these composite scaffolds have been widely used for various tissue engineering such as small-diameter blood vessels [49,58,80–83], cartilage [47], wound dressing [84–86], and pancreas [89]. For example, small caliber artificial vascular scaffolds made from poly(-L-lactide-co-caprolactone) (PLCL) and heparin-loaded silk fibroin, were developed for temporary bypass in modified Blalock-Taussig surgery by Jin's group [49]. In vitro tests indicated their capability in anticoagulation and mechanical strength without structural stratification. Moreover, simultaneous electrospinning of hydrogel precursor and

Table 2
Applications of multi-material electrospinning in various tissue engineering.

Objectives	Structures		Applications
Combining multiple functions	Well-mixing of distinct functional nanofibers by simultaneous electrospinning		Blood vessel [49,80–83] Cartilage [47] Skin [84–88] Pancreas [89] Heart Valve Leaflets [90] Tendon [50] Bone [91]
	Janus architectures with an intermixed interlayer by simultaneous electrospinning		Blood vessel [58] Skin [92] Bone [57]
	Core-shell fibers that generally by coaxial electrospinning		Blood vessel [63] Skin [93] Bone [64,94] Nerve [95] Cardiac [96,97]
	Sandwich-like architectures by sequential electrospinning		Bone [31,98–100] Cardiac [32] Skin [101–103]
Increasing scaffold porosity	Well-mixing of nanofibers by simultaneous electrospinning		Bone [30,104–106] Tendon/ligament [53] Meniscus [21,107–109] Intervertebral disc [110] Blood vessel [111]
	Hybrid nano/microfibrous structures by simultaneous electrospinning		Bone [30,105,106,112] Skin [54,113]
Mimicking *in vivo*-like gradients	Multi-layered fibrous structures by sequential electrospinning		Tendon-to-bone interfaces [114,115] Osteochondral tissues [116,117] Blood vessel [27,33,118–123] Skin [124–128] Dura mater [34,129,130]
	Multi-region structures by sequential electrospinning		Tendon-to-bone interfaces [43,44]
	Multi-region structures with a continuous transition region by simultaneous electrospinning or sequential electrospinning		Ligament-to-bone interfaces [41,42,131–133] Muscle-tendon junctions [55]
	Janus architectures with an intermixed interlayer by simultaneous electrospinning		Blood vessel [134] Skin [135]
Creating a novel functionality	Well-mixing of distinct functional nanofibers by simultaneous electrospinning		Vessels or peripheral nerves [136]
	Multi-layered fibrous structures by sequential electrospinning		Wound dressing [35,36]

synthetic polymers was used to fabricate gel-like nanofibrous scaffolds for a better biomimetic of the ECM, which is expected to integrate the merits of a nanofibrous architecture and a hydrogel material [50,90].

To accomplish optimal mechanical strength, biocompatibility, and bioactivity, an ideal nanofibrous scaffold should bear a fiber surface with maximal natural components to ensure cells only contact with the most biocompatible materials, and mechanical role material being wrapped inside. Fortunately, coaxial electrospinning provides a simple and flexible way to fabricate such core-shell structured fibers. Indeed, core-sheath nanofibers made from various material pairs have to date developed for tissue engineering applications, including poly (3-hydroxybutyrate-co-4-hydroxybutyrate) (P34HB)/poly (vinyl alcohol) (PVA) [94], poly(lactic-co-glycolic acid) (PLGA)/gelatin methacrylamide [63], polycaprolactone (PCL)/collagen [93], and PCL/dECM [64]. For example, a PCL/periosteal decellularized extracellular matrix (dECM) co-axially electrospun membrane (PEC) was fabricated as biomimetic periosteum to heal critical-sized bone defects [64]. As shown in Fig. 3 (A), it bore an exquisite core-shell structure, where the dECM was continuously coated onto the surface of PCL nanofibers. The implantation test demonstrated that the PEC can induce an intact mineralized membrane-like structure, while only the defect periphery formed discrete bone islands in pure PCL one, and the pure dECM membrane shape disseminated into the defects in a flake-like manner. Obviously, this novel PEC not only exhibited remarkably tensile strength and long-term durability to maintain the physiological shape, but also stood out biological properties for cell growth, bio-mineralization, and osteogenesis.

3.1.1.2. Incorporating antibacterial functions. The introduction of external scaffolds to repair some tissues such as skin and bone, is always accompanied by a strong possibility of bacterial infections. The bacterial infections would delay tissue regeneration and cause patient suffering, even leading to treatment failure. Therefore, an antibacterial scaffold is highly desirable for the tissues vulnerable to infections to mitigate such adverse bacterial contamination. However, no single biomaterial has so far been found to meet both promoting tissue regeneration and antibacterial properties simultaneously. Fortunately, multi-material electrospinning has appeared to tackle this challenge for skin and bone tissue engineering.

Considering one of the skin's essential functions being the protection of the body from microbes, some multi-component scaffolds with antibacterial functions along with accelerating skin healing process have been developed through sequential or simultaneous electrospinning as a matter of course. A hybrid patch of PCL nanofibers and gum tragacanth-

loaded PVA nanofibers was successfully fabricated by Zarekhalili et al. This patch exhibited appropriate mechanical, biological, and antibacterial characteristics for skin tissue engineering [87]. Compared with the chaotic dispersion of distinct nanofibers in the hybrid scaffolds, the elegant multilayer structures with spatial functionalization showed higher potential for serving as skin substitutions, owing to their capacity of layer-specially tailoring the fiber geometry, composition, and bioactivity to achieve the optimized overall performance, where generally the outer resist external bacterial invasion and the inner promote the skin regeneration [88,92,101,103]. As an example, Zhou et al. have designed a bilayer fibrous membrane as an ideal skin scaffold recently, which comprises an outer layer of ZnO nanoparticles-encapsulated random PCL fibers and an inner layer of aligned core-shell chitosan fibers [101]. In vivo wound healing tests demonstrated that this scaffold holds great potential for accelerated wound healing, through combining aligned chitosan fibers and active ZnO nanoparticles to synergistically eliminate inflammation, guide cell migration, and realize re-epithelization.

Another example is biodegradable guided bone regeneration membranes (GBRM), which have been increasingly used to restore a localized bone defect, especially for periodontal regeneration taking place in the oral environment [139]. By virtue of sequential and simultaneous electrospinning, multi-functionalized scaffolds with the inner layer facilitating bone regeneration and the outer layer inhibiting bacterial contamination were prepared from various biomaterials for calvarial or periodontal bone regeneration [31,57,98–100]. As an example, a hierarchical Janus GBRM (JGM) comprised an inner face of random gelatin nanofibers dispersed with hydroxyapatite and an outer face of aligned PCL nanofibers loaded with poly(methacryloxyethyltrimethyl ammonium chloride-co-2-Aminoethyl 2-methylacrylate hydrochloride) (P(DMC-AMA)), with an internal transition structure between them to avoid the occurrence of delamination, was developed by Wang's group for advanced bone regeneration [57]. In vitro experiment found the outer face facilitates the epithelia migrating along the aligned direction and effectively killing the invasive bacteria (Fig. 3 B), whereas the inner surface possesses favorable cell affinity and bioactivity for promoting adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 cells. The prominent effectiveness of JGM for in vivo repair of critical-size bone defects was further verified by its implantation to heal cranial defects in the rabbits.

3.1.1.3. Endowing electroconductivity. Recently, endowing the scaffold with electrical conductivity has been found important especially for electroactive tissues, such as cardiac [140] and neurons [141,142], owing to many physiological functions in the human body required to be regulated by electric signals. Multi-material electrospinning represents a promising solution to fabricate conductive scaffolds, on account of its high accessibility for integrating conducting materials (conducting polymers and carbon-based nanoparticles) into the scaffolds with controllable materials-specific distribution [74,143].

Deservedly, direct electrospinning of conducting polymers can give the scaffolds with electrical conductivity, unfortunately, most conducting polymers are unelectrospinnable or difficult to obtain high-quality nanofibers. Thus, coaxial electrospinning was applied to process these conducting polymers. For example, bead-free conductive core-sheath nanofibers consisted of PCL and poly[2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylenevinylene] (MEH-PPV) as the core and sheath of the nanofibers, respectively, was prepared for neural tissue engineering [95]. By amine-surface-functionalization, these core-sheath meshes showed enhanced neurite growth and differentiation of rat pheochromocytoma 12 (PC12) cells. Aside from the conducting polymers serving as the sheath, the conducting materials can be embedded in the cores of coaxial fibers, which may provide better biological cues for native tissue repair compared with homogeneous dispersion of the conducting nanomaterials in the fiber matrix by blending electrospinning [96,97]. Liu et al. demonstrated that the core-sheath fibers are more beneficial for the cell viability and elongation, ECM secretion, and beating rates of cardiomyocytes than the blending fibers, when loading the same content of carbon nanotubes [96].

In addition, sequential or simultaneous electrospinning was also used to generate conductive scaffolds with suitable biological and mechanical properties [32,91]. For example, tri-layered scaffolds were fabricated with sequential electrospinning for cardiac tissue engineering, where the middle nanofibrous layer of PCL acts as a mechanical supporting function and the two surface layers of alginate-graphene oxide nanofibers provide biochemical and electroconductive cues [32].

3.1.2. Increasing scaffold porosity

A significant challenge to the applications of electrospun scaffolds in tissue repair and regeneration is their densely compacted fibrous structures resulting in marked inhibition of cellular infiltration and tissue ingrowth [144]. To overcome this dilemma, multi-material electrospinning methods have been developed and investigated to increase pore size or loosen the scaffolds, by virtue of selective removal of sacrificial materials and combinations of micro and nanoscale fibers.

3.1.2.1. Sacrificial methods. The procedure of the sacrificial strategy typically involves creating a composite scaffold containing both a slow-degrading targeted polymer and a water-soluble polymer based on multi-material electrospinning. Then, the sacrificial fiber fractions are removed by washing out in the water, leaving the targeted polymer fibers without structural disruption. In this process, the scaffold porosity could be easily tuned by varying the ratio of targeted and sacrificial components. However, it is worth noting that over-proportioned sacrificial fractions may cause unacceptable losses to mechanical strength. Poly(-ethylene oxide) (PEO) is one of the best candidates for the sacrificial fiber material, owing to its excellent electrospinnability and high water solubility [145].

Baker et al. first reported the production of aligned PCL scaffolds with large pores, through simultaneous electrospinning of PCL and PEO nanofibers followed by dissolving the PEO nanofibers in water [146]. And mesenchxymal stem cells (MSCs) culturing test demonstrated that this scaffold has better cell infiltration than pure PCL scaffolds. To date, this sacrificial strategy has found extensive applications in tissue engineering, including bone substitutes [104], regulation of Synovial stem cells differentiation [147], restoration of meniscus [107], small diameter vascular grafts [111], tendon/ligament engineering [53], and intervertebral disc implant [110]. For example, Baker's group further examined the effectiveness of this sacrificial strategy in promoting functional anisotropic tissue formation with specific reference to the fibrocartilaginous knee meniscus [107]. Both in vitro and in vivo tests revealed that increasing the fraction of sacrificial PEO nanofibers up to >50%, elevated cell infiltration and improved ECM distribution, which in turn contributes to significant improvement in the tensile modulus of the engineered constructs to native tissue level (Fig. 3 C).

As the upgradation of the traditional sacrificial strategy inducing large pores, in-situ dissolution of sacrificial nanofibers containing specific functional factors can further expedite cell migration into the scaffolds [108,109,148]. For example, an active collagenase was released from PEO nanofibers in a burst manner, aiming to enable cell migration from the peri-wound matrix to the defect by loosening the surrounding matrix. Meanwhile, sustained release of platelet-derived growth factor-AB from hyaluronic acid nanofibers offers a chemoattractant gradient for further recruiting the cells into the scaffold [21]. Moreover, dissolving Trichostatin A-loaded PEO nanofibers can provide more space for cell infiltration and lead to the nuclear softening of endogenous meniscus cells, which synergistically enhance their capability of interstitial migration through the scaffold in an in vivo experiment [109].

3.1.2.2. Hybrid methods. In addition, a hybrid method integrating large microfibers with fine nanofibers into one scaffold, provides an alternative

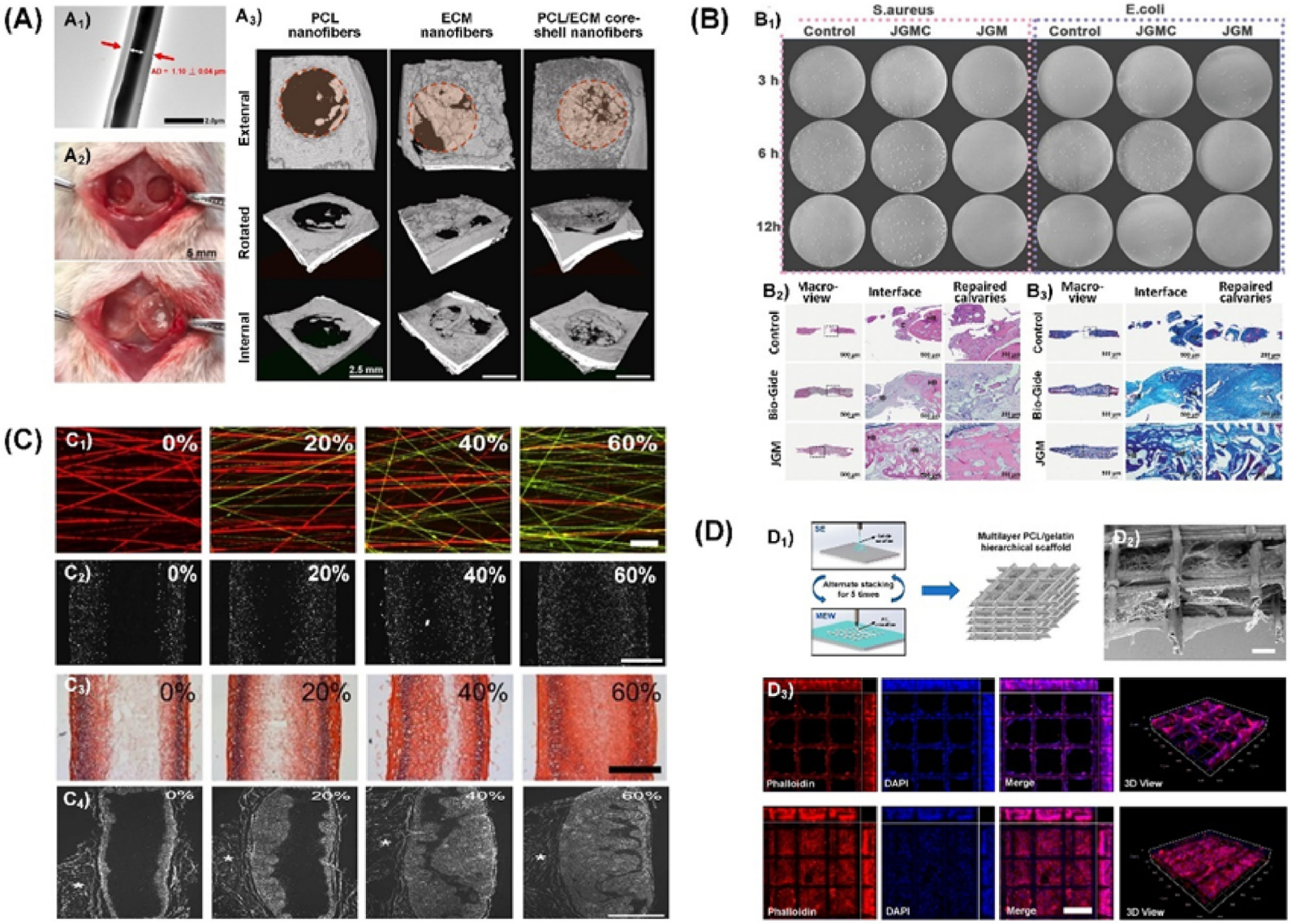


Fig. 3. (A) Transmission electron microscopy (TEM) of PCL core-dECM shell nanofibers (A_1), implantation of PEC into rats with critical-sized calvarial bone defects (A_2), and Micro CT images showing the efficacy of tissue-engineered periostea made from PCL, ECM, and PEC on healing critical-sized bone defects (A_3). Reproduced with permission [64]. Copyright 2022, Elsevier. (B) Photographs of bacterial viability on JGM to evaluate antibacterial function (JGMC, i.e., without incorporating HAP and P(DMC-AMA)) (B_1), and H&E (B2) and Masson's trichrome (B_3) staining images of newly formed bone after 8 weeks of implantation (HB, host bone; IB, immature bone; NB, new bone; C, connective tissue). Reproduced with permission. Copyright 2020, John Wiley and Sons [57]. (C) Fluorescent images of PCL and PEO nanofibrous composites with different relative numbers (C_1), and removal of PEO fibers for functional tissue formation: DAPI-stained (C_2) and picrosirius red-stained (C_3) cross-sections showing cell infiltration and matrix distribution respectively after 12 weeks of in vitro culture, and DAPI-stained cross-sections showing colonization by host cells after s.c. Implantation of 4 weeks (C_4). Reproduced with permission [107]. Copyright 2012, National Academy of Sciences. (D) Schematic illustration of the micro/nano hybrid scaffold fabrication (D_1), SEM image of the cross-section of the scaffold (D_2), Scale bar = 40 μm, and fluorescent microscope images displaying the penetration and distribution of Saos-2 cells on the control (upper) and the hierarchical (bottom) scaffold after 7 days culturing (D_3). Reproduced with permission [106]. Copyright 2021, Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

way to produce large pores with great pore interconnectivity. In the hybrid scaffolds, the nanofibers exhibit ECM-like characteristics benefiting cell adhesion and proliferation, while the microfibers are conducive to the formation of improved porosity and pore size facilitating cellular infiltration and providing robust mechanical support for 3D cell growth. In general, synthetic polymers with favorable mechanical properties are used for making microfibers, and natural ones with superior biological performance for nanofibers in these scaffolds.

To date, some material pairs including PLGA/collagen [30,112], poly(d,L-lactic acid) (PDLLA)/chitosan [113], and poly-3-hydroxybutyrate(PHB)/gelatin [54], have been prepared into nano/microfibrous hybrid scaffolds through traditional solution electrospinning for bone and skin tissue engineering. For example, Sanhueza et al. optimized the electrospinning parameters to enable simultaneous deposition of microscale PHB-fibers and nanoscale gelatin-fibers, serving as scaffolds for healing diabetic wounds [54]. Moreover, a strategy combining solution electrospinning with melt electrospinning provides a more effective way to obtain the desired discrepancy of fiber diameters between different materials, on account of melt electrospinning tending to produce microfibers. Kim et al. implemented this strategy to fabricate silk fibroin/PCL nano/microfibrous composite scaffolds and evaluated their capability to manage bone defects [105]. The in vivo tests showed the scaffolds can stimulate new bone formation, suggesting their potential for bone-regeneration.

Furthermore, executing melt electrospinning in a direct writing mode, termed melt electrospinning writing, allows precise control of the porosity and pore shape of the scaffolds. Thus, a sequential electrospinning process that alternately stacking of PCL-melt electrospinning writing layer and gelatin-solution electrospinning layer was proposed by Wang's team, to produce a micro/nano hierarchical scaffold for bone tissue engineering (Fig. 3 D) [106]. Cell penetration study that seeding osteoblast cells and culturing 7 days, demonstrated that the cells on the micro/nano scaffolds can grow and distribute evenly throughout the whole scaffolds, while no cells are found to bridge and grow between PCL microfibers of the control scaffolds.

3.1.3. Mimicking in vivo-like gradients

The heterogeneity of native tissues determined requiring a bionic scaffold to recapitulate the native gradients for the successful restoration of the native tissues [149]. Multi-material electrospinning has the potential to fabricate graded scaffolds with compositional, structural, or mechanical gradients, in stratified or continuous manners, for various tissue-engineering applications.

3.1.3.1. Tissue-to-tissue interfaces. In the musculoskeletal system, tissue interfaces such as tendon-to-bone, ligament-to-bone, muscle-to-tendon, and cartilage-to-bone, play a crucial part in tension or bear compression [150,151]. It was found that regenerating these interfaces faces a significant challenge as a result of their low self-healing capacity and complex architecture.

For reconstruction of the tendon-to-bone interface, nanofibrous scaffolds with the region or layer-wise differences, such as compositional, structural, and mechanical characteristics, have been fabricated by sequential and simultaneous electrospinning. Aiming to bridge the defects of massive rotator cuff tear (MRCT), Chen's team fabricated a two-segment patch, where one side of PLGA/collagen I nanofibers is applied to connect the tendon stump while another part of PCL/nano-hydroxyapatite (nHA) nanofibers is used to stimulate bone growth, by selective deposition the second material onto one side of the as-electrospun layer using a plastic plate [43]. The in vivo study in rabbit models exhibited this path can promote tendon and bone tissue ingrowth at two sides simultaneously for effective MRCT regeneration. However, this patch is not considered as an interfacial scaffold in a strict sense, owing to its incapacity to simulate the characteristics of the enthesis, a transitional tissue between the tendon and bone. Thus, the upgradation of this scaffold by adding an 'enthesis-mimicking' layer containing collagen II in combination with imitating anisotropic microarchitectures has recently been performed for better healing the MRCT by Chen's team [44].

Alternatively, Cui's group produced a bipolar fibrous membrane with a poly-L-lactic acid (PLLA) layer and a PLLA/nHA layer through sequential electrospinning followed by *in situ* biomineralization, to correctly mimic gradient non-mineralized and mineralized fibrocartilage of entheses for tendon-to-bone insertion regeneration [114]. The implant of the dual-layer membranes induced the reconstruction of the enthesis, which promote tendon-to-bone integration, thereby facilitating MRCT repair. Recently, they have further incorporated HKUST-1 and ZIF-11 microparticles into the tendon-face layer and bone-face layer of the poly(lactic acid) (PLA) fiber membranes, respectively, to achieve bipolar metal flexible scaffolds, which can realize the zone-specific and sustainable release of different metal ions [115]. Both in vitro and in vivo tests revealed that the bipolar scaffolds not only promote the gradient regeneration of the tendon and bone tissue synchronously, but also facilitate the fibrocartilage reconstruction that is important for the enthesis recovery, resulting in its integrated restoration ability of the tendon-to-bone interface (Fig. 4 A).

Analogously, the scaffolds for ligament-to-bone engineering are commonly designed into biphasic structures with a continuously graded transition region [41,131,132]. Samavedi et al. fabricated graded meshes by simultaneous electrospinning of nHA-PCL and poly(ester urethane) urea elastomer (PEUUR2000) solutions using two offset spinnerets. They found that both mineral and mechanical gradients along the length of the mesh created after selectively depositing mineral crystallites on the nHA-PCL fibers, and good biocompatibility of the meshes for MC3T3-E1 osteoprogenitor cells. These results indicated the graded meshes can closely mimic the ligament-to-bone transition for interfacial tissue engineering [131]. Subsequently, an improved strategy that uses a dual drum collector was proposed by the same group, to engineer shape-like bone-ligament-bone scaffolds with gradients in fiber orientation, composition, and mechanical properties, aiming to serve as an artificial bone-patellar tendon-bone graft for anterior cruciate ligament (ACL) replacement [132]. The potential of the graded scaffolds for in vivo ACL regeneration was further investigated [41]. Specifically, microfiber-reinforced nanofibrous scaffolds possessing fiber orientation and nHA/Bone morphogenetic protein 2 (BMP-2) gradients were produced by sequential electrospinning, Pilot animal experiments demonstrated the implanted scaffolds are beneficial for the generation of in vivo-like fibrocartilage tissues at the graft-bone attachment.

Moreover, some studies have been conducted to confirm the capacity of the biphasic scaffolds directing zonal differentiation of bone marrow stem cells (BMSCs), which might be beneficial for ligament-bone osteointegration [42,133]. For example, Jiang's team investigated the response of BMSCs onto structural/compositional gradient biomimetic scaffolds produced by sequential electrospinning [42]. The scaffolds had a gradient distribution of BMP-2 and nHA contents, along with the gradually changed fiber orientations from random to align (Fig. 4 B). The in vitro BMSCs cultured on the scaffolds demonstrated that the resulted gradients of BMP-2 and nHA can effectively induce zonal differences in bone-specific gene expression, indicating their promises in the regeneration of ligament-to-bone interfaces.

Concerning muscle-to-tendon junctions, multi-material electrospinning has not been widely explored, and very few studies are published on this topic until now. Ladd et al. developed a cytocompatible scaffold with regional variations in mechanical properties to replicate the patterns of muscle-tendon junctions (MTJ) [55]. Three-zone mats consisting of a PCL/collagen side, a transitional center, and a PLLA/collagen side were prepared using an offsetting simultaneous electrospinning method. The scaffold moduli from the PCL/collagen side to the PLLA/-collagen side varied from 4.490 to 27.62 MP, which recapitulates the stiffness differences of native MTJ to some extent. And in vivo assays

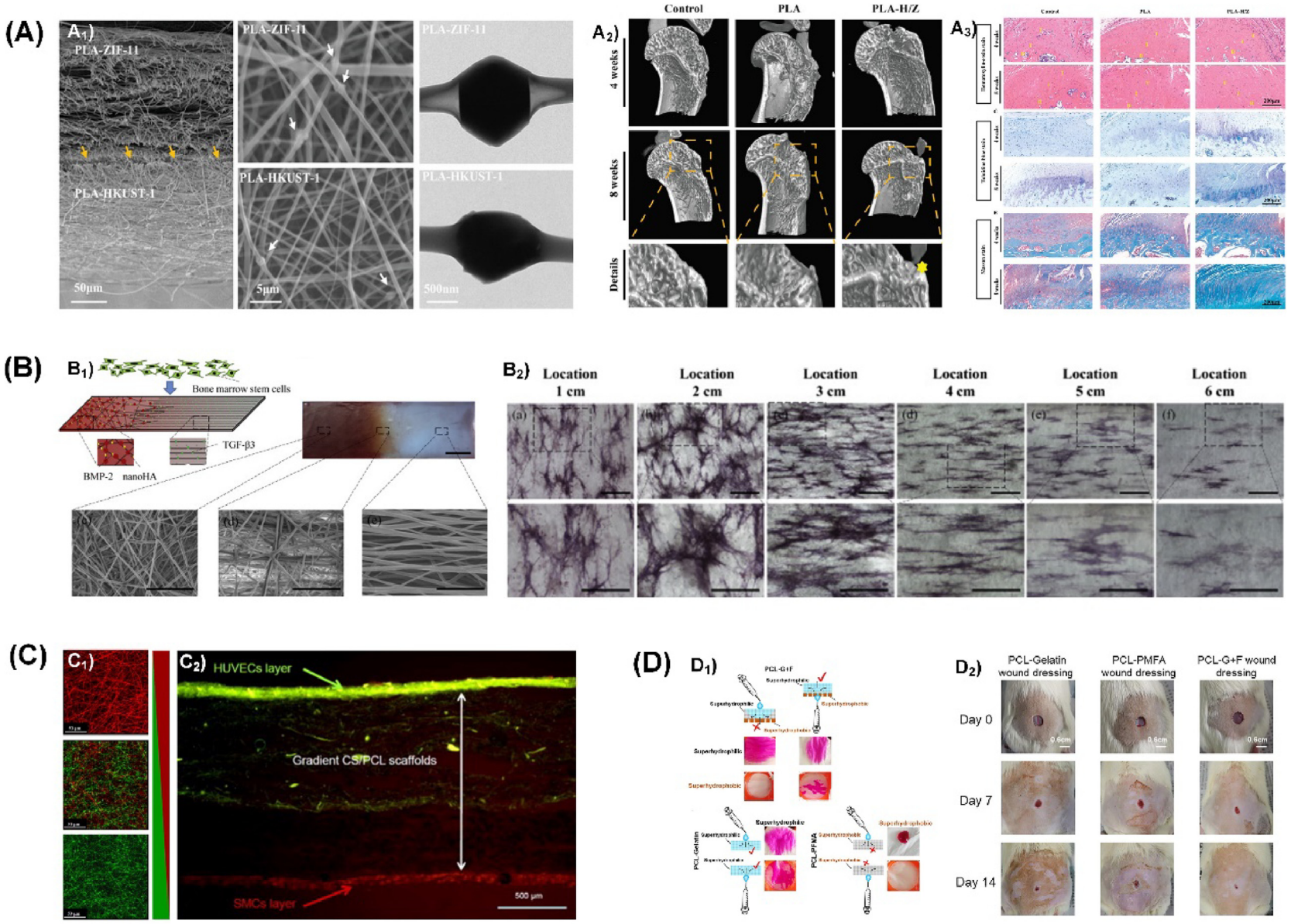


Fig. 4. (A) SEM images of the bipolar membranes (A_1), and testing their regeneration ability on rat rotator cuff tear models after 4 and 8 weeks compared with different groups: micro-CT reconstruction images for osteogenesis evaluation (A_2) and staining images showing tendon and fibrocartilage regeneration (A_3). Reproduced with permission [115]. Copyright 2022, John Wiley and Sons. (B) Schematic illustration, gross photograph, and SEM images of the graded scaffolds (B_1), and ALP staining of different regions in the BMSCs cultured on the scaffolds for 7 days; bar = 250 μm (B_2). Reproduced with permission [42], Copyright 2020, Elsevier. (C) Laser confocal scanning images showing material gradient in the depth direction (chitosan and PCL stained with red rhodamine and green FITC, respectively, and cross-section fluorescent images of blood vessel-mimicking cell structure. Reproduced with permission [134], Copyright 2012, Elsevier. (D) Simulation experiment using red rhodamine solution showing irreversible one-way drainage function of the wound dressing compared with the hydrophobic and hydrophilic-only one (D_1), and the skin injury models of SD rats treated with different wound dressings (D_2). Reproduced with permission [35], Copyright 2020, Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exhibited that the scaffolds are non-toxic and cytocompatible for C2C12 myoblasts and NIH3T3 fibroblasts.

At the cartilage-bone junction, an osteochondral tissue comprises cartilage, intermediate calcified cartilage, and bone. Multilayer nanofibrous scaffolds with both cartilage and bone biomimicking characteristics were developed for osteochondral tissue engineering by sequential electrospinning [116,117]. For example, Joseph et al. fabricated a biphasic scaffold consisting of a bioactive glass layer and a silk fibroin layer with a well-integrated interface to mimic the hierarchical osteochondral structures [117]. The silk fibroin region demonstrated a favorable elasticity for cartilage, while the bioactive glass region provided a stiff compression resistance for bone. More importantly, the biphasic scaffolds had the capacity for the growth and maturation of both osteoblasts and chondrocytes in a spatially confined fashion.

3.1.3.2. Blood vessels. Blood vessels have a three-layer structure including Tunica intima (inner), Tunica media (middle), and Tunica adventitia (outer)layers, where endothelial cells and smooth muscle cells lie in the inner and middle layers, respectively. This elegant structure gives the native blood vessels with not only distinguished elasticity, strength, and compliance, but also excellent haemodynamic and hemocompatible performance. Thus, it is reasonable to design multilayer scaffolds with morphological and compositional resemblance to native ECM for vascular engineering, considering whether avoiding structural mismatches with native matrix or replicating their physiological functions [152].

By sequential electrospinning collecting onto a rotating mandrel, a plenty of bilayer or trilayer scaffolds with tubular shape for small-diameter vessel engineering to date have been made from various multi-polymer systems, including PLA-PCL/Polyurethane (PU)-PCL/PLA-PCL [27], PCL-elastin-collagen with varying blending ratio [33], PLA/PCL [118], PCL/collagen/PLLA [119], PLCL-collagen/PLGA-silk fibroin/PLCL-collagen [120], and PLGA-gelatin-chitosan/PLGA-gelatin/PLGA-gelatin-graphene [121]. The studies above indicated that these multilayer biomimetic grafts can provide a realistic vascular substitution, with respect to mechanical (modulus and compliance) and biological (nonthrombogenic) properties, for vessel remodeling and regeneration. For example, Liu's group developed a biomimetic nanofibrous vascular graft with three material-specific layers [27]. The inner layer of PLA/PCL is conducive to endothelial cell affinity resulting in accelerating endothelialization. The middle layer of PU/PCL was responsible for offering excellent mechanical properties. The circumferentially-aligned outer layer of PLA/PCL was favorable for directing the organization of vascular smooth muscle cells along the circular direction.

Moreover, the incorporation of bioactive agents, such as growth factors and peptides, in a specific layer could be employed to organize human umbilical vein endothelial cells (HUVEC) and vascular smooth muscle cells (vSMCs) in a blood vessel-like manner [122,123]. For example, a trilayer vascular scaffold consisting of an inner vascular endothelial growth factor (VEGF)-loaded poly(ethylene glycol)-b-poly(L-lactide-co-ε-caprolactone) (PELCL)-gelatin layer, a middle platelet-derived growth factor (PDGF)-loaded PLGA-gelatin layer, and an outer PCL-gelatin layer was fabricated [122]. The spatiotemporal delivery of both VEGF and PDGF facilitated neovascular tissue formation and maturation through promoting endothelialization and inhibiting vSMCs hyperproliferation. In addition to multilayer architectures, vertical component gradient nanofibrous scaffolds of heparin and VEGF-loaded chitosan/PCL were fabricated through programmed simultaneous electrospinning followed by covalent bonding and bioaffinity binding [134]. Due to combining the positive effect of heparin and VEGF on human umbilical HUVEC with the inhibition of vSMCs by the heparin, the gradient scaffolds enabled the formation of a whole monolayer of HUVEC on their top side, and vSMCs adhered and proliferated onto their bottom surface, which is similar to the luminal and adventitial structure of natural blood vessels, as shown in Fig. 4 C.

3.1.3.3. Skin and dura mater. Anatomically, the skin comprises three interconnected layers: the top epidermis acting as a protective barrier, the middle dermis giving skin flexibility and strength, and the bottom hypodermis as a shock absorber. By mimicking the epidermis and dermis layers of skin, some asymmetric fibrous membranes were developed as ideal wound dressings for accelerating wound healing, through sequential or simultaneous electrospinning [124–128,135]. These asymmetric membranes generally presented a blocked outer layer that prevents physical damage, rapid dehydration, and pathogen penetration, as well as an inner porous layer with high exudates absorption and improved bactericidal activity for effective skin regeneration. For example, an asymmetric wettable composite dressing consisting of a highly hydrophobic outer layer and a hydrophilic inner layer was prepared for diabetic wound healing, via the first electrospinning of PCL onto a micron-pore-size mesh and subsequent electrospinning of pioglitazone-incorporated gelatin [128]. The hydrophobic outer layer with bioinspired micro-nanostructure played vital roles in waterproofing and prevention of bacterial adhesion, while the hydrophilic inner layer provided a biocompatible room for cell growth, proliferation, and angiogenesis. More importantly, the in vivo evaluation on db/db mice (type 2 diabetes) and STZ rats (type 1 diabetes) exhibited these asymmetric wettable had superior healing efficacy for full-thickness skin wounds, compared to traditional gauze and existing commercial dressings (Tegaderm).

Dura mater is a two-layer fibrous membranous connective tissue surrounding the spinal cord and brain, responsible for protecting cerebrospinal fluids from leakage and returning blood to the heart. To date, some multi-layer scaffolds fabricated by sequential electrospinning have been designed to replicate this unique structure of the dura mater for functioning as a novel dural substitute [34,129,130]. By covering the aligned silk fibroin/collagen-I fibers with the random silk fibroin fibers, a dual-layer heterogeneous fibrous scaffold was fabricated to mimic the structures and functions of native dura. Where the inner anisotropic layer is used to keep the quiescent phenotype of fibroblast and the outer dense layer can suppress myofibroblast adhesion [129]. Further, it was revealed that the biomimetic scaffolds can effectively accelerate the dura mater regeneration, along with suppressing epidural scar fibrosis, in a rabbit laminectomy model by in vivo study.

3.1.4. Creating a novel functionality

As mentioned above, multi-material electrospinning can controllably merge different functionalities of varying materials into a micro/nanofibrous architecture for constructing an ideal multifunctional scaffold. More importantly, it can be also applied to endow the scaffold with a novel functionality.

The mechanochemical property of native ECM that enables the ECM to adapt to mechanical loading, was imparted into multifiber hydrogel by simultaneous electrospinning of distinct fibers [136]. Specifically, aldehydes and hydrazides as complementary chemistries are introduced into distinct fiber populations of the fibrous hydrogel networks, and the fiber populations maintain a separated state until being brought into mutual proximity under mechanical load, resulting in the interaction of aldehydes and hydrazides by a chemical reaction. This fiber interaction binds the adjacent materials together, leading to in vivo-like force-responsive properties. By this characteristic, these adhesive fiber mats could be wrapped into a stable luminal structure for vessels and peripheral nerves.

Another novel functionality created by multi-material electrospinning is self-pumping, i.e., unidirectional drainage of excessive biofluid from hydrophobic site to hydrophilic site in the Janus fiber membranes, which shows great potential in accelerating wound healing [35,36]. For example, a Janus amphipathic wound dressing was fabricated by sequential electrospinning of a superhydrophilic PCL-gelatin and a superhydrophobic PCL-poly(perfluorodecyl methacrylate)--block-poly(dimethylsiloxane)-block-poly(perfluorodecyl methacrylate) [35]. This wound dressing has the ability to not only drain surplus fluids away from wounds, but also prevent bacteria and cell adhesion to the

dressing. Compared with the single-phase wound dressings, this amphipathic wound dressing could vastly promote wound healing in SD rats with skin lesions (Fig. 4 D).

3.2. Drug delivery

A drug delivery system refers to a formulation or device that is developed to deliver a drug to the body for administration and subsequent absorption into the bloodstream or target tissues. Various drug delivery vehicles including films, micelles, microspheres, nanoparticles and nanofibers, have been designed to optimize the effectiveness of pharmaceutical treatments by controlling drug release and enhancing drug stability. The incorporation of active principles in electrospun nanofibrous meshes has proven to be a highly efficient method for the *in situ* delivery of a wide range of drugs. The drug delivery based on electrospun nanofibers may be dominated by four main release mechanisms, as shown in Fig. 5. When nonbiodegradable polymers are employed as the matrix, drug release is primarily governed by diffusion. Water molecules penetrate the polymer, dissolve the drugs, and then facilitate their diffusion out of the polymer network. Conversely, in the case of biodegradable coaxial fibers, the release mechanism becomes more intricate, involving diffusion and polymer degradation.

Multi-material electrospinning allows a stronger control over single drug release profiles than single-material one, because of its capacity to fabricate new micro/macrostructures with advanced performance. Moreover, it also facilitates controlled co-delivery of multi-drug through encapsulating various active ingredients into diverse electrospinning materials, respectively, for many applications.

3.2.1. Tuning single drug release

A controlled release profile for specific drugs is indispensable for improving the therapeutic effect and reducing the toxicity of conventional dosage forms. Multi-material electrospun nanofibers have been widely employed to offer various controlled drug release behaviors depending on the drug characteristics and application scenarios, such as rapid, sustained, biphasic, and stimuli-responsive release, as shown in Table 3.

3.2.1.1. Rapid release. Rapid release (fast-dissolving) drug delivery systems are designed to dissolve or disintegrate quickly (typically within 60 s) in the mouth, allowing the drug to be absorbed rapidly into the bloodstream without the need for water to aid in swallowing [192]. Rapid release drug delivery systems offer several advantages over traditional oral dosage forms, such as tablets or capsules. These advantages include improved patient compliance, particularly among pediatric and geriatric populations, convenience, and enhanced bioavailability.

The oral delivery of active compounds for the fast onset of therapeutic action is a well-known therapy for numerous diseases, such as fever, heart attacks, aches, and spirit disease [75]. However, the 60% developed and 40% already used active pharmaceutical ingredients are poorly water-soluble. Therefore, the fast dissolution and permeation of water-insoluble drugs during oral administration faces significant challenges but is highly sought. In recent years, electrospinning approaches have emerged as a potent option for executing a "fast dissolving" strategy, due to nanoscale fiber diameter decreasing the diffusion layer thickness, large-surface area of the nanofibers meaning a more loaded drug can contact with the dissolution media, high porosity of nanofibrous mats facilitating the fast mass transformation of solvent and drug molecules, and maintaining loaded drug an amorphous state leading to no lattice energy barrier to dissolution [193]. Somewhile, it is however difficult to find a suitable solvent for synchronously having good solubility of the active ingredient and endowing the polymer's fine electrospinnability, using single fluid electrospinning. For instance, PVP K10 with its small molecular weight tends to dissolve more rapidly in water, thereby facilitating the very rapid dissolution of therapeutic drugs. However, it does not form many entanglements within the solution, and fail to effective drawing of the jet fluids. While a high molecular weight PVP K90 is an ideal filament-forming polymer.

Thus, coaxial electrospinning was exploited to incorporate materials without filament-forming capacities but having specific functions within the fiber structure. Using coaxial electrospinning to encapsulate unspinnable liquid containing PVP and quercetin by a spinnable liquid containing PVP, sodium dodecyl sulfate, and sucralose, Li et al. reported the preparation of an oral fast disintegrating drug delivery platform of core-sheath nanofibers [65]. The core-sheath nanofiber mats were able to rapidly release the contained poorly water-soluble quercetin within 1 min by in vitro dissolution studies, due to the hygroscopic and hydrophilic properties of PVP, as well as the huge surface area and greater porosity of electrospun nanofibers (average diameters of 600 nm). A similar research conducted by Wu and co-workers showed the coaxial electrospinning of sedative nanofibers membranes intended for the oral fast delivery of helicid, where an embedded sweetener (sucralose) in the shell plays the role in taste masking [154]. Additionally, an additional shell layer could be applied as an accelerator of the drug release [155–157]. For example, the dissolution rate of acetaminophen in the hydroxypropyl methyl cellulose core was improved, resulted from faster initial absorbance by the high-soluble and well-hygroscopic PVP shell [156].

Other than the use of a spinnable shell fluid in the above studies, the spinnable core fluid as backbone was also exploited to support the unspinnable shell liquid containing poorly water-soluble drug by modified coaxial electrospinning, endowing the core-shell nanofibers a desired functional performance [66]. Specifically, the core section was made from PVP K90 or PCL with filament-forming capacity, and the shell layers consisted of poorly water-soluble quercetin or tamoxifen citrate, surfactant sodium dodecyl sulfate and hydrophilic PVP K10 with a thickness smaller than 100 nm were prepared from the fluids without electrospinnability. In vitro dissolution tests demonstrated that a fast release profile of the model drugs from the shell layers by dissolving the PVP K10, regardless of the core matrices.

Recently, side-by-side electrospinning also exhibited its capacity to simultaneously treated with an unelectrospinnable fluid and an electrospinnable one to create Janus structural nanocomposites for rapid onset of drug therapeutic action [75]. One side of the Janus nanofibers contains

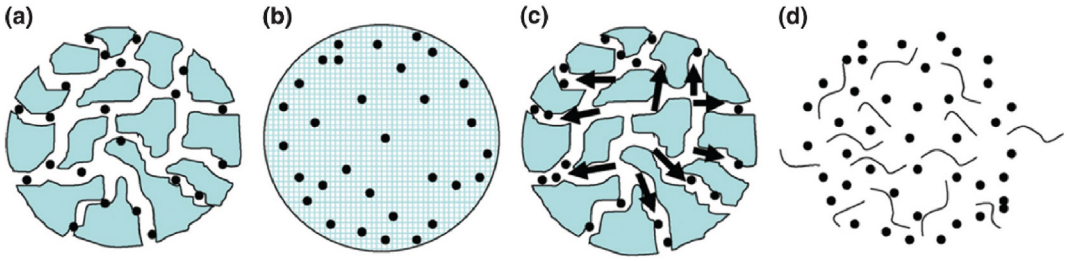
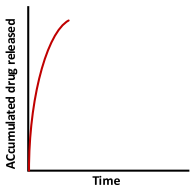
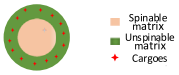
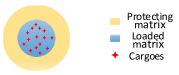
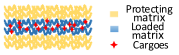
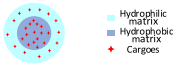
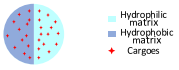
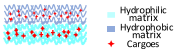
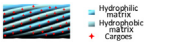
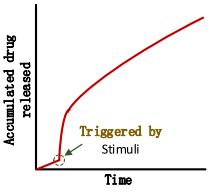
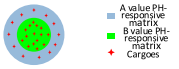
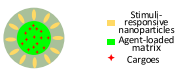
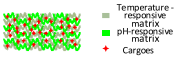


Fig. 5. Basic release mechanisms: (a) diffusion through micropores, (b) Diffusion through polymer networks, (c) osmotic pumping and (d) degradation or erosion. Reproduced with permission [153]. Copyright 2011, Elsevier.

Table 3
Applications of multi-material electrospinning to achieve different controlled drug releases. Polyvinylpyrrolidone (PVP), cellulose acetate (CA), polyacrylonitrile (PAN), ethyl cellulose (EC), polyethylene glycol (PEG), Chitosan (CS), poly (tetramethylene ether) glycol based-polyurethane (PTMG-PU), graphene oxide (GO), gold nanorods (GNRs), collagen (Col), gelatin (Gel).

Representative release curves	Principle		Matrix and Cargoes (Bold)	Ref
Rapid release 	Encapsulating unspinnable drug-loaded matrix by shell layers or accelerating the dissolution of drugs by the sheath		PVP K60-**Quercetin**/PVP K60-Sodium dodecyl sulfate-Sucralose	[65]
			PVP K10-**Helicid**/PVP K90-Sucralose	[154]
			PVP K60 and sodium hydroxide-**Quercetin**/PVP K60 and citric acid monohydrate	[155]
			Hydroxypropyl methyl cellulose-**Acetaminophen**/Sucralose and PVP	[156]
			PVA-**Antihistamine levocetirizine**/Na-taurocholate, citric acid, cyclodextrin, and PVP	[157]
	Supporting unspinnable drug-loaded shell by core		PVP K90 or PCL/PVP K10-**Quercetin** or **Tamoxifen citrate**	[66]
	Janus nanofibers		PVP K90-**Helicid**/PVP K10-Sodium dodecyl sulfate	[75]
Sustained release 	Isolating drug-loaded cores by a blank shell		PEO-**Doxorubicin**/PCL	[67]
			Gliadin-**Ferulic acid**/CA	[158]
			Vitamin C and Vitamin E derivative/PAN	[159]
			CA-**Ketoprofen**/CA	[160]
			PLA-**Curcumin**/PCL or PCL-**Curcumin**/PLA	[161]
			PEO-**5-fluorouracil**/Poly(ether-ester-urethane) urea	[162]
			PCL-**Rifampicin**/PCL	[163]
			PCL-**Metronidazole**/Zein	[164]
	Tri-layered fibers with graded concentrations		EC-**Ketoprofen** (high concentration)/EC-**Ketoprofen** (middle concentration)/EC-**Ketoprofen** (low concentration)	[165]
	Surrounding drug-loaded inner layers by hydrophobic outer layers		EC/Gel-**Curcumin**/EC	[37]
			PLGA and PCL/PLGA and PCL-**Ibuprofen**/PLGA and PCL	[166]
			PCL/PLGA-**Rhodamine B**/PCL	[167]
			Balangu gum/Gel-**Menthol**/Balangu gum	[168]
			PLA/**Dichloroacetate**-PLA/PLA	[169]
Biphasic release 	Insoluble core and hydrophilic shell		Zein-**Ketoprofen**/PVP-**Ketoprofen**	[68]
			EC-**Ketoprofen**/PVP-**Ketoprofen**	[170]
			EC-**Ketoprofen**/EC/PVP-**Ketoprofen**	[171]
			EC-**Ibuprofen**/PEG-**Ibuprofen**	[172]
	Protecting drug-loaded cores by a blank shell		PVP-**Modin**/CA	[173]
			CS-**Tetracycline hydrochloride**/PCL	[174]
	Janus nanofibers with hydrophilic and insoluble sides		PVP K60-**Ketoprofen**/EC-**Ketoprofen**	[76]
			PVP K10-**Ferulic acid**/Zein-**Ferulic acid**	[72]
			PVP K60-**Tamoxifen**/EC-**Tamoxifen**	[175]
	Multi-layered structures with hydrophilic and insoluble layers		Zein-**Ketoprofen**/PVP and GO-**Ketoprofen**/Zein-**Ketoprofen**	[38]
			PVP K30-**Ketoprofen**/EC-**Ketoprofen**/PVP K30-**Ketoprofen**	[23]
			PCL-**Tetracycline hydrochloride**/PVP-**Tetracycline hydrochloride**	[29]
	Hybrid nanofibrous yarns		PLLA-**Cefazolin**/PVA-**Cefazolin**	[176]
Stimuli-responsive release 	Triggering core-loaded drug release by dissolving the protected shell		**Lecithin-diclofenac sodium**/Eudragit S100	[177]
			PEO-**Indomethacin** or **Mebeverine hydrochloride**/Eudragit S100	[178]
			PEO-**Gadolinium (III) diethylenetriaminepentaacetate hydrate**/Eudragit S100	[179]
			Hydroxypropyl methylcellulose-**Carmofur** and **Rose bengal**/Eudragit S100	[180]
			Eudragit S100-**Aspirin**/Eudragit S100	[181]
			PVP-**Diclofenac sodium**/Shellac	[182]
			PU-**Rhodamine B**/Cellulose acetate phthalate	[183]
			Liposomes and PVA-**Salmon calcitonin**/PEO and sodium alginate	[184]
			CS nanoparticle and PVA-**Quercetin**/Sodium alginate and PEO	[185]
	Creating core-shell fibers from polymers with different PH value responses		Eudragit L 100-**Keyacid Blue dye**/Eudragit S 100-**Keyacid Uranine dyes** or Eudragit S 100-**Keyacid Uranine dyes**/Eudragit L 100-**Keyacid Blue dye**	[186]
	Doping "smart" nanoparticles in the shell to switch the core-loaded drug release		PEO-**BMP-2**/PCL and redox-responsive nanogels	[187]
			PEO-**Doxorubicin**/PCL and poly(*N*-isopropylacrylamide)-based nanogel	[188]
			Polyethylenimine-**Plasmid DNA**/PLLA, Gel, and GNRs	[189]
			PTMG-PU-**Paclitaxel**/CS, GO and GNRs	[190]
	Mixed different stimuli-responsive nanofibers		Poly(*N*-vinylcaprolactam) and EC-**Ketoprofen**/Eudragit S100-**Ketoprofen**	[191]

PVP K10 and sodium dodecyl sulfate, whereas the other side comprised PVP K90 and helicid. Compared with monolithic nanocomposites by blending electrospinning, these Janus structures demonstrated pronounced hydrophobic properties and the ability to boost the dissolution and transmembrane permeation of helicid.

3.2.1.2. Sustained release. A sustained release delivery system refers to a drug delivery system that can achieve a prolonged therapeutic effect by gradually releasing the therapeutic substance over an extended duration, typically days or months, following the administration of a single dose. This type of delivery system tends to maintain favorable therapeutic drug levels within the body for an extended period, thereby reducing the frequency of dosing, reducing side effects, keeping stable drug absorption levels in blood and plasma and improving patient compliance [194]. As an example, ciprofloxacin administered as an extended-release formulation, which permits convenient once-daily treatment, provides a more favorable peak concentration value and less interpatient variability than the immediate-release twice-daily formulation [195].

As mentioned above, the characteristics of the electrospun nanofibrous architectures determine that electrospinning-based drug delivery systems have intrinsically a predisposition to an initial "burst" of drug release. Sometimes, a controlled and sustained release profile is however desirable for systemic administration owing to some of its advantages, such as elevating the therapeutic effectiveness; mitigating the adverse side effects, and reducing the frequency of administration. Therefore, multi-material electrospinning has also been investigated to alleviate or even eliminate the initial burst release for achieving a long-lasting efficiency.

In general, a "protective layer" strategy, that is nonhygroscopic blank (drug-free) coating layer at either micro or macro-scale on the core-medicated sections, is applied to slow down the drug release. This strategy can come true at the nanoscale through loading active ingredients into the inner core of the core-shell nanofibers produced by coaxial electrospinning, while the shell part serves as the protective layer. To date, long-term drug release systems of various drugs have been obtained for prolonged therapeutic effect, including doxorubicin [67], ferulic acid [158], vitamin C and vitamin E derivative [159], ketoprofen [160], curcumin [161], 5-fluorouracil [162], rifampicin [163] and metronidazole [164]. For example, careob-like nanofibers were fabricated for wound healing promotion and hypertrophic scars inhibition in skin tissues [162]. It consisted of 5-fluorouracil-loaded dendritic mesoporous bioglass nanoparticles compounded with water-soluble PEO as the core and poly(ether-ester-urethane) urea as the shell. Differing from the direct electrospinning of 5-Fu and PEEUU blending, the core-shell structure can effectively control the degradation rate of nanofibrous patches. The animal experiment exhibited that a sustained release of 5-fluorouracil helps the repair of scar skin tissue defects.

Aside from the controlled release, the coaxial electrospinning also conferred an additional advantage to encapsulating fragile biological molecules (such as growth factors, enzymes, and DNA) without direct contact with organic solvents, avoiding their denaturation, where the bioactive agents are dissolved in the aqueous processed into the core by spinnable organic polymer solutions.

Additionally, a novel medicated nanofiber with gradient concentrations of the functional ingredient ketoprofen along a radial direction was generated for zero order drug delivery by triaxial electrospinning [165]. In this electrospinning process, all three working fluids (outer, middle, and inner) used ethyl cellulose (a non-toxic and biodegradable polymer) as the filament-forming matrix, but incrementally increasing ketoprofen concentrations from outside to inside. This innovative design leads to a drug delivery system able to provide a linear release for over 20 h.

In addition, sequential electrospinning provides an easy way to create macroscopic protective layers for the inner encapsulated active ingredients, by constructing sandwiched architectures [167,168]. Wang et al. prepared a multilayer mat with ethyl cellulose and curcumin-loaded gelatin nanofibers serving as the outer and inner layer, respectively [37]. The hydrophobic ethyl cellulose outer layers with a water contact angle of about 135[a], can form a physical barrier for hindering the inner layer from direct contact with the medium. Thus, the sandwiched mat showed a sustained release fashion of the encapsulated curcumin for 96 h by In vitro release test. Using the same method by Mao's group, a sandwiched scaffold loaded with ibuprofen in the inner layer was fabricated for the prevention of peritoneal adhesion [166]. This sandwiched scaffold provides a prolonged release of ibuprofen over 14 days, which can endow its capacity to significantly prevent the adhesion of fibroblasts and macrophages, potentially serving as an anti-adhesion barrier.

3.2.1.3. Biphasic release. The biphasic release profile is considered a mixture of immediate release and sustained release patterns, i.e., an initial burst release followed by a prolonged release. This two-stage release system can lead to promptly exercising the therapeutic effect as a result of a high drug content at the lesion site, as well as reduced adverse reactions and minimized administration times obtained by the maintenance of drug release for a long duration [196]. An excellent example of biphasic release is the release of diclofenac sodium as a nonsteroidal anti-inflammatory drug in the small intestine. In this case, an initial rapid release in the duodenum is applied to provide immediate pain relief in the first hour, followed by a gradual release to ensure a sustained and prolonged therapeutic effect [197].

Until now, to implement a biphasic release behavior, multi-material electrospinning has been designed to produce a variety of innovative nanofibrous architectures, including core-shell nanofibers by coaxial electrospinning [68,170–172], Janus nanofibers by side-by-side electrospinning [72,76,175], a multilayered nanofibrous film by sequential electrospinning [23,29,38], hybrid nanofibrous yarns by simultaneous electrospinning [176].

In these architectures, the core-shell nanofibers are the most widely one, in which the model drug is usually loaded in both the slow-degrading core matrix and the water-soluble sheath matrix for immediate and sustained drug release, respectively [68,170,171]. For example, triaxial core-shell fibers comprised of a ketoprofen-loaded cellulose acetate core layer, a middle drug-free cellulose acetate layer, and a ketoprofen-loaded PVP outer layer, have been developed for accurate dual-stage drug release, where its inner, middle, and outer sections had a size of 300, 60, and 50~80 nm, respectively [171]. Cellulose acetate is considered a fine candidate for drug carriers, owing to its biodegradability, biocompatibility, nontoxicity, and insolubility. By adding a bank cellulose acetate layer to generate the discrete drug distributions, the tri-layer drug delivery could offer more accurate release contents at the immediate phase and longer release time at the sustained phase, than the traditional core-shell systems. Recently, it has been found by some researchers that embedding drugs in the hydrophilic core enclosed by a hydrophobic drug-free sheath also can achieve a biphasic release, such as emodin-PVP/cellulose acetate [173] and tetracycline hydrochloride-chitosan/PCL [174]. In addition to the core-shell nanofibers, beads-on-a-string nanostructures prepared by coaxial electrospinning have also been exploited the biphasic drug release, where the ibuprofen is encapsulated in both the soluble PEG beads and the insoluble ethyl cellulose strings [172].

Like the core-shell structures, incorporating drugs into the hydrophilic and insoluble sides of the Janus nanofibers provides an alternative solution to execute the biphasic drug delivery [72,76,175]. Recently, tamoxifen citrate-laden Janus fibers with ethyl cellulose and PVP K60 as carrier matrices were fabricated through side-by-side electrospinning [175]. Using an eccentric spinneret led to the distinct shapes in each side of the Janus fibers, i.e., one is round while another is crescent. FTIR spectra test showed enhanced compatibility between the drug and the polymer matrices. The in vitro dissolution tests exhibited that these Janus fibers with a crescent PVP side and a round ethyl cellulose side are beneficial for quick burst release in the first stage, and prolonged

sustained release in the second stage.

Sandwich-layered nanofibrous mats by sequential electrospinning, also demonstrate their capabilities to engineer the biphasic release [23,38]. For example, tri-layered zein/PVP-graphene oxide/zein nanofiber mats were fabricated by Lee's group to obtain a time-regulated biphasic drug release behavior [38]. Zein with good biocompatibility was electrospun in the top and bottom layers to delay the release in the tri-layered system. It is verified by in vitro release experiments that regulating the thickness of the mats can be used to manage the release speed and sustained-release behavior. Furthermore, the introduction of graphene oxide into PVP nanofibers not only effectively improved the mechanical performance of mats, but also delayed the initial fast release. Apart from the sandwich structure, overcoating the random nanofibers onto the ordered microfibers to form a composite construct, was also developed for biphasic delivery of tetracycline hydrochloride, by combining far-field and near-field electrospinning [29]. Specifically, the fast dissolution of hydrophilic PVP nanofibrous membranes with mean fiber diameter (~1 μm) provided an initial rapid release, while the hydrophobic nature of the ordered PCL microfibers with a mean diameter of 25 μm led to the slow release.

By simultaneous electrospinning using two oppositely charged nozzles, the twisted hybrid nanofibrous yarns were exploited to manage the two-stage release profiles [176]. Cefazolin was loaded in the hybrid yarns consisting of PLLA and PVA nanofibers, in which the biodegradable PLLA is stable in aqueous solutions, while the biocompatible PVA is water soluble. In general, a higher twist rate cause reduced initial burst release and prolonged sustained release, owing to the lower structural porosity and higher fiber crystallinity. Compared with the pure PLLA yarns, the PLLA/PVA hybrid yarns could lead to a higher initial release rate and a larger total release amount.

3.2.1.4. Stimuli-responsive release. The stimuli-responsive materials that undergo rapid physicochemical transitions through response to a specific stimulus, have been introduced into drug delivery systems as a "turn" switch to regulate the release behaviors, aiming to achieve targeted drug release [198], which is termed as stimuli-responsive drug delivery systems. It has the ability to customize drug delivery systems to achieve greater control over dosing and targeted specificity by responding to external (exogenous) and internal (endogenous) stimuli. For instance, glucose-responsive drug delivery systems are developed for diabetes treatment by releasing a monitored amount of insulin in response to blood glucose concentration [199].

However, it is worth noting that direct electrospinning of a nanofiber from stimuli-sensitive polymers is usually insufficient to prevent release under undesirable microenvironmental conditions, since the high surface area of the electrospun nanofibers makes for a great part of the contained drug being present at the fiber surface, thereby tending to easily diffuse into the milieu.

Through coaxial electrospinning, producing core-shell nanofibers that incorporate drugs within the core protected by a shell of drug-free stimuli-responsive polymers depending on physiological triggers such as pH [177–183], enzymes [184,185], and redox gradient [187], has been proposed to resolve this problem. Thereinto, the most used stimuli-responsive materials are pH-sensitive polymers for site-specific drug delivery such as colon [177–182,185] and semen [183], which were mostly executed by Williams's team. For example, core-shell fibers consisted of the mucoadhesive PEO as drug-loaded cores and the pH-sensitive Eudragit S100 polymer as protected shells, were prepared for site-specific releasing indomethacin or mebeverine hydrochloride [178]. The methacrylate-based Eudragit S100 is insoluble below pH 7, but dissolves freely when the pH exceeds 7. Dissolution experiments exhibited that these fibers can render no noticeable release in stomach-like acidic environments, while sustained release over 6–22 h once transferring into a pH 7.4 medium representative of the intestinal tract.

Moreover, multi-pH responses release could be also obtained by coaxial electrospinning [186]. Specifically, two different Eudragit polymers, i.e., Eudragit L 100 (dissolved at pH $\geq$ 6) and Eudragit S 100 (dissolved at pH $\geq$ 7), were made into the core and sheath, respectively. No incorporated material releasing occurred at pH 5 owing to both Eudragit polymers being unsolvable. A sustained release from the Eudragit L 100 core was obtained by dissolving the Eudragit L 100 and protection from Eudragit S 100 sheath at pH 6. The Eudragit S 100 shell release and the perhaps remaining Eudragit L 100 core release would appear at pH 7. When switching the materials of core and sheath, very different pH responses are achieved.

As upgradation, thermally or photothermally responsive nanoparticles, such as redox-responsive c-6A PEG-PCL nanogel [187], thermally changed poly(*N*-isopropylacrylamide)-based nanogel [188], and photothermal gold nanorods (GNRs) [189,190], were embedded into the sheath layers to tune the sheath permeability for switched release from the core. For example, core-shell nanofibers with diameter ranged between about 140 and 260 nm composed of plasmid DNA-loaded polyethylenimine and GNRs-distributed PLLA and gelatin were prepared by Zheng et al. for high-efficiency surface-mediated gene transfection [189]. Activated by appropriate near-infrared irradiation, the GNRs with photothermal property in the sheath layer led to the local heating, thereby enhancing the permeability of the nanofibers, which accelerates the plasmid DNA release from the nanofiber core.

Additionally, a temperature and pH-responsive drug delivery system for ketoprofen was prepared by simultaneous electrospinning of thermosensitive poly(*N*-vinylcaprolactam) blended with ethyl cellulose and pH-sensitive Eudragit L100 [191]. It was confirmed that these hybrid mats not only have the dual-responsive sustained release behavior, but also are nontoxic and beneficial for cell proliferation.

3.2.2. Controlled multidrug delivery

Considering the complex and heterogeneous nature of living tissues and diseases, applying a single therapeutic agent for tissue regeneration or disease treatment may be sometimes unsatisfactory. Thus, a multidrug delivery system with independently controlled release profiles of each drug is desired for the combined therapy [200]. Multi-material electrospinning also provides a facile way for spatially and temporally controlled co-delivery of multiple drugs, through respectively incorporating different drugs, instead of the single drug, into different compositions of the multi-material electrospun nanofibers [201–204]. Because of the above advantages, it has been widely used in wound healing, tissue regeneration, and cancer treatment, in the fashion of either synergistically accomplishing a single therapeutic effect or playing their respective roles in executing distinct functionalities, as shown in Table 4.

3.2.2.1. Synergistic delivery. During skin injury, the regularly-occurring bacterial infection is detrimental to the wound healing process. Compared with applying a single antibacterial agent alone, synergistic delivery of different antibacterial agents based on multi-material electrospun nanofibers has been applied for more effective prevention of wound bacterial infection [39,69,73,205]. For example, Yang's group prepared ciprofloxacin-loaded PVP/silver nanoparticles (AgNPs)-loaded ethyl cellulose Janus nanofibers, by a side-by-side electrospinning process [73]. The rapid release of ciprofloxacin from the hydrophilic PVP side inhibited bacterial growth during the initial stage, while the sustained release of AgNPs from the hydrophobic ethyl cellulose side ensured a long-term antibacterial effect. And antibacterial activity tests showed that collaborative release of ciprofloxacin and AgNPs from the Janus nanostructures provided an improved performance against bacteria.

With regard to bone tissue engineering, dual controlled-release of BMP-2 and dexamethasone through incorporating different parts of core-shell nanofibers has been shown to facilitate osteogenic differentiation of MSCs into osteogenic cells [206,207]. For instance, locating

Table 4
Applications of multi-drug delivery. Silver nanoparticles (AgNPs), nerve growth factor (NGF), glial cell line-derived growth factor (GDNF), brain-derived neurotropic factor (BDNF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), silk fibroin (SF), and connective tissue growth factor (CTGF).

	Applications	Functions	Structures	Cargoes-Matrix	Ref
Gaining a synergistic effect	Wound treatment	Antibacterial	Janus fibers	**Ciprofloxacin**-PVP/**AgNPs**-EC	[73]
			Janus fibers	**Lavender oil**-PCL/**AgNPs**-CA	[205]
			Bi-layer mats	**AgNPs**-PVA and CS/**Chlorhexidine**-PEO or PVP	[39]
			Core-shell fibers	**Imipenem** and **Cilastatin**-PVP and Gel/**Vancomycin**-PEO and CS	[69]
	Bone repair	Osteogenic differentiation	Core-shell fibers	**BMP-2**/**Dexamethasone**-PLCL and Col	[206]
			Core-shell fibers	**BMP-2**-PLLA/**Dexamethasone**-Zein	[207]
	Nerve repair	Effective neurogenesis	Tri or tetra-layered mats	**NGF**-PDLLA/PDLLA/**GDNF**-PLGA or PDLLA/**NGF**-PDLLA/PDLLA and PLGA/**GDNF**-PLGA	[208]
			Well-mixed mats	**NGF**-PDLLA/**GDNF**-PLGA	[51, 209]
			Well-mixed coaxial fibers	**Docosahexaenoic acid**-PLA@PLA/**BDNF**-PLA@PLA	[210]
	Cancer treatment	Effective killing cancer cells	Four-layered mats	PLLA/**Dichloroacetate**-PLLA/PLLA/**Oxaliplatin**-PLLA	[211]
			Tri-layer nanofibers	**5-fluorouracil**-PVA and CS/PLA and CS/**Doxorubicin** and **Paclitaxel**-g-C3N4, CS and PLA	[212]
Executing multiple functions	Wound treatment	Accelerating skin healing/Antibacterial	Tri-layered mats	**EGF** and **bFGF**-PCL/CS and PEO/**Silver sulfadiazine**-PCL and Col	[213]
			Well-mixed mats	**Phenytoin sodium**-PVA/**Tetracycline hydrochloride**-CA	[164]
			Core-shell fibers	**Silver-CS nanoparticles**-PVA/**Phenytoin**-PCL	[214]
			Core-shell fibers	**G. Sylvestre**-Gel/**Minocycline**-Gel and PCL	[215]
			Core-shell fibers	**L-arginine**-poly-3-hydroxybutyric acid/**Bacitracin nanoclay**-sodium alginate	[216]
			Core-shell fibers	**Copper** and **Decellularized Wharton's jelly matrix**-PLCL/CS	[217]
			Core-shell fibers	**Vancomycin**-PEO, SF and Col/**Flurbiprofen**-PEO	[218]
			Well-mixed	**Curcumin**-Gel/**Surfactin**-PCL	[219]
			Core-shell fibers	**Tea polyphenols**-PVA/**E-poly (L-lysine)**-PCL	[220]
		Antibacterial/Pain relief	Core-shell fibers	**Ciprofloxacin hydrochloride**-Gel/**Gabapentin** PLGA	[221]
			Bi-layer mats	**Mupirocin**-PCL/**Lidocaine hydrochloride**-CS	[40]
			Well-mixed	**Mupirocin**-PLLA/**Lidocaine hydrochloride**-PLLA	[52]
			Well-mixed	**Mupirocin**-PCL/**Lidocaine hydrochloride**-CS	[222]
		Accelerating skin healing/Pain relief	Core-shell fibers	**Curcumin**-PCL/**Lidocaine hydrochloride**-CS and PEO	[223]
			Bi-layer mats	**Curcumin**-PLLA/**Diclofenac sodium**-PEO	[224]
	Bone repair	Osteogenesis/Antibacterial	Well-mixed	**Icariino**-PCL/**Moxifloxacin**-Gel and PCL	[225]
			Core-shell fibers	**Naringin**-PVP/**Metronidazole**-PLGA	[226]
		osteogenesis/Angiogenic effect	Core-shell fibers	**BMP-2**-PVA/**CTGF**-SF and PCL	[227]
			Core-shell fibers	**BMP-2**-PLA/**Tauroursodeoxycholic acid**-PLA	[228]
			Core-shell fibers	**Deferoxamine**-PCL/**Dexamethasone**-PCL	[229]
	Tendon healing	Antibacterial activity/Lubrication effect	Core-shell fibers	**Hyaluronic acid**/**AgNPs**-PCL	[230]
			Core-shell fibers	**Hyaluronic acid**-PEO/**AgNPs**-PLA	[231]
			Core-shell fibers	**Hyaluronic acid** and **ibuprofen**-PEO/**AgNPs**-PEG and PCL	[232]
	Vascular graft	Accelerating endothelialization/Improving vascular smooth muscle regeneration	Tri-layer mats	**MicroRNA-126**-PELCL and PELCL-Arg-Glu-Asp-Val/**MicroRNA-145**-PELCL/PCL	[233]
			Bi-layer mats	**MicroRNA-126**-PELCL and PEG/**MicroRNA-145**-PLGA	[234]
	Cancer treatment	Killing tumor cells/inhibiting angiogenesis	Bi-layer mats	**Carmustine**, **Irinotecan**, and **Cisplatin**-PLGA (75:25)/**combretastatin**-PLGA (50:50)	[235]
			Trilayered beads-on-a-string	**Doxorubicin**-Glycerin/PLA/**Apatinib**-PCL	[70]
		Preventing recurrence/Inhibiting metastasis	Beads-on-a-string	**Doxorubicin hydrochloride**-PEG/**Matrix metalloproteinases-2 inhibitor disulfiram**-PLA	[236]
		Killing immunogenic cell/Reprograming macrophages	Beads-on-a-string	**Doxorubicin**-Poly(β-amino ester)-chondroitin sulfate and Glycerin/**Imiquimod (R837)**-PLGA	[237]

dexamethasone in the zein shell layer contributed to rapid release at the initial stage, while the release of BMP-2 from the PLLA core was slow with a steadily increasing profile [207]. The in vitro experimental results exhibited the potent osteogenic differentiation resulted from the synergistic effects of BMP-2 and dexamethasone.

Neurotrophic factors such as nerve growth factor (NGF) and glial cell line-derived growth factor (GDNF) have been demonstrated to benefit neurite outgrowth and neural differentiation. Therefore, Liu's team has conducted extensive studies on the effect of the dual release of GDNF and NGF on peripheral nerve regeneration [51,208,209]. In a study, a well-mixing of GDNF-loaded PLGA nanofibers and NGF-loaded PDLLA nanofibers was obtained by simultaneous electrospinning [51]. The ability of GDNF and NGF hybrid nanofibers to promote neural differentiation was stronger than that loaded with a single growth factor, although they could induce dose-dependent neurite extensions independently. Polyunsaturated fatty acids such as docosahexaenoic acid play both structural and signaling roles in the central nervous system. Hybrid core-shell nanofibers, where docosahexaenoic and brain-derived neurotropic factor (BDNF) are incorporated in the core, were prepared for their sustained release by combining coaxial electrospinning and simultaneous

electrospinning [210]. The significant enhancement of their synergistic effect on spinal cord injury treatment has been demonstrated in rat models.

In addition to tissue restoration, multi-material electrospun nanofibers were also utilized for the time-programmed release of multiple anticancer drugs. Four-layered fibrous mats (fiber diameter in the range of 200–600 nm) with an oxaliplatin-loaded layer sealed between two drug-free layers and a naked dichloroacetate-loaded layer, were fabricated for the fast release of dichloroacetate followed by sustained release of oxaliplatin, aiming to synergistic killing cancer cells [211]. Implanting on murine models of cervical carcinoma found that these dual-drug mats show improved antitumor recurrence efficiency and lowered toxicity to healthy cells than monolayered fibrous ones. In another example, 5-fluorouracil and doxorubicin/paclitaxel were loaded into the inner layer and the outer layer of the tri-layer nanofibers with an average diameter of 210 nm, respectively [212]. Compared with single-layer nanofibers, these tri-layer nanofibers displayed a higher MCF-7 breast cancer cell killing ratio in the in vitro tests. The above results indicated that multi-material electrospinning provides a promising strategy for controlled release of multidrug to improve the combined cancer therapeutic efficacy.

3.2.2.2. Multifunctional delivery. Apart from bacterial inhibition, an ideal wound dressing should enable wound repair in an orderly and timely process and minimize pain. Thus, the combination of antibacterial drugs with proliferative agents such as growth factors [213], phenytoin [164,214], herbal extract [215], arginine [216], and copper/decellularized wharton's jelly matrix [217], has been applied to achieve a good prognosis over a short time. For instance, a dual-drug delivery system based on core-shell nanofibers, where silver-chitosan nanoparticles responding to antibacterial activity are loaded in the water-soluble PVA core and phenytoin served as proliferative agents are embedded in the biodegradable PCL shell, was integrated into wound dressings by Mohamady Hussein's group [214]. The results demonstrated that the wound dressings with dual-drug carriers not only render a higher cell growth rate and form larger colonies, but also had a biocidal effect against gram-positive and gram-negative bacteria, which is confirmed as a promising wound dressing.

In addition, shortening the inflammatory phase is also vital for accelerating wound healing. Therefore, anti-inflammatory drugs were combined with antibacterial drugs to gain a better healing efficacy. Different release profiles of the two kinds of drugs were declared to help wound healing from different studies. Wen et al. prepared core-shell nanofibers for faster release of anti-inflammatory flurbiprofen (2–6 days) loaded in the shell than anti-bacterial vancomycin (about 20 days) loaded in the core [218]. While the prolonged release of curcumin (anti-inflammatory agents) and rapid release of surfactin (antibacterial agents) relying on PCL/gelatin nanofibrous composites were developed in Hadizadeh's study [219]. Like inflammation, the excessive reactive oxygen species also leads to delayed wound healing. Thus, the application of dual-delivery of antioxidant and antibacterial agents in wound treatment was performed by Lan et al. [220]. The incorporation of tea polyphenols and ε-poly (L-lysine) into PVA/PCL core-shell nanofibers gave quick bacteria inhibition and long-term antioxidant activity, respectively.

Considering one of the most main symptoms of wounds is pain, incorporating dual-drug into multi-material electrospun fibrous structures was also employed to simultaneously carry out antibacterial and pain-relieving functions [40,52,221,222]. In a study, a well-mixing of lidocaine hydrochloride (a local anesthetic)-loaded chitosan nanofibers and mupirocin-loaded PCL nanofibers were applied to achieve the rapid release of lidocaine for pain management and sustained release of mupirocin for the prevention of bacterial infection [222]. Another combination of diverse functions is accelerating skin healing and pain relief [223,224]. For instance, a bilayer nanofibrous patch consisting of a curcumin-loaded PLLA mesh and a diclofenac sodium-loaded PEO mesh was fabricated for mouth ulcer treatment [224]. Curcumin released from PLLA meshes induced prominent anti-inflammatory and antioxidant properties, which are beneficial for promoting wound healing. And the diclofenac sodium-loaded PEO nanofibers could not only reduce pain but also inhibit bacterial growth.

Like wound healing, the introduction of multiple agents has endowed the multi-material electrospun nanofibers with antibacterial and osteogenic functions for bone tissue engineering [225,226]. In a study, a dual-drug delivery system with a short-term release of metronidazole and a long-term release of naringin was achieved based on coaxial mats [226]. In vitro tests found that it not only inhibits anaerobic bacterial colonization over 21 days, but also is beneficial for spreading and proliferation of MC3T3-E1 cells and induces high expression of alkaline phosphatase. During the bone repair process, especially for large bone defects, vascular ingrowth is crucial to providing nutrients and oxygen. Thus, some researchers have focused on the incorporation of angiogenesis promoters and osteogenesis inducers within multi-material electrospun nanofibers to enhance vascularized bone regeneration, in which transient release of the angiogenesis agents imparts a pro-angiogenic effect while the sustained release of the osteogenesis agents facilitates bone formation [227–229]. For example, Cui et al. fabricated a core-shell nanofibrous mat loaded with dexamethasone in the core layer and deferoxamine in the shell layer [229]. In vivo study in rat calvarial defect model showed this dual-drug programmed releasing enables eminent bone regeneration.

In tendon tissue engineering, core-shell nanofibrous membranes loaded with dual agents were developed by Chen's team to heal post-surgical wounds [230,231]. In general, hyaluronic acid as the core exerted an effective lubrication effect for smooth tendon gliding and reduced fibroblast adhesion, and AgNPs embedded in the shell were used to prevent bacterial infection. Moreover, they have further loaded the ibuprofen in the hyaluronic acid core to endow the membranes with anti-inflammation [232].

With respect to vascular tissue engineering, microRNA-126 and microRNA-145 were encapsulated into different layers of multilayered nanofibrous membranes to accelerate endothelialization and improve vascular smooth muscle regeneration, respectively [233,234]. For example, Wen et al. developed a trilayered vascular graft consisted of an inner microRNA-126-loaded PELCL and PELCL-Arg-Glu-Asp-Val layer, a middle microRNA-145-loaded PELCL, and an outer PCL layer [233]. PELCL was specifically chosen for preparing the vascular grafts by electrospinning, due to its favorable biocompatibility, reasonable biodegradability, and fair flexibility. The fast release of microRNA-126 from the inner layer was beneficial to proliferation and intracellular nitric oxide production of vascular endothelial cells, and the sustained release of microRNA-145 from the middle layer could encourage toward a contractile vSMC phenotype. Thus, the trilayered grafts with the spatiotemporal release of the two miRNAs were considered as a promising substitute for small-caliber blood vessels.

Antiangiogenic cancer-therapeutic strategies aim to selectively destroy the tumoral vasculature, depriving the tumor of nutriment and oxygen supply, and thereby resulting in a necrotic center in the tumor. Thus, sequentially co-delivering both chemotherapeutic and anti-angiogenic drugs has been proposed to synergistically treat glioblastoma [235] and breast cancer [70].

By triaxial electrospinning, trilayer structured fibers with internal periodic chambers with controlled volume from 4.1 to 17.6 μm^3 of doxorubicin-contained glycerol surrounded by the middle PLA layer and outer PCL layer containing apatinib, were developed as locally dual-drug delivery devices by Zhou's team [70]. When the devices are implanted near a solid tumor, chemotherapeutic doxorubicin could rapidly release and diffuse into the tumor for rendering the apoptosis of the cancer cells, due to swelling-induced rupture of the periodic chambers resulted from water absorption by glycerol, and vascular inhibitor apatinib was released in a sustained manner for a long term, which can inhibit

angiogenesis inside the tumor, thereby reducing the cancer cells proliferation. Subsequently, the same team has further incorporated different combinations of anticancer agents into this hierarchical structure with periodically arranged chambers to achieve an excellent antitumor efficiency, including doxorubicin hydrochloride killing the residual tumor cells to avoid tumor recurrence cooperating with matrix metalloproteinases-2 (MMP-2) inhibitor disulfiram inhibiting tumor invasion to block its metastasis for breast cancer [236], as well as doxorubicin-micelle inducing immunogenic cell death while imiquimod (R837) reprograming tumor-associated macrophages for cancer.

4. Summary and outlook

Over the past two decades, there has been extensive research on multi-material electrospinning, which surpasses its single-material counterparts in the fabrication of complex nanofibrous structures for biomedical applications. This review explores and compares various modalities of multi-material electrospinning. Sequential electrospinning and simultaneous electrospinning offer the flexibility to construct heterogeneous fibrous structures at the macroscopic level using multiple materials, without requiring significant upgrades to conventional electrospinning setups, regardless of electrospinning compatibility between different materials. Coaxial electrospinning and side-by-side electrospinning provide advantages in controlling the internal microarchitecture of nanofibers and integrating unspinnable materials into the nanofiber structures.

The review also introduces emerging applications of multi-material electrospun structures in tissue engineering and drug delivery. The utilization of multi-material electrospinning has enabled the development of advanced scaffolds, including the synergistic integration of multiple characteristics into a scaffold, enhanced scaffold porosity for improved cell infiltration, and the recapitulation of the heterogeneity found in native extracellular matrices (ECMs). These advancements bring electrospun scaffolds one step closer to their ultimate use in clinical applications. In terms of drug delivery, the complex fibrous architectures prepared by multi-material electrospinning have opened up numerous opportunities. They allow for precise control over the temporal and spatial release profiles of single drugs and enable the co-delivery of multiple drugs in an individually controllable manner.

Future research into multi-material electrospinning may be aimed in some promising directions.

1. Pushing multi-material electrospinning from far-field to near-field mode The existing multi-material electrospinning is mainly conducted in the far-field mode (spinneret-collector distance typically > 5 cm), thus it is prone to produce randomly deposited fibrous mats due to the bending instability of the jet. By reducing the spinneret-collector distance and the applied voltage, near-field electrospinning ensures certain positions of the deposited fibers. Furthermore, controlling relative motion between the spinneret and the collector with a programmable path, allows to create predefined micro/nanopatterns. Therefore, it is believed that future studies on developing multi-material electrospinning based on near-field mode, may prove useful for constructing 3D fibrous structures with customizable shape and compositional diversity as more biomimetic scaffolds.
2. Exploitation of dECM-based electrospun scaffolds with applicable physical performances Although multi-material electrospinning enables fabricating scaffolds from some natural biomaterials, it is far away from representing the biochemical complexity of native ECM for effective tissue regeneration. Tissue-specific dECM made from natural ECM by selective removal of cellular components while retaining bioactive compositions (collagen, growth factors, and other proteins), is considered as the best choice available for providing physicochemical cues. However, the poor biophysical properties and hard electrospinnablity of the dECM vastly limits the tissue-specific dECM applied in the construction of fibrous scaffolds for tissue restorations. Therefore, the exploration of multi-material electrospinning techniques that facilitate endowing dECM-based electrospun scaffolds with favorable biophysical properties such as structural, mechanical, and electroconductive cues, represents a promising prospect for translating the tissue-engineered scaffolds from the bench side to the bedside.
3. Developing smart drug delivery in closed-loop manner As mentioned above, by virtue of multi-material electrospinning, a great deal of controlled or targeted systems have been actively explored and showed excellent performance over passive drug delivery. However, these drug delivery systems essentially adopt an open-loop controlled strategy, which hardly realizes using the minimized drug dose to obtain the optimized therapeutic efficiency without adverse side effects. Thus, the utilization of multi-material electrospinning to design more smart drug delivery that allows real-time sensing of the in vivo efficacy to determine the drug release in a closed-loop manner is a vital tendency, because of its great advantages over the controlled arrangement of various materials to gain an innovative functionality. For example, sophisticated organization of cancer hallmark-sensitive materials and other assistant materials, may render tuning the amount of drug release according to the concentration of cancer biomarkers, resulting in maximizing drug utilization, mitigating the side effects, and reducing the administration times.

Overall, the advances in multi-material electrospinning techniques, hold great promise in the domain of engineering tissue engineering and drug delivery through engineering complex fibrous structures from diversified materials.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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