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Progress in electrospun composite nanofibers: composition, performance and applications for tissue engineering

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The discovery of novel methods to fabricate optimal scaffolds that mimic both mechanical and functional properties of the extracellular matrix (ECM) has always been the "holy grail" in tissue engineering. In recent years, electrospinning has emerged as an attractive material fabrication method and has been widely applied in tissue engineering due to its capability of producing non-woven and nanoscale fibers. However, from the perspective of biomimicry, it is difficult for single-component electrospun fiber membranes to achieve the biomimetic purposes of the multi-component extracellular matrix. Based on electrospinning, various functional components can be efficiently and expediently introduced into the membranes, and through the complementation and correlation of the properties of each component, composite materials with comprehensive and superior properties are obtained while maintaining the primitive merits of each component. In this review, we will provide an overview of the attempts made to fabricate electrospinning-based composite tissue engineering materials in the past few decades, which have been divided into organic additives, inorganic additives and organic–inorganic additives.

1. Introduction

Electrospinning is a famous fabrication method to fabricate ultrafine fibres by spraying solutions or melts under a strong electric field. An electrospinning apparatus typically consists of three parts: an injection device, a high voltage power supply and a grounded collector.[1] The strong electrostatic field between the injection device and the collector causes the liquid to form a jet, which is stretched in the electric field, resulting in the deposition of nanoscale fibres on the collector.[2] The electrospinning technology was first discovered in the 1930s and began to attract wide attention and underwent rapid development in the 1990s. In 1993, Jayesh Doshi and Darrell H. Reneker[3] first systematically summarized the electrospinning technology from its mechanism to its applications and demonstrated that some organic polymers could be electrospun into nanofibers. After this, the number of studies in this field has been increasing exponentially,[4] and the feasibility of obtaining nanoscale fibres has attracted the attention of lots of research groups to apply electrospinning in the field of biomedical engineering such as in controlled drug delivery,[5] biosensing[6] and tissue engineering;[7] electrospun fibres have gained wide attention for applications in tissue engineering.

As the key factor in tissue engineering, the tissue engineering scaffold should serve as a substitute for the native extracellular matrix, mimicking both its mechanical and functional properties.[8,9] In the attempt to construct scaffolds with nanoscale structures, several techniques has been put into practice such as electrospinning,[1,2,10] self-assembly,[11] phase separation,[12] and vapour phase polymerization.[13] Among various scaffold processing techniques, electrospinning has attracted tremendous interest due to its versatile advantages:[1,2,8,9] (1) it can produce non-woven fibres from the microscale to the nanoscale with adequate mechanical properties, which can physically mimic the structural dimensions of the extracellular matrix *in vivo*; (2) it can produce scaffolds with high porosities and large face-area-to-volume ratios, which are conductive to cell adhesion, spreading, growth and proliferation; (3) it can be applied to a variety of polymers, including both synthetic polymers and natural polymers; (4) numerous components, such as small molecules and nanoparticles, can be added to the electrospinning solutions and electrospun into membranes; (5) the properties of electrospun fibres can be feasibly tuned by altering the parameters, manipulating the collector structures and other methods; and (6) it can be combined with other scaffold fabrication methods to fabricate composite scaffolds. All these merits contribute to the wide applications of electrospinning in tissue engineering.

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Over the past few decades, various polymers have been electrospun into nanofibers as scaffold materials, such as polyether,[14,15] poly(glycolic acid) (PGA),[16,17] poly(lactic acid) (PLA),[17] poly(lactic acid-*co*-glycolic acid) (PLGA),[17] poly(ε-caproactone) (PCL),[18] polyamide (PA),[19,20] polyimide (PI),[21] poly(ester amide) (PEA) and polyurethane (PU).[22,23] However, these single-component electrospun nanofibers generally possess monotonous properties and cannot perform the optimal functions of multi-component natural ECM or the specific purposes of tissue engineering applications; meanwhile, limitations such as inadequate cell infiltration and poor mechanical properties[8] further hinder their potential applications. The creation of ECM-mimicking scaffolds that can facilitate the restoration, maintenance and improvement of tissue functions has become a challenge in the field of tissue engineering.[24] In recent years, the multi-component, dynamic and tissue-specific ECM has been inspiring researchers to introduce other functional ingredients to produce biomimetic composite scaffolds with improved performance as well as mechanical and functional integrity which single-component electrospun nanofibers cannot achieve. To date, numerous electrospun nanofibers functionalized with a variety of additives have been constructed as tissue engineering scaffolds; they generally possess outstanding physicochemical and biological properties and greatly meet the needs of practical applications. These studies have indicated a new direction for the development of scaffold materials. Therefore, it is of great value to systematically summarize and provide an outlook of the development of electrospun composite nanofibers for tissue engineering applications. In this review, we provide an overview of electrospinning-based composite tissue engineering materials and divide it into organic additives, inorganic additives and organic–inorganic additives. This review includes the applications and the practices of the construction of composite materials towards wound dressings, nerve tissue engineering, bone tissue engineering, cartilage tissue engineering, vascular grafts and tumour modelling, with emphasis on interpretation of the advantages of each component and the aggregate potential of the material (Fig. 1). At the end of this review, current challenges and future perspectives for electrospinning-based composite tissue engineering materials will be discussed.

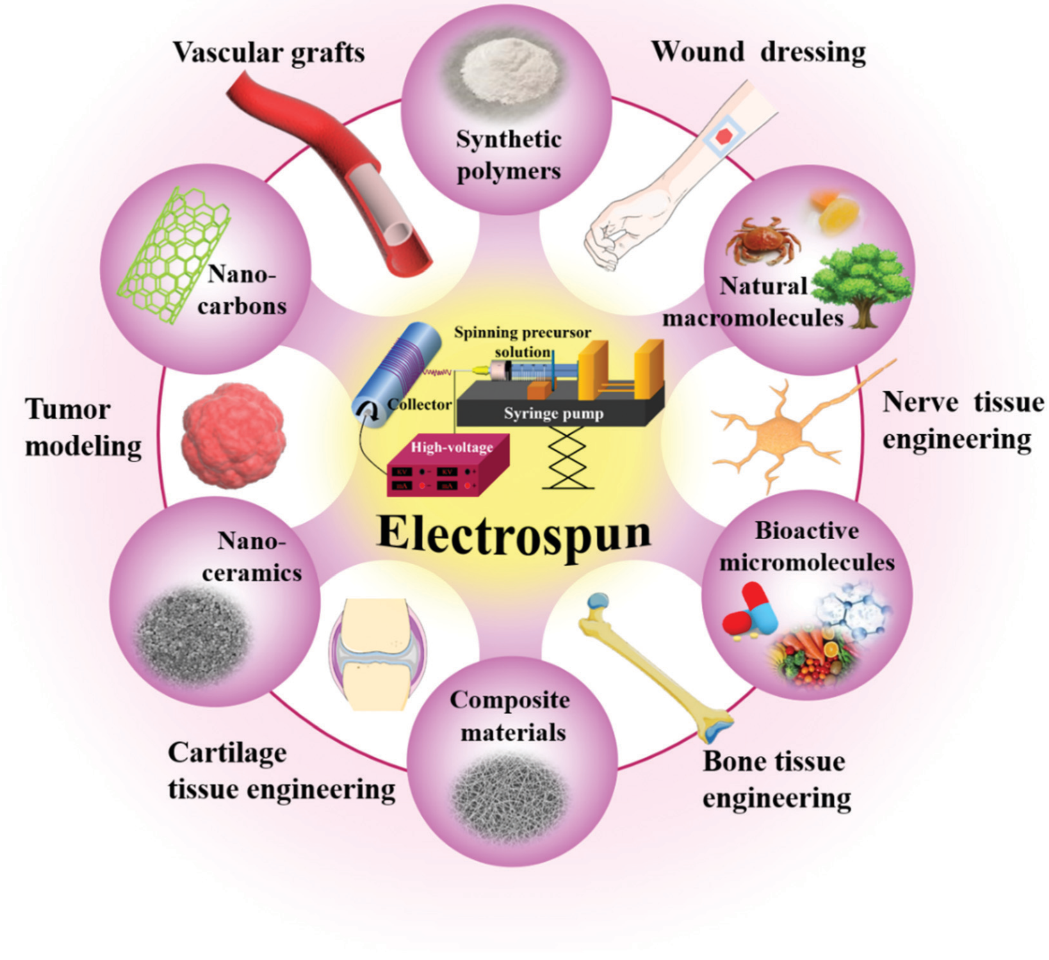

Fig. 1 Schematic of the fabrication of composite nanofibers and their biomedical applications.

2. Electrospun nanofibers functionalized with organic additives

Some studies on electrospun nanofibers include organic ingredients as additives, generally, these additives are synthetic polymers or natural components. Synthetic polymers are essential and act as the main body in electrospinning due to their adjustable mechanical properties, controllable degradation rates, narrow molecule weight distributions, stability and feasibility of modification and processing.[25–27] Several polymers have been approved by FDA in recent years, such as PGA, PLA, PLGA, PCL, and PEG.[28]

Natural ingredients are widely found in organisms, and their fascinating biocompatibility, biodegradability, hydrophilicity, cell affinity and other attractive properties have received much attention in tissue engineering.[2] Macromolecular natural ingredients such as collagen and some medicative micromolecules all demonstrate observable improvements when applied in tissue engineering. Therefore, introducing these functional ingredients into nanofibers is a promising approach to improve the performance of scaffold materials. In addition to the conventional method, other fabrication and modification techniques, such as coaxial electrospinning, emulsion electrospinning and melt electrospinning, have been developed in recent years; these techniques endow fibres with unique properties, such as core–shell structures,[51,52] hollow morphologies,[53] porous and wrinkled topologies[54] and oriented alignments.[55] The development of these novel electrospinning techniques simplifies the introduction of functional components and consequently favours the preparation of high performance composite nanofibers.

2.1. Functionalization with synthetic polymers

Synthetic polymers have received much attention in the electrospinning arena and have been widely applied in tissue engineering. Due to their different molecular compositions and conformations,[25,26] different polymers usually demonstrate different physicochemical properties (*e.g.* degree of crystallinity, solubility, hydrophilicity, characteristic temperature, degradability, stimuli-responsive properties, shape memory properties), as do their correlating electrospun nanofibers. In the past decades, various synthetic polymers have been successfully electrospun into nanofibers for biomedical applications; at the same time, scientists have been making efforts to combine different characteristics of different polymers to obtain superior materials. The co-electrospun fibres not only retain their own advantages, but also enable them to complement each other. Also, scientists have utilized the different physicochemical properties of polymers to fabricate special structures towards specific applications. For example, PGA is introduced into fibrous systems to improve the mechanical properties due to its high crystallinity (45% to 55%) and poor solubility in organic solvents. PEG, a polyether with good hydrophilicity, is widely used to enhance the solubility of hybrid systems. PEA promotes biological properties and enzyme-catalysed biodegradability, while PCL favours long-term implanted scaffolds due to its inert nature. In addition to stimuli-responsive polymers, polymers containing carboxylic acids or amine groups,[56] possessing lower critical temperatures (LCST),[57,58] incorporated with magnetic particles[59] and containing photosensitive functional groups[60,61] respectively respond to changes in pH, changes in temperature, magnetic field signals and light signals. Furthermore, polymers consisting of two-phase structures (a fixed phase and a reversible phase) are used in shape memory applications. These examples are demonstrated in Table 1.

2.2. Functionalization with natural components

However, despite the merits of adjustable and facile processing and the excellent mechanical properties provided by synthetic polymers, they possess inherent limitations of bioactivity and biocompatibility and thus still cannot meet the elaborate demands of biological scaffolds. Therefore, natural components are generally introduced into fibres to improve their overall performance. Naturally occurring components have been widely used in tissue engineering applications due to their abundance in nature, biocompatibility, biodegradability, bioactivity and other fascinating merits, such as anti-inflammatory and antibacterial properties.[25] Applied natural polymers include protein-based polymers, such as collagen,[62] gelatin,[63] silk fibroin,[64] and keratin,[65] and polysaccharides, such as bacterial cellulose,[66] chitosan,[67] hyaluronic acid,[68] heparin,[69] agarose[70] and alginate.[71] These natural polymers are either naturally present in the extracellular matrix or have similar structures to the extracellular matrix, which is conducive to cell adhesion and growth. Therefore, they are often used in the construction of tissue engineering scaffolds together with synthetic polymers. By incorporation into synthetic polymers, natural polymers with poor processability can be successfully electrospun into nanofibers for tissue engineering applications.

Collagen is the most commonly used natural polymer in biomedical applications due to its superior biocompatibility and excellent biological characteristics.[72] Fariba *et al.*[73] compared the performance of electrospun scaffolds fabricated with pure PCL, collagen coated with PCL and PCL blended with collagen. The PCL/collagen hybrid scaffold showed a medium degradation rate and mechanical properties and possessed the most profound tissue-cell response. Wang *et al.*[74] developed a multilayer scaffold as a dual substitute in which the inner PLA layer decreased the adhesion of tissue, the middle PCL-PLA layer provided mechanical properties and the outer collagen layer endowed the scaffold with improved bioactivity. In the work of Brown *et al.*,[75] they modified a PLGA scaffold with type I collagen to simulate the ECM of hepatocytes (Fig. 2). The results indicated that the addition of collagen distinctly catalyzed protein synthesis in hepatocytes. Some research groups also introduced collagen to modulate mechanical properties. Jiang *et al.*[76] built mechanical biomimetic PCL-PTHF/collagen nanofibers to induce cartilage regeneration. The characterization results demonstrated that the fibres containing collagen had lower moduli than those that did not contain collagen; this implies that the introduction of collagen softened the fibres. As a result, the softer nanofibers could induce chondrogenesis more efficiently. Gelatin is a hydrolysed product of collagen with high hydrophilicity and large numbers of functional groups for chemical crosslinking.[77] Several applications of gelatin in building bioscaffolds have verified that

Table 1 Examples of composite scaffolds of multiple synthetic polymers

Matrices	Reinforcements	Main improvements	Ref.
PLA	PBLG	Improved physicochemical properties, biodegradable properties, cell adhesion, viability and proliferation	29
PLA	PEG	Faster degradation behaviour, increased hydrophilicity and plasticity	30
PLA	PLGA	Improved biodegradable properties and hydrophilicity	31
PLA	PHB	Enhanced crystallinity and higher mechanical resistance	32
PLA	Polyaniline (PANI) or poly(aniline-*co*-m-ABA) (PANI-*co*-m-ABA)	Honeycomb-like morphology, deceased average molecular weight and nanofiber diameter, increased solubility and conductivity	33
PLA	PVA	Increased storage modulus and decreased crystallinity, faster degradation	34
PCL	PLA	Higher mechanical properties and bioactivity, promoted osteogenic differentiation and new bone formation	35
PCL	Polypeptides	Improved biocompatibility and antibacterial properties	36
PCL	PGA	Improved mechanical properties and hydrophilicity	37
PCL	PLGA	Improved mechanical properties, increased biocompatibility, cell attachment and cell proliferation	38
PCL	PVA	Improved hydrophilicity, degradation behaviour and cell behaviour	39
PCL	4,4′-Diphenyl-methane-diisocyanate (MDI) and γ-aminopropyltriethoxysilane (APS)	Shape memory response	40
PCL	PEO	Improved hydrophilicity and water-mediated shape memory properties	41
PGA	PLA	3D interconnected pores and narrow pore size distribution	42
PLGA	PEG	Increased biocompatibility, cell attachment, cell growth and cell proliferation, improved function recovery	43
PVA	PAA	Improved water stability	44
PU	PEG	Enhanced hydrophilicity and excellent hemocompatibility, decreased tensile strength and elastic modulus, increased elongation at break	45
PU	Poly(glycerol sebacate) (PGS)	Improved hydrophilicity and biocompatibility, decreased elastic modulus and increased maximum elongation	46
PU	PLGA	Increased hydrophilicity, surface roughness and cell attachment	47
PNIPAAm	PAA/PU	Tailored lower critical temperature (LCST) and aqueous stability: PAA adjusted the LCST to a higher value and provided pH sensitivity; hydrophobic PU improved the longevity in water	48
PMMA	PNIPAAm	Improved electrospinnability, reversible and reproducible thermo-responsive swelling behaviour	49
PLA	Oligo lactic acid (OLA)	Thermally activated shape memory response	50

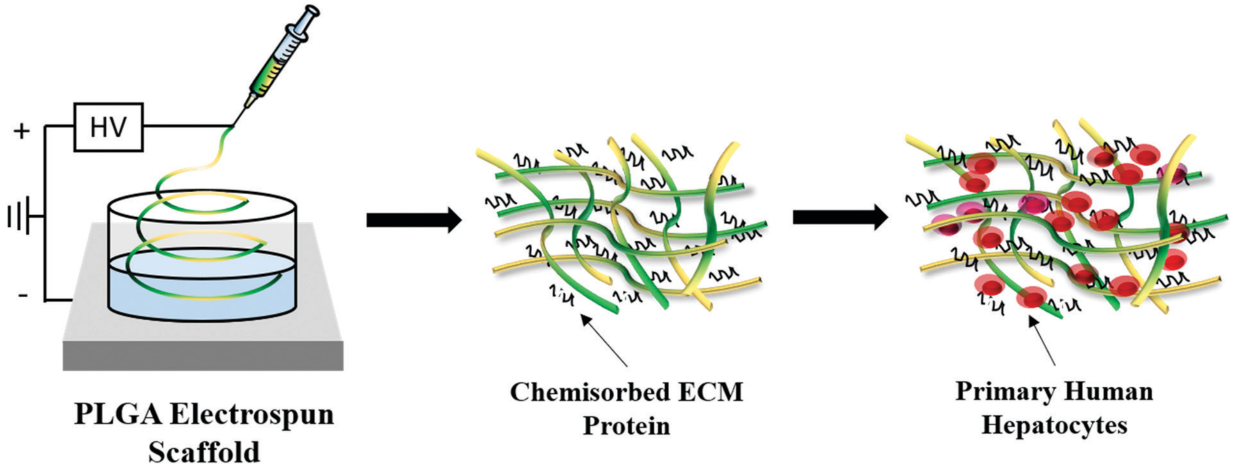

Fig. 2 Schematic of the fabrication of nanofibrous PLGA electrospun scaffolds modified with type I collagen. Reproduced with permission from ref. 75. Copyright 2018 Elsevier Ltd.

gelatin can increase cell adhesion, proliferation and spreading.[77,78] Zhang *et al.*[2] successfully electrospun a mixed solution of PCL and Gelatin Type A. The experimental results indicated that the introduction of gelatin provided good hydrophilicity and cellular affinity, and the favourable ability of degradation promoted cell migration. In the work of Detta *et al.*,[79] composite meshes were obtained through coaxial electrospinning with the combined mechanical characteristics of polyurethane and the natural cytocompatibility of a biopolymer. Wang *et al.*[80] fabricated a tubular scaffold with a PLA outside layer and a silk fibroin–gelatin inside layer. The PLA layer imparted the scaffold with good biomechanical properties and the silk fibroin–gelatin layer improved the biocompatibility and the bioactivity of the scaffold. Characterization tests demonstrated enhanced cell affinity (fibroblasts and vein endothelial cells), migration and proliferation.

Bacterial cellulose (BC) is another interesting biomaterial that is utilized in tissue engineering. Due to its high purity, high crystallinity and biocompatibility, BC is expected to improve the mechanical properties of synthetic or natural fibres.[81,82] Liu *et al.*[83] incorporated BC nanowhiskers into PLA to obtain hybrid nanofibers. The characterization results indicated that the BC nanowhiskers facilitated the nucleation process and the crystallinity of PLA. Chitosan is a broadly utilized polysaccharide which is derived from chitin.[84–86] Similar to gelatin, chitosan is another natural fibre with fascinating biocompatibility, biodegradability and bioactivity.[84–86] Zhu *et al.*[87] modified PLA film with chitosan and heparin. In cell adhesion tests conducted on the PLA films, the PLA/chitosan film and PLA/chitosan/heparin film demonstrated progressively increased fibroblast attachment. The cells on the PLA/chitosan/heparin film were almost spindle-shaped and were extensively spread, while the cells on the PLA film displayed a spherical morphology. Chitosan is also inherently endowed with antibacterial performance due to its abundance of positively charged groups; thus, it has wide application. Chanda *et al.*[85] built a bilayer scaffold hybridized with three components, namely PCL, chitosan and hyaluronic acid. The composite scaffold was endowed with enhanced swelling, degradation, hydrophilicity and water vapour transmission rate; also, improved cell behaviours, such as proliferation, growth and migration, were found. Hamsici *et al.*[88] reported the novel production of electrospun cyclodextrin nanofibers through host–guest interactions; the nanofibers were modified with an adamantane-conjugated, laminin-derived peptide epitope. This hybrid system, which combined graphical and biochemical factors, effectively induced cell adhesion and *in vitro* neural differentiation.

Naturally occurring components applied in tissue engineering also include some bioactive molecules, generally antibiotics,[89] oligopeptides,[90] medicative ingredients[91] and growth factors,[92] which can be easily and efficiently incorporated into nanofiber membranes through electrospinning.[93,94] These bioactive molecules are loaded on or released from the scaffold and act as regulatory factors in tissue regeneration. Curcumin is a naturally occurring polyphenolic compound derived from turmeric; it possesses antibacterial, anticancer, anti-inflammatory and angiogenic properties.[95] Ranjbar-Mohammadi *et al.*[95] constructed a curcumin-loaded PCL/gum tragacanth (mainly a combination of polysaccharide and alkaline minerals) scaffold for wound healing applications. In their work, curcumin, which is hydrophobic, unstable *in vivo* and poorly bioavailable, is stabilized by the delivery of electrospun nanofibers, resulting in good antibacterial effects. Lima *et al.*[91] combined a copolymer membrane with extract of *Arrabidaea chica Verlot* for wound dressing applications. The results showed adequate mechanical properties, good water vapor transmission rates and good lesion microenvironment control. In He *et al.*[93]'s research, *naringin* and *metronidazole*, two antibacterial agents, were respectively loaded on PVA and PLGA for periodontal regeneration. Through a coaxial electrospinning approach, distinct core/shell microstructures and anti-infective mats were obtained with good cell spreading and proliferation and high alkaline phosphatase expression. Guo *et al.*[96] developed biodegradable nanomats incorporated with TGF-β3 for annulus fibrosus (AF) regeneration. Bone marrow stem cells (BMSCs) were used in this work; these can be easily extracted but cannot differentiate into AF cells or express correlating proteins. However, when regulated by TGF-β3, which is a chondrogenesis inducer, the expressions of collagen II and aggrecan both increased while the level of collagen I decreased. Other examples of bioactive molecules are provided in Table 2.

3. Electrospun nanofibers functionalized by inorganic additives

In recent years, some biocompatible inorganic nanocomponents have been utilized as reinforcements to fabricate composite tissue engineering materials by electrospinning. Due to their small sizes, high surface-to-volume ratios, superior mechanical properties and inherent electrostatic properties,[97] inorganic nanoscale components endow nanofibers with improved functions, such as mechanical properties, hydrophilicity, surface roughness and porosity. In addition, electrospun nanofibers hybridized with

Table 2 Examples of composite scaffolds functionalized with natural bioactive molecules

Matrix	Bioactive molecules	Main improvements	Ref.
PCL/chitosan	Tea tree oil	Wider range of antibacterial activities compared with PCL/chitosan	99
PCL/PEG/PLGA	Curcumin	Antioxidant effects and accelerated dermal wound healing	100
Silk fibroin	RGD/YIGSR/REDV peptides	Better cell adhesion, proliferation and migration	101
PLGA	RGD/YIGSR peptides	Better cell adhesion and faster cardiomyocytes	102
PEG/PLA	Basic fibroblast growth factor (bFGF)	Enhanced cell adhesion, proliferation, and secretion of collagen	103
PCL/gelatin	Stromal cell derived factor-1a (SDF-1a)	Facilitated recruitment of BMSCs and formation of new bone	104
PLA/PCL/BSA/dextran	Vascular endothelial growth factor (VEGF)	Promoted MSCs proliferation and cardiovascular regeneration	105
PLLA	Transforming growth factor-β1 (TGF-β1)	Increased glycosaminoglycans and collagen production compared to pure PLLA	106
Collagen/PCL	Stromal-cell-derived factor-1α (SDF1α)	Radially aligned structure, elongated morphology of NSCs, improved NSC responsiveness	107
PLA/PU	Lecithin	Enhanced growth, proliferation, and viability of hepatocytes	108
PU/dextran	Ciprofloxacin HCl drug	Improved cell adhesion and antibacterial activity	109
PU	Rosemary oil	Increased surface roughness and tensile strength, improved anticoagulant properties	22
PU	Grape seed oil/honey/propolis	Enhanced thermal stability and decreased surface roughness, improved blood compatibility and cell viability	110

inorganic components demonstrate enhanced bioactivity, which has been widely verified. In this section, the application of nanoceramics and nanocarbons in electrospinning for tissue engineering and some weighted results are discussed.

3.1. Functionalization by nanoceramics

Ceramics are widely used materials due to their superior physical properties, such as mechanical and electrical properties and high chemical and thermal stability.[98] With the rapid development of nanomaterials, various and versatile nanoceramics with the merits mentioned above as well as some novel properties due to size effects and surface effects[97] have been obtained, and fascinating improvements have been demonstrated in many fields. In the arena of biomedical engineering, nanoceramics are used as reinforcements in the construction of tissue engineering scaffolds due to their physicochemical and bioactive properties. Electrospinning is a promising fabrication method to product nanoscale fibrous scaffolds; at the same time, it provides a simple way to hybridize nanoceramics with nanofibers. The ceramics-doped nanofibers always demonstrate enhanced mechanical and degradable properties. For example, CaP ceramics are the most commonly researched inorganic materials incorporated into polymer-based scaffolds in bone tissue engineering, and their enhancing effects have been widely verified.[111–117] In addition, surface-charged nanoceramics alter the morphologies and surface functions of membranes, consequently enhancing their cell adhesion and other cellular behaviors.[118–120] Moreover, due to their natural presence in the body, some inorganic compositions show inherent biocompatibility, biodegradability and bioactivity. Furthermore, some studies have found that positively charged metallic ions can be released from the particles; this endows the membranes with physiological regulative effects, such as gene expression, tissue regeneration and metastasis.[121–126] In other work, doped nanoparticles also showed antibacterial functions in wound dressing applications.[127–129] In this section, an overview of the practical and enhancing effects of nanoceramics-doped electrospun nanofibers observed in recent years is given.

3.1.1 Enhanced mechanical properties. Nanoceramics are usually endowed with high mechanical properties stemming from the electrostatic forces and covalent bonds between atoms.[98] Good mechanical properties are often required in bone tissue engineering, where biodegradable polymers are often used to build scaffolds but cannot meet the requirements of bone regeneration due to their lack of mechanical strength. Thus, the hybridization of nanoceramics and electrospun nanofibers appears to be necessary for optimization of bone tissue scaffolds. In bone tissue engineering, the most commonly incorporated nanoceramics are calcium phosphate compounds such as hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HA) and tricalcium phosphate ($Ca_3(PO_4)_2$, TCP). Other inorganic materials include $CaCO_3$, $CaSO_4$–$2H_2O$, and aluminium oxide ceramics.

Hydroxyapatite (HA) is one of the most common CaP compounds existing in the body; together with collagen, it constitutes the bone tissue ECM.[114] Combining nanofibers and nano-hydroxyapatite (nHA) can simulate the real bone tissue environment, which results in predictable improvements in biocompatibility and mechanical properties and achieves optimized biomimicry. Drupitua *et al.*[114] utilized a conventional method by dispersing the nHA particles into an electrospun solution and then using an electrospinning technique to obtain hybrid nanofibers. A series of mechanical characterization tests were carried out, and the results indicated increased tensile strength, enhanced hardness, chain stiffness and improved creep-resist properties in the composite system. Khakestani *et al.*[115] loaded nHA into PLA solution to fabricate composite fibrous membranes. The tensile stress–strain curves showed higher tensile strength and Young's modulus in the nHA-doped PLA nanofibers than in neat PLA nanofibers. Ao *et al.*[116] obtained a similar enhanced Young's modulus and tensile strength that were much higher than those of commonly used polymer fibres, such as PLA. In terms of its natural *in vivo* existence, HA also demonstrates good biocompatibility,[117] which will be discussed in a later section.

Other ceramic nanoparticles have been applied in tissue engineering to obtain enhanced mechanical properties. Castro *et al.*[130] introduced Si nanoparticles into PCL membranes. When homogeneously dispersed in the electrospun fibres, the Si nanoparticles endowed the composite fibrous membranes with significantly improved mechanical properties. Ullah *et al.*[131] incorporated zinc oxide nanoparticles (n-ZnO), of which the particle size is under 50 nm, into chitosan–collagen porous scaffolds. The mechanical test results demonstrated similar enhancement of tensile strength. In other work, silicate compounds were doped into fibres, analogously providing significant mechanical modifications.[132,133]

The deficiency of mechanical properties limits the utility of polymers in hard tissue engineering, while the incorporation of inorganic components compensates for the limitations of the fibrous system by enhancing the intermolecular forces between the polymer chains or the cross-linking between the inorganic particles and polymeric components;[134] these composite biological scaffolds have been widely studied.

3.1.2 Enhanced biocompatibility and bioactivity. Biocompatibility and bioactivity are crucial properties that a tissue engineering scaffold should demonstrate. Although electrospun membranes are widely used in tissue scaffolds due to their high surface-to-volume ratios, porosities and nanoscale structures similar to the ECM, their surfaces usually lack sufficient charge and roughness to promote cell adhesion. Nanoceramic particles show size effects, surface and interface effects and surface charges. The incorporation of inorganic nanoparticles can not only retain the original advantages of the nanofibers, but can also endow electrospun membranes with better biocompatibility and bioactivity and promote cell adhesion, migration, growth, and proliferation as well as other cell behaviours. Considerable studies have reported that the introduction of nanoceramic particles alters the hydrophilicity, porosity, and surface morphology of the substrate, imparts electrical properties and consequently brings about improvement of biological properties.

ECM proteins are key mediators of cell/material interactions, and their density and conformation play influential roles in cell adhesion and cellular response.[135] Meanwhile, electrostatic interactions and hydrophobic effects are crucial points in the absorption processes of proteins.[118] Research has verified that materials with certain hydrophilicities and surface charges can effectively promote the adsorption of proteins on the surface of materials, thus affecting the behaviours of cell migration, growth and proliferation. Ghorbani *et al.*[119] mixed polymer solutions with zinc-doped hydroxyapatite and electrospun them into nanofibrous scaffolds. The results indicated that the composite nanofibers have higher roughness, which is important in cell adhesion. Esfahani *et al.*[120] deposited zinc-doped nHA on nylon 6 membranes and studied the kinetics and isotherms of protein adsorption. The protein adsorption experiments showed that electrostatic interactions rather than the physical structure increased the amount of bovine serum albumin on the surface of the membranes. Khakestani *et al.*[115] built nHA-coated PLA mats that showed a change of contact angle from 130° to 90°. In other work, Su *et al.*[132] fabricated PLA mats coated with a chitosan/calcium silicate mixer. Water contact tests demonstrated satisfactory hydrophilicity improvement, where the contact angle decreased from more than 100° (pure PLA and nHA-coated PLA) to around 35.1° with the coating of calcium silicate. They also studied the influence of doped calcium silicate on protein adsorption. Characterization results indicated that these particles caused a decrease in pH of the ECM and thus increased its attractiveness to collagen and fibronectin, which are found in bone tissue; this is favourable to cell adhesion and growth.[132]

High porosity and interconnection is another important requirement for cell migration, nutrient transportation and waste excretion. Augustine *et al.*[136] reported an electrospun P(VDF-TrFE) (poly(vinylidene fluoride-trifluoroethylene)/zinc oxide) nanocomposite scaffold. Compared with the neat fibres, the composite membrane incorporated with zinc oxide particles showed a more porous morphology and microscale cavities, which benefited cell migration, nutrient supply and blood vessel penetration. Cell compatibility and cytotoxicity studies demonstrated that the scaffold containing ZnO had higher viability as well. In further studies conducted *in vivo*, histological evaluation revealed extensive networks of collagen fibres and neovascularization both on the surface of and throughout the ZnO-containing scaffold. Meanwhile, the number of new blood vessels depended on the percentage of added ZnO due to its electrical nature and stimulating properties.

In addition, surface roughness is considered in discussion of cell adhesion. Zhang *et al.*[137] built a novel scaffold consisting of poly-3-hydroxybutyrate-*co*-3-hydroxyvalerate (PHBV)/poly-aspartic acid (PAA) fibres and deposited nanohydroxyapatite. FE-SEM images and water contact tests demonstrated that the incorporation of nHA endows the membrane with a rougher surface and better hydrophilicity, which can increase initial cell viability. In addition, the deposition of nHA decreased the degradation rate, thus maintaining the structural completeness of the scaffolds. Further characterization illustrated improved mineralization and cell behaviour. Some magnetic particles have also been applied in tissue engineering in recent years.[59,138] Heng Zhang *et al.*[59] mingled Fe_3O_4 particles dissolved in hexane with PCL–PEG–PCL copolymer dissolved in CH_2Cl_2 followed by electrospinning. MTT analysis and fluorescence microscopy showed that the membranes incorporated with Fe_3O_4 particles can enhance cell adhesion and growth. A. F. Lubambo *et al.*[138] conducted similar studies, and the results showed more active cell behaviours. Furthermore, metallic ions dissolving in body fluids will participate in physiological regulation, such as acting in signal transduction pathways, altering the activity of enzymes and affecting gene expression.[121–126] For example, Valerio *et al.*[121] found that a high concentration of Ca^{2+} in the ECM increased the release of glutamate, which is related to bone mechanosensitivity. In addition, Ca increases the expression of growth factors.[122] M. Yamaguchi *et al.*[123] found that Zn activated protein synthesis and increased ATPase activity in bone tissue engineering. Similar results were found in the discoveries of Horiuchi *et al.*[124] In other work, Ullah *et al.*[131] found that ZnO catalysed the production of reactive oxygen species (ROS), which played a role in proliferation and differentiation. Moreover, Zn plays an important role in gene expression.[125,126]

3.1.3 Antibacterial effects. Most materials doped with nanoscale inorganic particles, such as Ag_2O, CuO, ZnO, and TiO_2, are endowed with antibacterial effects.[139] These particles show two general mechanisms of antibacterial activity. One mechanism can account for the antibacterial activity of metal particles such as Ag^+ and Cu^{2+}. The positive ions can adhere to the cell wall, penetrate the cell wall and then cause protein coagulation based on electrostatic forces.[140] The other mechanism occurs in some oxide compounds, such as TiO_2 and ZnO. The antibacterial performance of these oxides stems from their photocatalytic properties.[141] When the oxides are exposed to light of a specific wavelength, they activate O_2 and H_2O molecules adhered on the surface and generate reactive oxygen species (ROS), including hydrogen dioxide (H_2O_2), hydroxyl radicals ($OH^{\bullet-}$) and peroxide ($O_2{}^{2-}$).[139,141] ROS demonstrate high oxidation reactivity, which plays an important role in their antibacterial performance. Combining nanoscale inorganic particles provides a feasible and facile way to endow materials with antibacterial functions.

Zhang *et al.*[142] developed Ag nanowires/PVA hybrid nanofibers with antibacterial properties. Antibacterial tests against *S. aureus* indicated that the neat PVA membranes displayed no antibacterial properties, while the addition of Ag nanowires achieved a bacterio-stasis rate over 99%. Mokhena *et al.*[127] blended chitosan dissolved in 2% acetic acid and silver nitrate to obtain silver nanoparticles (AgNPs) and then coated them on PEO/SA membranes. Antibacterial effect studies indicated that the AgNPs-doped electrospun nanofibers showed high antibacterial efficiency against both Gram negative and Gram positive bacteria. Interestingly, chitosan and its derivatives show capability to stabilize and reduce metal oxides,[127] together with inherent bacterio-stasis;[139] they are conjugated with metallic particles to provide antibacterial functions. Tra Thanh Nhi *et al.*[128] built multicoated electrospun PCL/gelatin/nanosilver membranes for wound healing applications which also possessed good antibacterial ability. The high antibacterial efficiency is based on the penetration of the small silver ions into the membrane through electrostatic interactions.[128,140] The membrane leakage effect of silver nanoparticles can be clearly observed.[140] Other metallic ions also possess antibacterial properties; for example, electrospun membranes doped with TiO_2 were developed by Toniatto *et al.*[129]

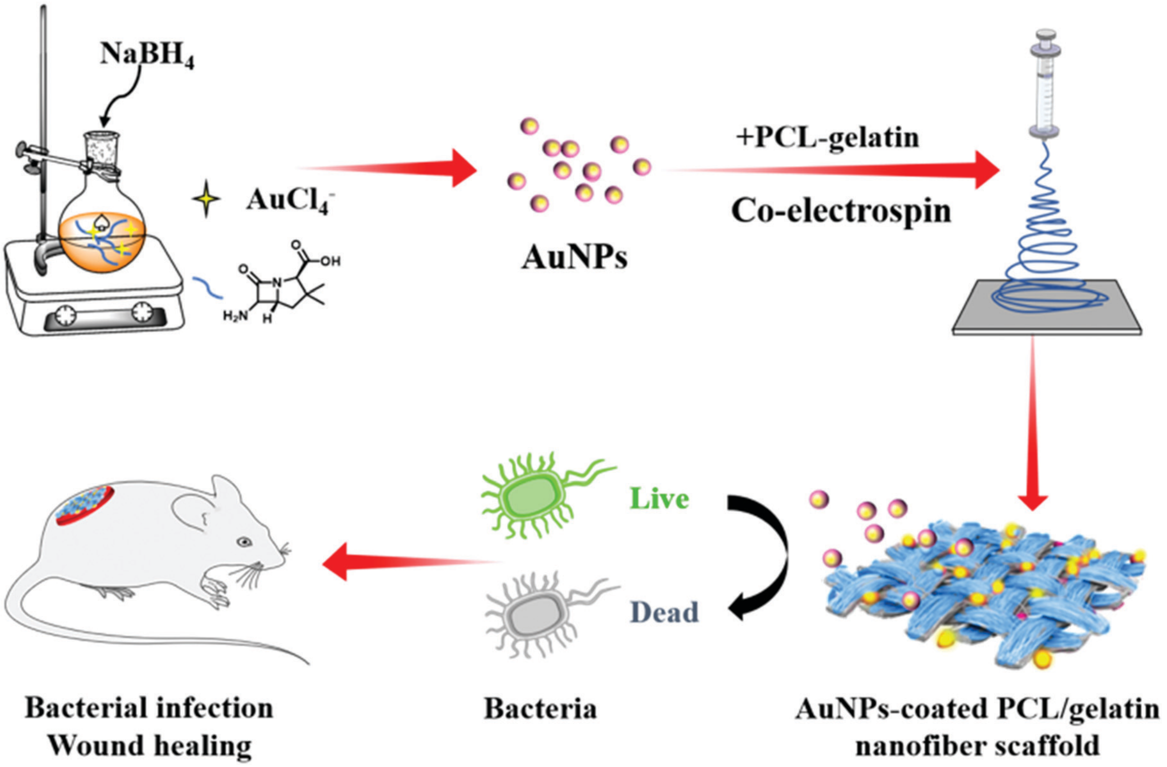

Fig. 3 Schematic of the synthesis of antibacterial AuNPs and their application for wound healing. Reproduced with permission from ref. 143. Copyright 2017 American Chemistry Society.

In their work, time-dependent and concentration-related antibacterial effects and the activation of TiO_2 were observed. Yang *et al.*[143] coated pharmaceutical intermediate-modified gold nanoparticles (AuNPs) onto PCL/gelatin nanofibers for wound dressing applications (Fig. 3). This AuNPs-coated scaffold demonstrated remarkable antibacterial properties even when confronted with multidrug-resistant bacteria. In the research of Ahmed *et al.*,[144] enhancement of antibacterial properties was also obtained by the addition of ZnO nanoparticles. Introducing metallic nanoparticles into nanofibers often brings about antibacterial effects. Polymers provide proper sites to load the particles and achieve controlled release of the particles, resulting in enhancement of the antibacterial effects.

Due to their size effects, high surface-to-volume ratios and electrostatic properties, nanoceramic particles have extremely attractive properties. The advantages of combining inorganic nanoparticles with organic nanofibers have been shown, and they demonstrate promising potential in the field of tissue engineering. On the other hand, the hybridization mode often results in asymmetrical distribution and weakens the properties of the materials. Therefore, exploration of a more uniform and controllable hybridization mode will be a future development direction.

3.2. Functionalization by nanocarbons

Nanocarbons are carbon materials with nanoscale sizes at least in one dimension;[145] they include carbon nanotubes (CNTs),[145–147] graphene oxide (GO),[148,149] nanodiamonds,[150] and fullerenes. Nanocarbons have small sizes, large surface areas and high electrical conductivity; thus, nanocarbons show intriguing properties and are eligible choices as reinforcements in electrospun nanofibers to improve performance[145–151] (Fig. 4). Among the many studies that have been conducted, carbon nanotubes and graphene are the two most commonly used nanocarbons to date in tissue engineering. Carbon nanotubes are allotropes of carbon with cylindrical nanostructures; based on their number of walls, they can be classified as single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs) and multi-walled carbon nanotubes (MWCNTs).[146] Mechanical, physicochemical and consequent biocompatible reinforcements can always be seen in nanocarbon-doped TE membranes. Three drawbacks handicap the application of carbon nanotubes: susceptibility to agglomeration, hydrophobicity and cytotoxicity.[146] Thus, the dispersion and cytotoxicity of carbon nanotubes are problems that require prompt solution, and various means of surface modification and coating by or hybridization with polymers are under study. Graphene is a single layer of carbon atoms[148] arranged in a hexagonal lattice,[145] and graphene oxide (GO) is a type of graphene with versatile properties. Graphene oxide is composed of sp^2 and sp^3 carbon atoms as well as oxygenated groups, which endow it with hydrophilicity and a wrinkled texture; it demonstrates fascinating bioactive enhancements, such as cell adhesion, proliferation and differentiation. Other nanocarbons, such as fullerenes and nanodiamonds, have been less researched than the former two in the TE arena. Nanocarbons can be hybridized into electrospun nanofibers by conventional electrospinning,[146] coaxial

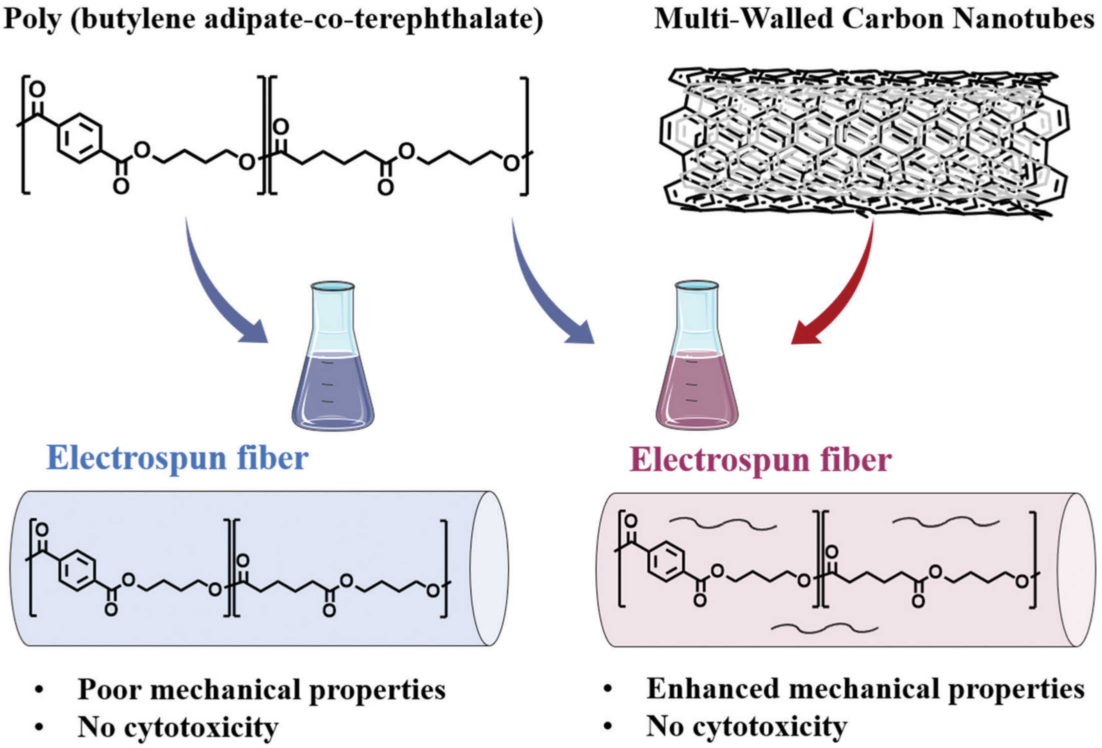

Fig. 4 Schematic of the fabrication of PBAT nanofibers and PBAT nanofibers doped with multi-walled carbon nanotubes. Reproduced with permission from ref. 146. Copyright 2015 Elsevier B.V.

electrospinning[52] and coating.[152] The novel nanocomposite fibres possess unique mechanical and electrical properties and thus receive much attention in bone regeneration, myogenesis and nerve tissue engineering. Usually, electrospun membranes incorporated with nanocarbons prompt cell adhesion, spreading, proliferation and differentiation due to the changes in physicochemistry, morphology and topology. Minoo *et al.*[153] electrospun PVA doped with single-walled carbon nanotubes (SWCNTs). The crystallinity in PVA was apparently increased with the addition of SWCNTs, which induced nucleation crystallization. Rodrigues *et al.*[146] mixed multi-walled carbon nanotubes (MWCNTs) into poly (butylene adipate-*co*-terephthalate) (PBAT) for bone tissue engineering. PBAT is flexible and has several intriguing properties but lacks adequate mechanical properties; the carbon nanotubes compensate for this limitation.[146] Oxygen plasma was used to graft oxygenated groups on the walls to increase hydrophilicity and decrease cytotoxicity. The experimental results indicated strengthened mechanical properties and osteogenic differentiation of MG63 cells. Liu *et al.*[154] developed PLGA/MWCNTs electrospun nanofibers for cardiac tissue regeneration. The characterization results indicated that addition of traces of MWCNTs improved the mechanical properties observably. These fibrous mats maintained good biocompatibility compared with PLGA scaffolds, and enhanced protein production was observed. Shao *et al.*[155] fabricated both randomly oriented and aligned PLA/MWCNTs nanofibers for osteoblast research. In their work, in addition to similar enhancements of the mechanical properties and degradation rate, application of electrical stimulation on the conductive aligned nanofibers demonstrated a significantly positive effect on the elongation of osteoblasts. Mohammadi *et al.*[148] built a PCL/GO nanocomposite scaffold for bone engineering. With the addition of GO, the electrospun fibres demonstrated decreased diameter and enhanced degradation rate as well as better protein absorption for improvement of hydrophilicity. Analogously, Song *et al.*[149] used PCL, a relatively inert polymer, as the main component to study the bioactive features of GO. Compared with a PCL scaffold, the PCL/GO scaffold was more hydrophilic due to its numerous oxygenated groups; this resulted in better cellular response, such as cell attachment, proliferation and differentiation, of two kinds of cells, namely osteo- and neuro-like cells. Nanocarbons are also applied in wound healing. In the work of Zhang *et al.*,[156] they fabricated both PLA/GO and PLA/PEG-GO nanofibers; several results indicated that the latter had superior thermal stability, wettability and tensile strength, derived from the enhanced interfacial adhesion between PLA and GO aided by PEG.

Nanofibers incorporated with nanocarbons exhibit preferable mechanical and biocompatible properties. The multiple valence of the carbon atom indicates high reactivity; therefore, nanocarbons can be easily modified by grafting other molecules and can be applied to different nanofibers to meet different performance requirements. The cooperation with electrospinning not only alleviates the dispersion problem but also decreases the cytotoxicity of the nanocarbons, which enables the introduction of nanocarbons into tissue engineering. In recent years, polymer/nanocarbon hybrid systems have caught much attention; however, the application of their fascinating properties still needs further research.

4. Electrospun nanofibers functionalized with both organic and inorganic additives

Due to the fact that ECM is a complex mixture of both organic and inorganic compounds,[146] the construction of multi-component composite membranes composed of two ingredients is a common pursuit of researchers. Most organic components tend to enhance the biocompatibility and biodegradability of biomaterials, while inorganic components change their physical properties or provide functions for specific applications.[146,157] Some organic natural ingredients are also described as safe agents in the carrying of inorganic substances and bioactive agents.[158] Inorganic components can also change the properties of organic components and improve their processability.[159] Composite materials not only maintain the advantages of the properties of each component but also obtain comprehensive properties that the single component materials do not possess, arising from the complementation and correlation of the properties of each component. Thus, by combining different materials from both organic and inorganic realms, it is feasible to construct biomimetic scaffolds with mechanical, biological and functional properties.[146,160,161]

ECM is a hybrid system in dynamic equilibrium composed of both organic and inorganic components.[146] In tissue engineering, biological scaffolds must simulate both mechanical properties and functional properties, which can temporarily replace and promote cell growth, proliferation and differentiation.[113] In this bionics process, the components contained in real ECM must be taken into account. Therefore, scientists are starting to consider combining organic and inorganic components to bring together their strengths and achieve synergy. Generally, organic components are the main components in the construction of scaffolds, and various organic components are added to improve the main properties, such as mixing polymer materials to change their hydrophilicity and degradation or adding natural components to increase biocompatibility. On the other hand, the addition of inorganic components is often used to achieve special purposes,[59] such as to increase mechanical properties, play an antibacterial role, or improve bioactivity. According to a large number of studies, it can be concluded that biological scaffolds with single or rare components rarely meet the requirements; meanwhile, biological scaffolds with multiple components have emerged at the right moment, and a large number of experimental results have confirmed their superior functions.

Based on the various studies above, some work has combined electrospun nanofibers with more than two components to aggregate more advantages. A novel electrospun chitosan/PVA/ZnO nanofibrous membrane was developed by Ahmed *et al.*[144]

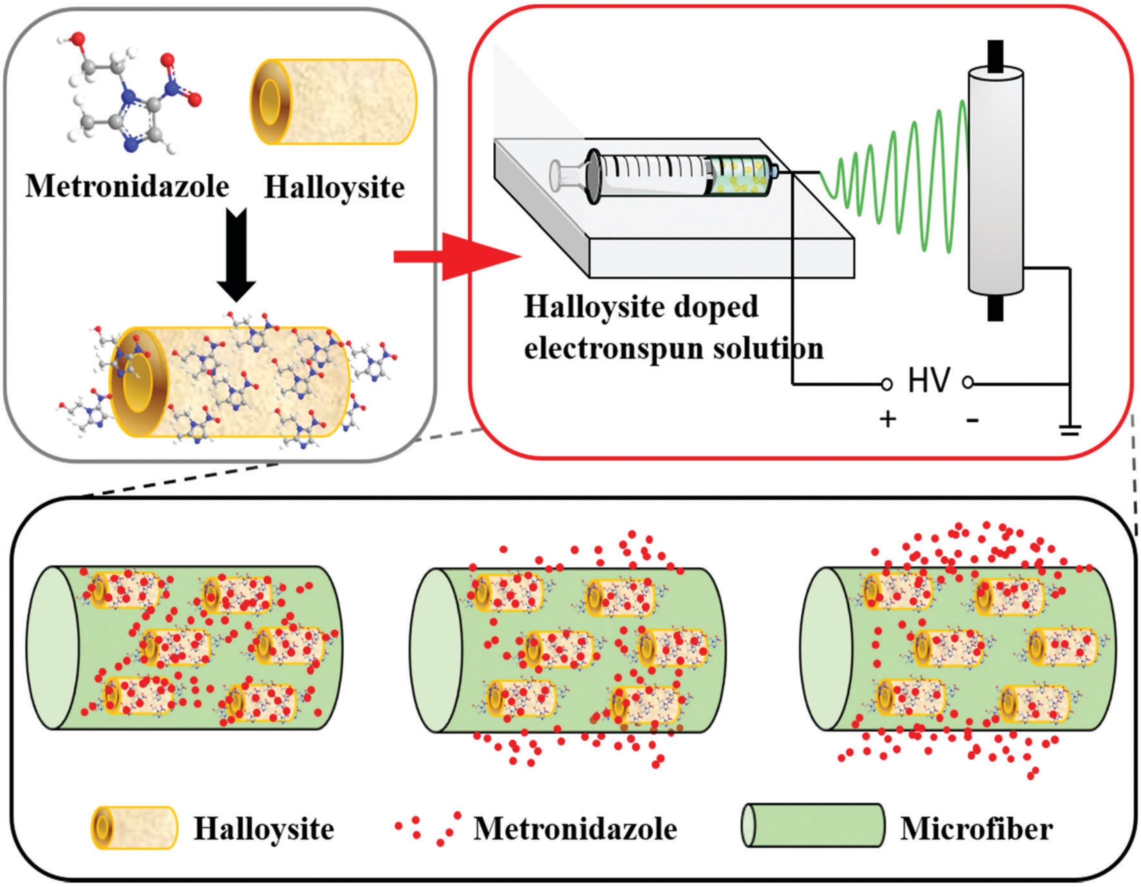

Fig. 5 Schematic of electrospun microfiber membranes embedded with drug-loaded clay nanotubes. Reproduced with permission from ref. 163. Copyright 2015 American Chemistry Society.

which contained synthetic polymers, natural components and ceramic nanoparticles; improved performance was indicated from many aspects. In the characterization of the biomaterial, chitosan/PVA/ZnO nanofibrous membranes exhibited enhanced antibacterial and antioxidant potential, in contrast with chitosan/PVA membranes. At the same time, the PVA fibres were considered to enhance the mechanical properties and hydrophilicity, and chitosan was considered on the basis of its antibacterial effects, biodegradation, and biocompatibility. Du *et al.*[162] developed ascorbyl palmitate (AP)-loaded poly(caprolactone)/silver nanoparticles (AgNPs)-embedded poly(vinyl alcohol) hybrid nanofiber mats *via* dual-spinneret electrospinning. Large amounts of hydroxyl groups of PVA caught and stabilized the Ag^+, successively causing nucleus growth and aggregation of the AgNPs. Due to the incorporation of AgNPs, the wound dressing mats demonstrated high antibacterial activity against *E. coli* and *S. aureus*, while the loaded AP weakened the cytotoxicity of AgNPs toward cell growth and proliferation. In the wound healing analysis, increased wound healing performance could be observed as AgNPs and AP were introduced into the mats. Xue *et al.*[163] developed composite membranes for tissue or bone regeneration by electrospinning PCL/gelatin microfibers doped with drug-loaded halloysite clay nanotubes (Fig. 5). In their work, they built a "nano in micro" structure by embedding the drug-loaded clay nanotubes (nanoscale) in the fibres (microscale); thus, they achieved sustained release of metronidazole (an effective drug against anaerobic bacteria) as well as good inhibition of bacterial growth. In the research of Sedghi *et al.*,[164] they built a multi-component composite scaffold for bone engineering applications containing graphite oxide (GO), Zn–curcumin complex (Zn–CUR), PCL polymers, PVA polymers and chitosan. Strong interactions between the GO nanosheets and polymer chains *via* SEM and GO were considered to improve the mechanical performance. CUR was considered to be favourable for bone tissue regeneration by supplying a highly bioactive surface and, together with Zn, provided numerous pharmaceutical effects. In the research of Yang *et al.*,[151] chitosan/PVA/graphene oxide nanofibrous membranes were prepared. Spindle and spherical graphene oxides were well dispersed in the fibres and enhanced the properties of chitosan. Characterization of the contact angles indicated that the addition of GO increased the hydrophilicity of the mats because it elongated the distance between the fibres, which facilitated the permeation of water. In the antibacterial tests, the observed inhibition zones showed good antibacterial activity against Gram positive and Gram negative bacteria. Clearly, nanofibers offer fundamental properties, such as mechanical properties, hydrophilic properties and some biological properties. In the past several years, many research groups have started to make efforts to fabricate multi-component composite materials; these materials, which aggregate advantages from many aspects, will receive wide attention.

5. Conclusion

Electrospinning has been verified as a powerful and versatile fabrication method applied in tissue engineering. For nanoscale fibres and scaffolds with high porosities and large face-area-to-volume ratios, electrospinning attracts much attention. However, due to the composite environment in the extracellular matrix and the finite properties of the single component nanofibers, more components should be aggregated into nanofibrous membranes to enhance their overall properties.

In this review, we have attempted to provide an overview of the different practices of fabricating electrospinning-based composite tissue engineering materials. Based on the structural and physicochemical characteristics, we discussed the properties of synthetic polymers and natural polymers used in tissue engineering. Through the combination of different materials, changes in the mechanical properties, hydrophilicity, degradability, and stimulus responsiveness of the materials allow them to be applied in different fields. In the section on the active molecules, we included the extracts of natural ingredients, antibiotics, functional peptides, growth factors, *etc.*, which are either grafted onto materials or carried by the scaffold and then released into the environment. In the section on inorganic reinforcement, we mainly discussed nanoceramic particles and carbon nanomaterials. Inorganic components are introduced into the scaffolds in direct ways, such as conventional electrospinning and coaxial electrostatic spinning, as well as in indirect ways, such as coating and layer-by-layer stacking. These inorganic components generally enhance the mechanical properties of composites and observably improve their biological performance. In addition, the antibacterial nature of some inorganic nanoparticles has led to their widespread application in wound dressings. Through the above discussion, we can reach a conclusion that the introduction of other components, both organic and inorganic, greatly modifies the properties of nanofibrous membranes.

In recent years, electrospinning has been finding a place in the field of tissue engineering, and some novel multi-component composite materials are becoming growing research trends. It can be predicted that electrospinning to obtain micro-nano sizes, anisotropic distribution and adjustable properties will still play an important role in tissue engineering applications in the future, especially in vascular tissue engineering and neural tissue engineering, because scaffolds with orderly orientations and different diameters can be easily obtained by altering the receiving devices. However, a biomimetic composite scaffold material is not a random addition of functional materials but an ordered arrangement of multiple components. Therefore, future work should focus on ordered combinations of materials to maximize the degree of biomimicry, *e.g.* obtaining multiscale and multilayer nanofibers by upgrading the preparation process. Moreover, in addition to the physicochemical properties of biocompatibility, degradability and biological activity which are traditionally considered, the scaffolds should be made more intelligent or their controllability should be increased; that is, they should be endowed with the ability to respond to microenvironmental variations and to be actuated by external signals. In addition, the post-treatment process of electrospinning nanofibers needs to be enhanced and combined with production techniques to improve the physicochemical properties of the nanofibers and meet functional requirements. The combination of electrospinning with other fabrication methods and the construction of three-dimensional scaffolds *in vitro* are also urgent topics to be developed.

Conflicts of interest

The authors confirm that this article content has no conflicts of interest.

Acknowledgements

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