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REVIEW

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Electrospinning nanofibers of microbial polyhydroxyalkanoates for applications in medical tissue engineering

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Abstract

Differently to most chemically synthesized medical materials, polyhydroxyalkanoates (PHAs) are intracellular carbon and energy storage granules, which is a family of natural bio-polymers synthesized by microorganism's materials. Due to excellent biocompatibility reasonable biodegradability and versatile material difference, PHAs are well medical biomaterials candidates for applications in tissue engineering and drug delivery, including commercial PHB, PHBV, PHBHHx, PHBVHHx, P34HB and few uncommercial PHAs. Electrospinning nanofibers with the size of 10–10,000 nm can improve the mechanical properties and decrease the crystallinity of PHA, meanwhile simulate the structure and function of native extracellular matrix of cells. Hence, PHAs electrospinning nanofibers as engineered scaffolds have been widely used for tissue engineering scaffolds in cardiovascular, vascular, nerve, bone, cartilage and skin; also, as carriers for application in drug delivery system. In this review, we highlight the extraction and properties of medical PHAs from natural or engineered microorganism, and microstructure, current manufacturing techniques and medical applications of electrospinning nanofibers of PHAs. Moreover, the current challenges and prospects of PHAs electrospinning nanofibers are discussed rationally, providing an insight into developing vibrant fields of PHAs electrospinning nanofibers-based biomedicine.

KEYWORDS

drug delivery, electrospinning, nanofibers, polyhydroxyalkanoates (PHAs), polymers, tissue engineering

1 | INTRODUCTION

Biomedical material is an important branch of materials science and engineering. Among them, the biodegradable polyester materials are poly(lactic acid) (PLA),[1] poly(lactic-co-glycolic acid) (PLGA),[2] poly(ε-caprolactone) (PCL),[3] and polyhydroxyalkanoates (PHAs),[4] and so forth. Compared with PLA and PLGA approved by the Food and Drug Administration (FDA) as implant materials, PHAs are a kind of non-cytotoxic polyester synthesized by a variety of bacteria under the condition of excessive carbon and nitrogen sources. It is noteworthy that degradation products of

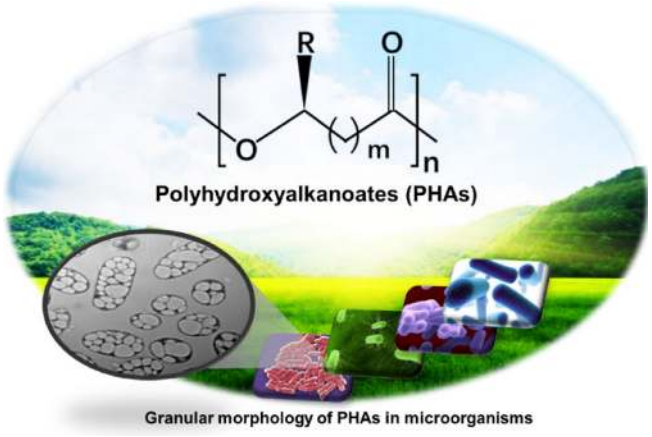
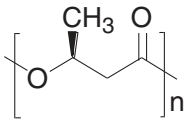
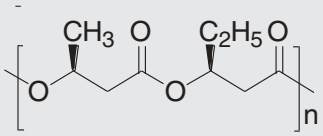
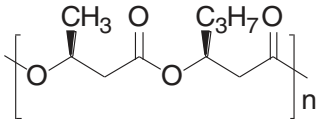
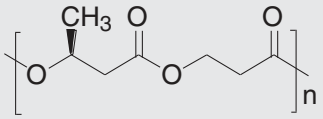
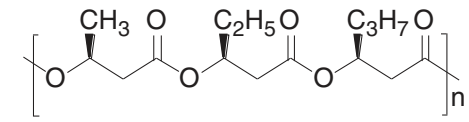


FIGURE 1 The general structure and granular morphology of PHAs in microorganisms

PHAs are not toxic and immunogenic in vivo. And its physicochemical properties of PHAs ranging from hardness to high elasticity make it suitable for different application needs. For example, the PHBHHx-based polyurethane hydrogel can maintain transparency when implanted in rabbit eyes and shows negligible inflammation and long-term preservation of the retinal structure over 6 months.[5] Studies showed PHAs is harmless to the body partial and the whole body after implantation organism, neither cause adverse reactions such as tissue or cell toxicity, allergy, stimulation, hemolysis, rejection, mutation, aberration, and canceration, nor prevent the normal activity of tissue cells on its surface or interfere with the natural regeneration process of cells. And PHAs is equipped with the function of conduction, promotion, stimulation, and induction of its own tissue growth. In addition, the mechanical properties of the implants are close to the tissue in the implanted area, which can avoid the trauma caused by the implant material to the normal surrounding tissue due to stress concentration. Meanwhile, the strength, hardness, and elastic modulus of PHAs matches with the implanted hard tissue. More importantly, the degradation time of the material matches the time of tissue growth, allowing the implant material to be replaced by its own tissue within a certain period.[6–13] Therefore, PHAs have been widely studied as tissue engineering materials and drug delivery matrices. As an extended family, the general structure of PHAs is shown in Figure 1. This article reviews five common commercials PHAs, including poly(3-hydroxybutyrate) (PHB), poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx), poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (P34HB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate) (PHBVHHx). The chemical structure of five common commercial PHAs are shown in Table 1.[14–16] The structural diversity and variability of

TABLE 1 Chemical structure formulas of five common commercial PHAs

Materials	Chemical structures
PHB	
PHBV	
PHBHHx	
P34HB	
PHBVHHx	

Abbreviations: P34HB, poly(3-hydroxybutyrate-co-4-hydroxybutyrate); PHAs, polyhydroxyalkanoates; PHB, poly(3-hydroxybutyrate); PHBHHx, poly(3-hydroxybutyrate-co-3-hydroxyhexanoate); PHBV, poly (3-hydroxybutyrate-co-3-hydroxyvalerate); PHBVHHx, poly (3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate).

PHAs physicochemical properties make it an important member of biomaterials (BMs).

PHAs materials has a wide range of applications in tissue engineering. Electrospinning (EPS),[17] solvent casting,[18,19] salt leaching,[20] and 3D printing[9] are all commonly used techniques in this field. However, solvent casting and salt leaching show unsatisfactory drawbacks: long preparation period results in the loss of a high percentage of the loaded drug in case of scaffolds. On the other hand, thin membrane with dense surface layer skin may contain residual contamination when using the above two techniques, which causes poor control over internal architecture and limited mechanical properties.[21] The high cost, long working hours and lack of conditions for mass production are main disadvantage for application of 3D printing technology. High-voltage ESP is a new fiber manufacturing technology in which electrically charged polymer solutions, or melts, are stretched by electric field forces to fibers a few hundred nanometers in diameter. Compared with thin-film and other carriers, EPS can respond to environmental changes more quickly and regulate the release rate of active substances flexibly, and easy to operate. Also, the EPS products with a large specific surface area, cost-effective, high porosity and good mechanical properties make it a widely used

TABLE 2 Carbon sources used by different microorganisms to produce PHAs

Source		Microbial strains	Yields (%)	References
Carbohydrate	Sugarcane molasses	*Bacillus cereus*	61.07	25
	Glucose	*Pseudomonas putida* KT2440	/	26
	Cellulose	*Saccharophagus degradans*	19.2	27
Organic salt	Acetate	*Glycogen accumulating organisms*	41	30
Waste	Oxidized polypropylene	*Cupriavidus necator*	42	32
	Palm oil mill effluent (POME)	Bacterial isolation and screening from POME spilled area	/	33
	Wood waste and sewage	Bacterial isolation and screening from wood waste and sewage area	50.3	34
	Olive mill wastewater	*Cupriavidus necator*	91.3	36
	Waste sludge	/	60.3	36
	Waste cooking oil	*Pseudomonas aeruginosa*	21.8	37
	Animal fat and glycerol	*Bacillussubtilis/Pseudomonas aeruginosa/Bacillus tequilensis / Bacillus safensis*	9/26/39/27	38
	Peanut oil	*Cupriavidus necator*	51	39
	Offal hydrolysis	/	80	40
	Sewage from the agricultural and food processing industries	*Bacillus megaterium*	24	41
	Waste fish oil and glycerol	*Salinivibrio sp*. M318	51.7	42
	Vinasse	*Haloferax mediterranei*	70	43
	Steamed soybean wastewater	*Pseudomonas sp*. 61–3	35	44
	Hydrolyzed paper recycling waste fines	Recombinant *Escherichia coli* harboring PHA biosynthesis genes	/	45
Phenolic compound	Toxic pollutant phenol	*Bacillus strain*	/	46
Light and CO_2		*Spirulina sp*.	/	47
		Synechocystis *sp*. PCC6803	10	48

Note: Yields: PHAs as a percentage of dry cell weight.
Abbreviation: PHA, polyhydroxyalkanoate.

material. At the same time, the EPS fibers can simulate the human extracellular matrix (ECM) environment, greatly improving the biocompatibility of the material, making the loaded drugs more stable, and promoting the repair of adjacent tissues.[22] Based on the advantages of PHAs and EPS. PHAs nanofibers extend wide-ranging applications in biomedical (cardiovascular, vascular, nerve, bone, cartilage, skin, drug delivery). Compared with other bio-polyesters, the development history of PHAs is shorter and has a greater potential for improvement and application. In the past few years, people have devoted themselves to explore the application of PHAs in medical devices.[23,24] This article reviews what has been achieved in the latest PHAs nanofibers in medical applications and looks to the future prospects for PHAs nanofibers as tissue engineering materials.

2 | PREPARATION AND PROPERTIES OF PHAs

2.1 | Biological synthesis

PHAs are polyesters of hydroxy alkanoic acids and are produced by large numbers of bacteria as intracellular carbon and energy storage compounds. The most used carbon sources of PHAs are carbohydrates,[25–29] and organic salt[30,31] (Table 2). Recent literature has clearly highlighted that the reuse of wastes as bacterial media, which can not only greatly reduce the cost of PHAs production and of waste treatment, but also obtained a clean environment. The wastes tested including municipal waste,[33,49–51] sludge fermentation supernatant,[52] food production waste,[32,36,38,40,42,53,54] pulp waste,[55] and various agricultural wastes.[44,56] However, despite the wide

variety of possible feedstock, very few studies have dealt with toxic substances contained in industrial wastewaters for PHAs production. Zhang et al.[57] used phenol as the carbon source for PHAs, and an alternative way of producing PHAs is to use of cyanobacteria.[47,58]

2.2 | PHAs extraction methods

Solvent extraction is the most widely used method for extracting PHAs. Commonly used solvents are divided into a halogenated, non-halogenated and mixed solvent (halogenated and non-halogenated). The advantage of using halogenated solvents (chloroform,[59] dichloroethane,[60] dichloromethane, and 1,2-dichloropropane[59]) is that high purity and high molecular weight PHAs can be obtained, so it is suitable for medical applications (Table 2). Unfortunately, the high cost and long operation procedure limit its application to some extent. Moreover, it is not easy to extract more than 5% (W/V) PHB from solutions containing PHAs. And the natural ordering of polymer chains in PHAs particles may be destroyed, the use of many toxic and volatile halogenated solvents poses a great challenge to the environment. The common non-halogenated solvents are cyclic carbonate,[61] methyl lactate,[59] acetic acid,[59] methyl tert-butyl ether,[62] 1,2-propylene carbonate,[63] propionic acid, propyl butyrate, isoamyl valerate,[64] and so forth. However, Large-scale use of non-halogenated solvents may cause serious damage to the environment. The mixed solvents of dimethyl carbonate and NaClO are the most commonly used.[65] And the advantage of mixed solvent application would not harm the environment significantly, and can improve the recovery of PHAs and save costs.

Extraction PHAs by enzyme digestion is a common method, and enzymes frequently used enzymes include glycosidases, lysozyme, cellulase, bromelain, and trypsin.[66–68] And high quality PHAs can be obtained in mild operating conditions. However, the high cost and complex operation procedures of the enzyme use cannot be ignored.

Mechanical cell division is widely used to release intracellular proteins, and the concept has been used to recover PHAs from bacterial cells. Ball milling,[69] sodium dodecyl sulfate (SDS)[70] high pressure homogenization and ultrasonic are the common mechanical crushing methods. The application of the bead mill does not involve any chemical substances, which greatly reduces the pollution to the environment and PHAs products. The advantages of SDS high-pressure homogenization method are that more PHAs with higher purity can be obtained and more environmentally friendly. However, the disadvantages of the mechanical crushing method cannot be ignored. The long operation time, the requirement for precise process parameters and the formation of little cell fragments during the biological separation process greatly limit its development.

2.3 | PHAs mechanical and physical chemistry properties

The mechanical properties of PHAs are determined by their monomeric composition, and depends on their chain length and the distance between the R-group and the ester bond. PHB presents brittleness at ambient temperature, poor impact resistance, and is extremely unstable in the melting state, the processing temperature range is narrow (162.0–179.0 °C) and its crystallinity up to 60%–80%. In addition, PHBV is also a high crystallinity polymer, which exhibits a crystal structure like PHB. Kutrioka et al.[71] observed the crystallinity of PHBV is more than 50% within the scope of the whole content of HV (0–95 mol%). Among these copolymers, P34HB introduces a more flexible 4-hydroxybutyrate (4HB) chain segment, and after copolymerization with the 3-hydroxybutyrate (3HB) chain segment, the toughness of the material is significantly improved. And with the increase of 4HB content, the tensile strength of the material decreases. As seen from structural formula of the P34HB, which is a typical semicrystalline polymer, the spatial regularity of P34HB chain was destroyed with the introduction of 4HB during the crystallization of P34HB. The 4HB monomer unit is excluded from the PHB crystal lattice, which dramatically reduces the crystallization ability of PHB, leading to a slower crystallization rate, a lower degree of crystallinity, and a high likelihood of post-crystallization. However, compared with PHB, the thermal stability and toughness of P34HB are improved to some extent by introducing a 4HB monomer. Relevant data shows that the Elongation at break of PHBHHx (107.7%–270.0%) and PHBVHHx (276.9%–739.7%) are both higher than PHB (4.5%–5.0%). It is suggested that the introduction of 3HHx decreased the mechanical strength and improved the flexibility of multi-component copolymers compared with the pure PHB. And the incorporation of 3-hydroxyhexanoate (3HHx) and 3-hydroxyvalerate (3HV) monomers with soft and non-crystal properties provide the material with more ductile and more rigid properties, respectively (Table 3). Many research advances have been demonstrated that the potential for biosynthesis of new materials is almost unlimited. It is believed that with further research, more and more PHAs will be synthesized.

TABLE 3 Mechanical and physical chemistry properties of commercial PHAs

PHAs	T_m (°C)	T_g (°C)	R_m (MPa)	E (%)	X_c (%)	References
PHB	162.0–179.0	−1.2 to 4.0	18.5–43.0	4.5–5.0	60.0–80.0	72–75
PHBV	120.0–170.0	−1.7 to 5.0	2.4.0–80.0	30.0–123.0	58.1–65.7	71,75–80
PHBHHx	52.0–151.0	−1.8 to 4.0	4.5–10.14	107.7–270.0	25.0–43.0	75,81
P34HB	50.0–166.0	−4.2 to 7.4	23.1–25.8	3.7–13.0	80.0–90.3	82–85
PHBVHHx	69.6–152.1	−2.6 to −1.2	8.0–15.7	276.9–739.7	/	75,86–88

Note: T_m, melting temperature; T_g, glass transition temperature; R_m, Tensile Strength; E, Elongation at break; X_c, crystallinity.
Abbreviations: P34HB, poly(3-hydroxybutyrate-co-4-hydroxybutyrate); PHAs, polyhydroxyalkanoates; PHB, poly(3-hydroxybutyrate); PHBHHx, poly (3-hydroxybutyrate-co-3-hydroxyhexanoate); PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate); PHBVHHx, poly(3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate).

2.4 | Biocompatibility

PHAs are biodegradable, and their corresponding biodegradable products are not harmful to cells and tissues. This will constitute higher compatibility between cell and tissue. PHB is not just an inert storage polymer restricted to certain bacteria, but a ubiquitous, interactive, solvating biopolymer involved in important physiological functions. Low molecular weight PHB, complexed to other macromolecules (c-PHB), is widely distributed in biological cells, complexation modifies the physical and chemical properties of c-PHB, and as a result that c-PHB can be found in the cytoplasm and intracellular fluids as well as in membranes and lipoproteins.[89] Based on this discovery, it is reasonable to speculated that oligomonomers and monomers of PHB are not toxic to the cell. PHAs have been studied in vitro, five commercial materials (PHB,[90] PHBV,[91] PHBHHx,[92] P34HB,[93] and PHBVHHx[94]) were co-cultured with cells, respectively. Results showed that cell cultures in direct contact with PHAs exhibited high levels of cell adhesion and activity. The investigation showed that these materials can be used to make matrices for in vitro proliferous cells. Doyle et al.[95] demonstrated that materials based on PHB produce a consistent favorable bone tissue adaptation response after implantation periods up to 12 months. PHBV scaffold showed good wound healing efficiency in mice skin wound healing experiments.[96] Wang et al.[97] implanted the Neural stem cells (NSC)-carrying PHBHHx film in vivo into the lesion region in a rat traumatic brain injury (TBI) model, the results showed that PHBHHx did not induce additional reactive gliosis and supported the in vivo survival and growth of the transplanted stem cells. Furthermore, full cartilage defects in rats were created and P34HB scaffolds were implanted to investigate the safety and biological compatibility within 8 weeks.[98] In vivo implantation experiments in rabbits proved that the interaction between PHBVHHx and tissues was mild, and there was no obvious foreign body reaction or severe inflammation.[87] In brief, many experimental results showed that PHAs have good biocompatibility and is one of the excellent raw materials for medical tissue engineering.

2.5 | Biodegradability

Microorganisms, both bacteria and fungi, have the capacity to degrade PHAs by aerobically and anaerobically.[99] Generally, the degradation process is carried out by intra or extracellular PHAs depolymerase produced by the microorganisms. Common PHAs biodegradation products including oligomers and monomers, and which are also not toxic to the cells and tissues. The research illustrated the degradation products of PHBHHx have shown positive effects on mouse fibroblast growth and are not harmful to murine beta cells.[100,101] For mammals, PHAs are degraded by enzymes present in blood and tissues. The polymers were degraded at different rate and depending on the type of fluid. Bovine serum was the most effective for polymer degradation, followed by pancreatin juice. In vitro studies have shown that pancreatin plays a key role in P3HB degradation.[102] Meanwhile, P3HB is mainly degraded under acidic conditions through acid hydrolysis of the ester bond in higher organisms.[103] The biodegradable properties of PHAs also make it one of the hottest BMs for tissue engineering.

3 | ELECTROSPINNING TECHNIQUE

3.1 | The method of electrospinning

EPS is the most used method to produce nanofibers. The EPS device consists of three parts, which are the high voltage power supply, the receiver and the liquid supply system. The EPS technique involves consists of placing a

polymer solution into a syringe and then pushing it to the tip of the syringe by external pumping applied by a mechanical piston. The increase of electric field with the gradual increase of the voltage, and based on this, the droplet will gradually stretch at the spinners. If the voltage reaches a critical value, the droplet stretch state will also change to a certain extent, and the droplet will quickly reach equilibrium and form a Taylor cone. Charged droplets will quickly form a high-speed jet phenomenon from the top of the Taylor cone under the action of the electric field force. Finally, as the solvent evaporates, the nanofibers are deposited on the surface of an oppositely charged grounded collector.

3.2 | Characteristics of PHAs electrospinning

Up till now, the morphology of EPS nanofibers (50–1000 nm) is varied. Firstly, the morphology of a single nanofiber can be changed by changing the structure of the nozzles. There are four types of EPS nozzles, single-nozzle (solid),[104,105] coaxial nozzle (hollow, core-shell),[106,107] microfluidic device as the nozzle (Side-by-side bicomponent fibers)[108] and multichannel nozzle (multichannel).[109] The morphology of the receiver can also be changed to obtain different deposition morphology of random,[110] aligned,[111] and 3D patterned[112,113] nanofibers. PHAs are natural polyesters produced by microorganisms under carbon source excess and limiting nutrient conditions. However, these biopolymers possess low mechanical and thermal properties, decreasing their potential applications in the medical field. PHAs EPS fibers improve the mechanical properties and decrease the crystallinity of PHAs, including PHB and its copolymers, which is attributed to the metastable structure (β-form) formation. Meanwhile, fibers produced with PHAs blended with other polymers have shown improved mechanical and biological properties. Gelatin (GEL), zein, and cellulose acetate are the main natural polymers that have been blended with PHAs for EPS scaffolds. For scaffold produced by coaxial EPS, GEL has been used as a shell and PHAs as the core. In conclusion, PHAs have been combined with different synthetic polymers and plasticizers to increase the biocompatibility, mechanical properties of PHAs. Meanwhile, the application of EPS in the development of PHAs-based scaffolds seems to be an attractive method to change the mechanical/biological properties, increasing and enhancing PHAs applications in tissue engineering. Besides, the biocompatibility, mechanical properties, and morphology of the scaffold are important attributes, and specific surface area, volume, and size of the pores have a considerable effect on cell adhesion, growth and proliferation. In the case of incorporated biologically active substances, and their release is also influenced by the internal structure of nanofibers.[114] Studies show that PHAs nanofibers have bead,[115] solid,[116] porous,[117] rough,[90] and core-shell[118] structures. (Figure 2 and Table 4) The rough PHB/nHA (spray) nanofibers were prepared by simultaneous EPS and electro-spraying, this nanofiber surface roughness generated by the bio-ceramic deposition, which could result in a significant increase in the specific surface area and favorable to cell attachment.[90] In summary, nanofibers mimic structural and functional characteristics of native ECM, and therefore they have been widely used for tissue engineering scaffolds.

4 | MEDICAL APPLICATIONS

Substantial advances have been made over the last two decades in the field of PHAs, Due to PHAs are renewable natural resources, good biocompatibility and hemocompatibility[134,135] as well as high affinity to a wide variety of cells,[136,137] which makes it even more advantageous for biomedical application.[138] PHAs has become a research hotspot in the field of BMs in recent years. Especially in EPS of PHAs, which have been widely employed in cardiovascular, vascular, nerve, bone, cartilage, skin, drug delivery, and so forth (Figure 3).

4.1 | Cardiovascular tissue engineering

Cardiovascular disease is one of the diseases with the highest incidence and fatality rate in the world. Autologous blood vessels and early artificial synthetic blood vessels (inner diameter less than 6 mm) have problems in small-caliber blood vessel transplantation, which are prone to thrombosis and intimal hyperplasia due to slow blood flow, resulting in low long-term patency. Therefore, polymeric materials are used increasingly for surgical reconstruction of cardiovascular tissues and several studies indicated the benefits of BMs by reducing remodeling after Myocardial Infarction (MI) and inducing stem cell function in the cardiac.[139,140]

The development of BMs for myocardial tissue engineering requires a careful assessment of their performance with regards to functionality and biocompatibility, including the immune response. PHB, PCL, silk, PLA, and polyamide (PA) scaffolds are generated by EPS with a no crosslinked collagen membrane (Col) control material.[141] Results showed that implantation of PCL, silk, PLA, and PA patches on the

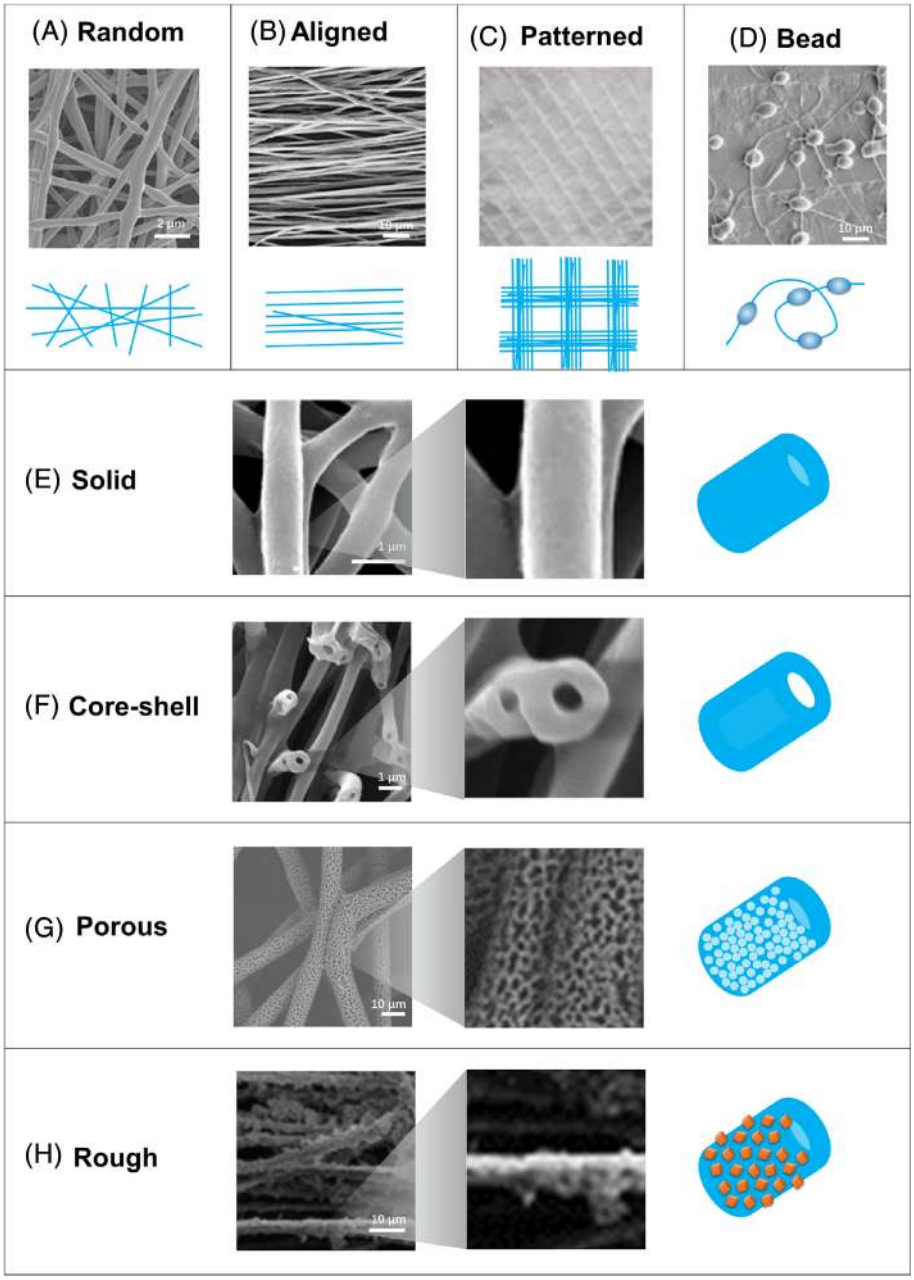


FIGURE 2 Structures of polyhydroxyalkanoates (PHAs) nanofibers. (A) Random: The deposition morphology of PHAs nanofibers is random.
Reproduced from Reference 119, with permission from 2012 John Wiley & Sons, Ltd.
(B) Aligned: The deposition morphology of PHAs nanofibers is aligned.
Reproduced from Reference 111, with permission from Taylor & Francis.(C) Patterned: The deposition morphology of PHAs nanofibers is patterned.
Reproduced from Reference 113, with permission from MDPI.
(D) Bead: Single PHAs nanofiber is a string of beads.
Reproduced from Reference 115, with permission from Lifescience Global.(E) Solid: Single PHAs nanofiber has a solid structure.
Reproduced from Reference 116, with permission from 2017, American Chemical Society.
(F) Core-shell: Single PHAs nanofiber has core-shell structure.
Reproduced from Reference 85, with permission from Taylor & Francis.(G) Porous: Single PHAs nanofiber has a porous structure.
Reproduced from Reference 117, with permission from 2014 Wiley Periodicals, Inc.
(H) Rough: Composite PHA nanofibers blended with hydroxyapatite nanoparticles.
Reproduced from Reference 90, with permission from 2014 Elsevier B.V

TABLE 4 Characteristics of PHAs electrospinning

Materials	Solvent	*C* (%)	*T* (°C)	*H* (%)	*V* (kv)	Structure	*D* (nm)	References
PHB	CHL	7	25	/	81	Solid	/	198
PHB	CHL	1	/	/	20	Solid	/	177
PHB	CHL: DMF	14	30	/	25	Rough	950	90
PHB	CHL	4	/	/	20	Solid	/	199
PHB	HFIP	1–5	/	/	/	Solid	190–690	121
PHB	CHL: TFE	5	/	/	12	Porous	500–540	117
PHB	TFE	10	30	/	25	Solid	420–480	172
PHB	TFA	9	/		21	Solid	575–1806	181
PHBV	CHL: DMF	10	24–26	37–42	16	Solid	600–2000	154
PHBV	HFIP	6	/	/	10	Solid	720	119
PHBV	TFE	2	30	/	20	Solid	400	195
PHBV	CHL: DMF	19	/	/	8/17	Solid	330–583	200
PHBV	TFE	2	/	/	12	Porous	811–1293	81
PHBV	CHL: DMF	24	/	/	16	Core-shell	672.9	118
PHBHHx	DCM: DMF	12	40	40–50	14	Solid	973	201
PHBHHx	CHL	12	/	/	15	Solid	/	202
P34HB	CHL: DMF	5	/	/	20	Solid	/	169
P34HB	CHL: DMF	2–10	/	/	10–30	Bead	913	115
P34HB	CHL	6	/	30–60	/	Solid	/	203

Note: C, concentration; T, temperature; H, humidity; V, voltage; D, the diameter of nanofibers.
Abbreviations: CHL, chloroform; DCM, dichloroethane; DMF, *N,N* dimethylformamide; HFIP, 1,1,1,3,3,3- hexafluoro-2-isopropanol; P34HB, poly (3-hydroxybutyrate-co-4-hydroxybutyrate); PHB, poly(3-hydroxybutyrate); PHBHHx, poly(3-hydroxybutyrate-co-3-hydroxyhexanoate); PHBV, poly (3-hydroxybutyrate-co-3-hydroxyvalerate); TFE, tetrafluoroethylene.

TABLE 5 Types of drugs loaded with PHAs

Drug classification	Drug	Application	References
Antisepsis and inflammation	Gentamicin sulfate	Skin	120
	Kanamycin sulfate	Skin	121
	Silver	Skin	122
	Dodecyl trimethylammonium chloride	Skin	118
	Black Soldier Fly	Skin	123
	Osthol	Skin	124
	Phenolic compounds	Skin	125
	Donor S-nitroso glutathione	Skin	126
Chemotherapy drugs	Paclitaxel	Cancer	127
	5-fluorouracil, oxaliplatin, paclitaxel, cisplatin and irinotecan	Cancer	128
Other	Graphene oxide	Bone	129
	Curcumin	Vessel	130
	Pectin	Retinal	131
	Capsaicin	Patch	4
	Fish-scale powder	Bone	132
	Plai oil	Patch	133

Abbreviation: PHA, polyhydroxyalkanoate.

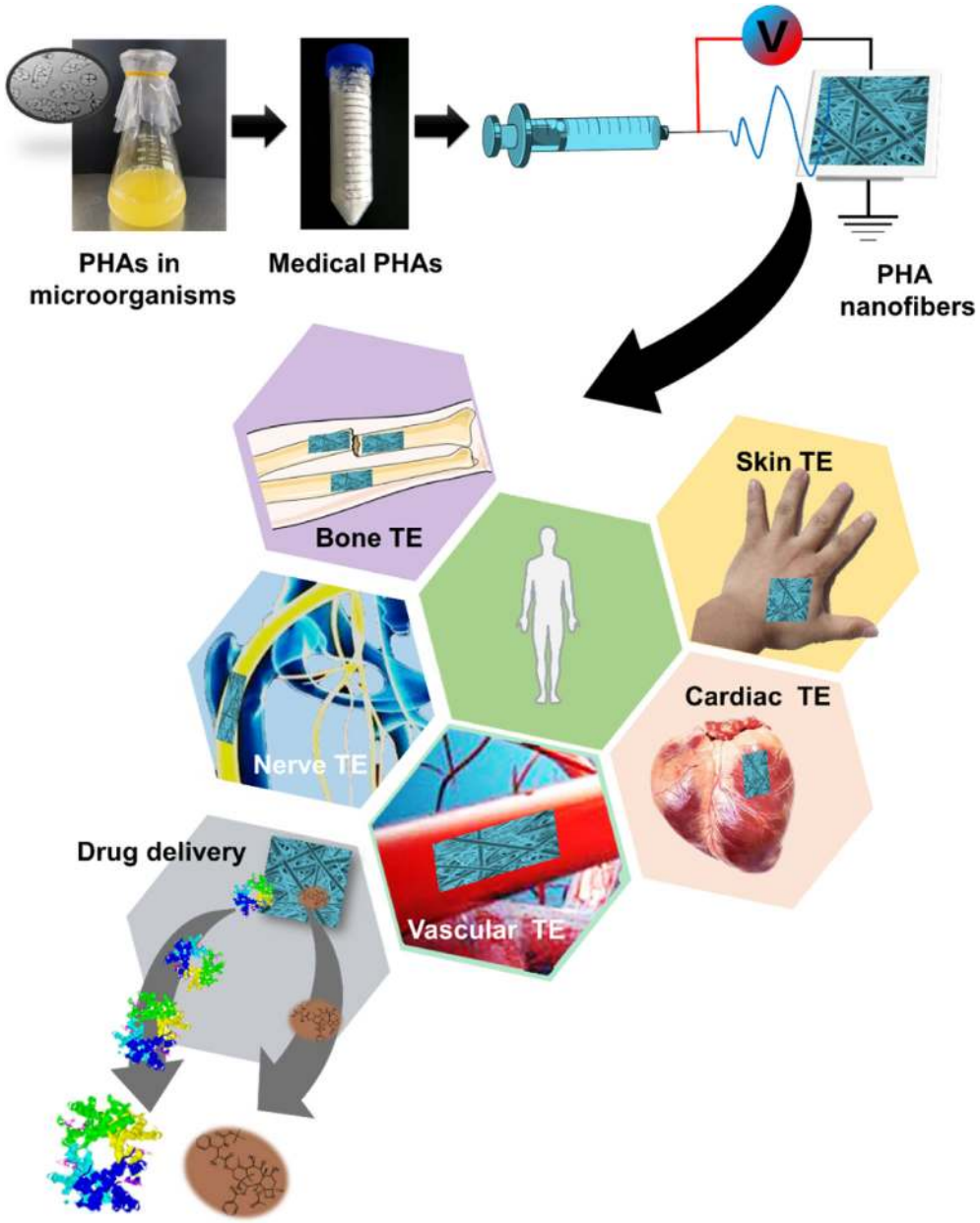


FIGURE 3 Schematic of electrospinning nanofibers based on microbial polyhydroxyalkanoates (PHAs) for medical applications

epicardial surface of healthy rats induced a classical foreign body reaction pattern, with encapsulation of polymer nanofibers and induction of the nonspecific immune response, whereas Col and PHB patches were progressively degraded. Importantly, Col and PHB modified the inflammatory response to an M2 macrophage phenotype in cardiac tissue, and only PHB induced significant angiogenesis. Interestingly, although PHB and PCL induced cell adhesion to a similar degree, the physicochemical properties of PHB prevented cell spreading, a feature that could be advantageous to meet safe requirements in clinical protocols. Moreover, Castellano et al.[141] demonstrated that poly(hydroxybutyrate) is a superior scaffold for cardiac repair for the first time.

4.2 | Vascular tissue engineering

P34HB has highly adjustable elasticity and strength, by adjusting the content of 4HB, materials with different mechanical properties and biodegradability can be prepared, and can induce elastin formation. Therefore, it is of great significance to explore the application of P34HB in artificial blood vessel materials.[142] Block copolymerization can add new properties to PHAs. For example, poly(ether-ester urethane) (PUs) multiblock copolymers synthesized from distal hydroxylated PHBHHx and poly(ethylene glycol) PEG via a melting polymerization (MP) process using 1,6-hexamethylene diisocyanate (HDI) as a non-toxic coupling agent and showed better mechanical and biological properties.[143,144] The block

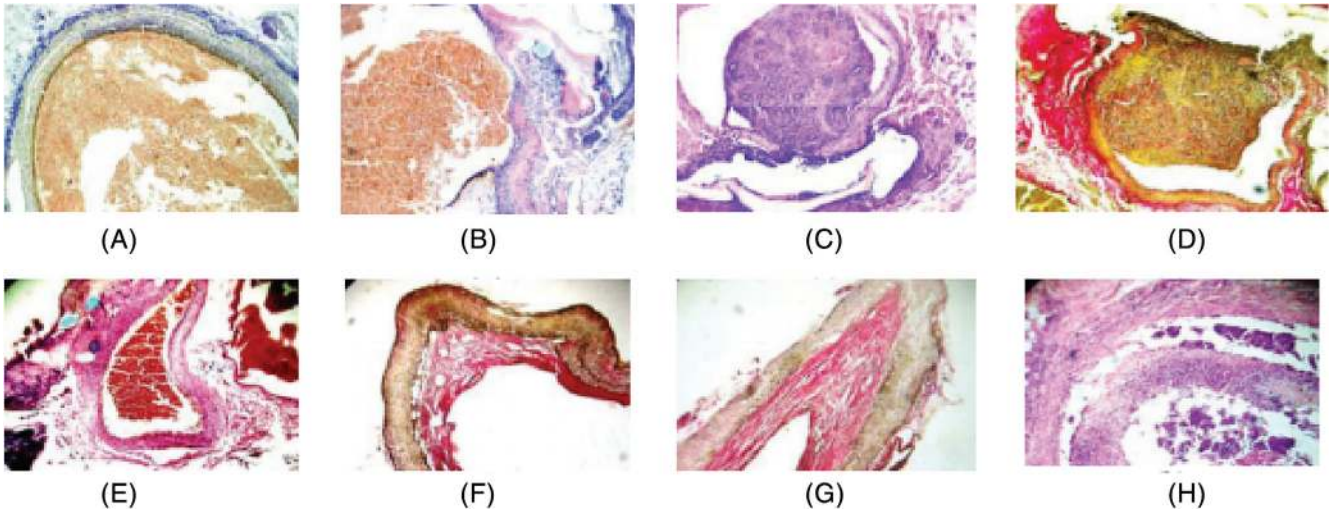


FIGURE 4 Histological examination of PHBV/Valerate/PCL small-diameter vascular graft (A) short-term implantation, complete patency; H&E staining, u100; (B) short-term implantation, parietal thrombus; H&E staining, u200; (C) short-term implantation, thrombus with 66% graft lumen occlusion; H&E staining, u50; (D) short-term implantation, thrombus with 66% graft lumen occlusion; Van Gieson staining, u50; (E) 12 month implantation, complete patency; H&E staining, u50; (F) 12 month implantation, parietal recanalized organized thrombus, Van Gieson staining, u100; (G) 12 month implantation, connective tissue hyperplasia in the graft lumen, Van Gieson staining, u100; (H) 12 month implantation, inflammatory infiltrate in the part of the arterial wall; H&E staining, u200.
Reproduced from Reference 148, with permission from 2015, AIP Publishing

copolymers had a lower platelet adhesion than the raw materials and the amount of platelet adhesion could be controlled by varying the segmental length of P34HB-diol, suggesting that these polyurethanes are candidates as a blood vessel material.[143,144] With the increasing studies of PHAs in cardiovascular tissues, researchers have found that the shape and thickness of artificial blood vessels are also closely related to blood vessel transplantation. For instance, two EPS PHBHHx grafts with a wall thickness of about 200 μm were prepared by EPS, including straight and corrugated structures with an inner diameter of 6 mm. These results showed that the straight grafts had similar mechanical behaviors to commercial vascular grafts and better in terms of circumferential tensile breaking strength, Young's modulus and radial compliance.[145] With the deepening of research, Gao et al. PHBHHx small-diameter vascular grafts (inner diameter: 6 mm) with two different shapes and three different wall thicknesses (121.32 ± 8.99, 284.70 ± 11.45, 425.20 ± 11.24 nm) were successfully fabricated by EPS. Results indicated that the corrugated vascular grafts with the wall thickness of 425.20 ± 11.24 μm were prepared and will have greater application prospects in the field of vascular tissue engineering.[146]

It was reported that γ-polyglutamic acid and polylysine were introduced into the P34HB EPS nanofibers scaffold by a layer upon layer self-assembly technique, and the selenium-containing catalyst selenocysteine was loaded to construct an artificial vascular material with catalytic function of NO in situ formation.[147] Li et al. experimental results showed that this NO-producing material could inhibit the activity of smooth muscle cells, which is expected to prevent vascular restenosis caused by excessive proliferation of smooth muscle cells in the early stage of artificial vascular transplantation. Their studies will be helpful for artificial vascular to overcome the problem of intimal hyperplasia after transplantation. Blood vessel material based on composite materials of bacterial cellulose and PHBV, PHBV and PCL were also reported, respectively.[148,149] So far, PHAs based blood vessel materials have been developed with the required bio-and mechanical properties, more in-depth research is still in progress (Figure 4).

4.3 | Nerve tissue engineering

The rehabilitation of partial or complete loss of nerve action is an important phenomenon because of the complexity of the human nervous system. Meanwhile, neural reconstruction of the human adult is also limited. However, bioengineered scaffolds can help to repair long peripheral nerve gaps by employing suitable polymer compositions within the body. Polymeric scaffolds develop tissue regeneration by a mimic cellular environment that would be suitable for cell attachment, proliferation, and differentiation.

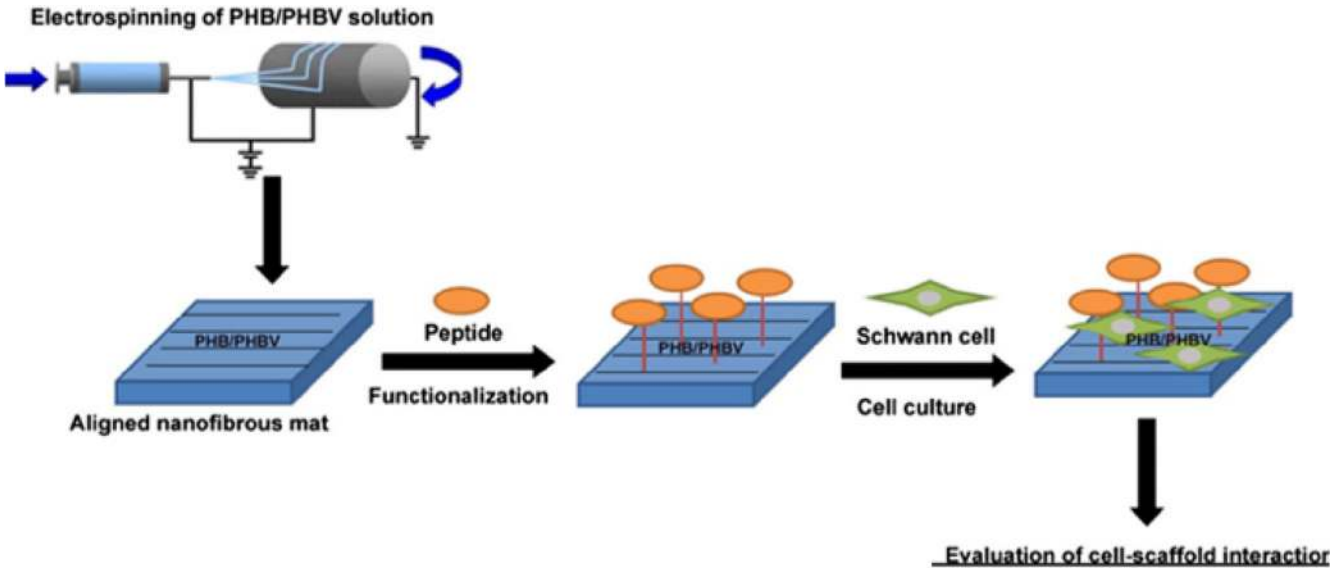


FIGURE 5 Electrospun composite scaffolds combining poly (3-hydroxybutyrate) (PHB) and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) were biofunctionalized with different biomolecules to mimic naturally occurring extracellular matrix motifs for nerve regeneration.
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A scaffold fabricated from synthetic polymers alone has poor cell functionality because of hydrophobic structure and lack of surface cell recognition sites.[150] Synthetic polymers with their hydrophobic properties were not employed alone in producing neural scaffold. So by incorporation of other natural products which could improve the biocompatibility and biodegradability of the EPS scaffolds, such as chitosan (CTS),[151–153] collagen,[154] laminin,[155] and oleic acid.[156]

Interestingly, magnesium, oil, and N-organic-L-semi-material processing (N-acetyl-L-cysteine [NAC]) combined with PHAs materials are used for neuron repair and can regulate the crystallinity of PHBV.[157] Many investigations indicate that magnesium has shown potential for improving functional recovery after peripheral nerve injury via its neuroprotective properties.[158] The inclusion of magnesium ions could further provide an electrical cue to assist nerve regeneration and muscle innervation.[159] Oleic (octadecanoic) acid forms a large percentage weight composition of sciatic nerve lipids (45% weight in the rat sciatic nerve) and myelin fatty acids.[160,161] Furthermore, it has shown neurotrophic-factor-like effects in the central nervous system.[162] Similarly, NAC has shown potential as a neuroprotective and growth-promoting agent in peripheral nerve injuries and as an adjunct therapy to pain management strategies in nerve injuries and neuropathies.[163,164] In 2019 study, Ramburrun et al.[156] synthesized triple-cue EPS aligned nanofibrous films (physical cue) of PHBV blended with magnesium-oleate (MgO) (chemical cue) and NAC (therapeutic cue) with potential incorporation into hollow nerve guidance conduits for an enhanced regenerative strategy. Their results showed that the synergistic activity of MgO and NAC increased PC12 proliferation by 32.6% compared to the control. MgO has dual effect as a non-toxic plasticizer and PC12 cell proliferation promoter via nucleation and neurotrophic-like effects, respectively. Controlled release of NAC imparted neuro-protectant effects on PC12 cells and promoted neurite extension, thus, making EPS PHBV-MgO nanofibrous films a versatile and promising approach for axonal guidance in peripheral nerve repair strategies.[156] This integration of physical, chemical, and therapeutic clues has the potential to further explore in vivo whole-body studies.

>In addition to adding natural polymers to polyester, in recent years, through a combination of BMs and stem cells, tissue engineering strategies for restoring and regenerating damaged peripheral nerves have recently been used to meet the challenges posed by nerve injury. Biazar et al.[165] designed PHBV nanofibrous conduits which were with GEL and then Schwann cells were injected into the conduits. These conduits were implanted into a 30 mm gap after resection of the sciatic nerve in a rat model, evaluated by macroscopic assessments and histology after 4 months of surgery. The results showed that the sciatic nerve truck had been reconstructed with the restoration of nerve continuity, formation of nerve nanofibers with myelination, and re-innervation of target skeletal muscle.

According to the contact guidance theory, the ability of the cell to migrate depends on the morphology,

chemical, and/or mechanical properties of the surface of the material contacted by the cell. Therefore, the suitable substrate for nutrition outgrowth is extremely important. A lot of researches showed that aligned PHAs nanofibers are more conducive to repair nerve than random nanofibers[150,151,154,155,166–168] (Figure 5).

4.4 | Bone tissue engineering

In bone tissue engineering, the ideal bone repair material must be biocompatible and bioactive, capable of initiating osteogenesis and have a similar composition as well as structural properties to bone. As a nanofibrous scaffold for bone tissue regeneration that mimics the fibrous structure of the bone matrix. Although the mechanical properties of all the PHAs based nanofibers have not been yet compared with those of human bone tissues, functionalized EPS scaffolds based on biocompatible and biodegradable PHAs, which will hold relevance as temporary supports for stem cell development and differentiation with a high therapeutic potential in tissue regeneration processes.[76,169,170]

We also found an interesting phenomenon that the arrangement of PHAs nanofibers has a relatively small effect on the induction of osteogenesis compared with nerve repair. Due to bone scaffolds must present excellent biomechanical properties, but bare polymers have poor performance. The development of new BMs with high osteogenic capacity is urgently pursued. A large number of studies have indicated that hydroxyapatite (HA),[90,171–174] GEL,[171] CTS,[175] fibrinogen (FG),[176] poly(ethylene glycol) (PEG),[93] nanotholits,[177] and other substances are added into PHAs nanofiber to enhance the proliferation, differentiation, and osteogenesis of stem cells and improve the mechanical properties of PHAs materials. However, some researchers indicate that the increase of mechanical properties (especially ductility or toughness) was not significant. To enhance the mechanical properties of polymer matrices, some studies have proposed to add different new materials to PHAs based on the latest research. As reported by Toloue et al., there exists few studies on the bioactivity properties of alumina nanostructures. Although alumina is known as an inert ceramic, and its nanostructured type is affected by osteoblast adhesion compared to conventional structures.[178] Their experimental results showed that when MG-63 cells were cultured on alumina-containing scaffolds, the tensile strength of PHAs increased by >10 times, and the viability of cells on the scaffold also increased significantly.[175] Zhou et al. investigated that the capability of in vivo bone repair of EPS P34HB/GO scaffold for the first time.[179] The results showed that GO reduced the nanofibers diameter and enhanced porosity, hydrophilicity, mechanical properties, cellular performance, and osteogenic differentiation of scaffolds.[179] Adenosine, found in humans, has been confirmed to promote osteogenic differentiation of mesenchymal stem cells and bone progenitor cells. PHBV doped with adenosine has been shown to have an excellent capacity for bone regeneration in 2019[180] (Figure 6).

4.5 | Cartilage tissue engineering

The cartilaginous plays a critical role in the load-bearing joints, particularly during dynamic loading. Current treatments for joint osteoarthritis attain low clinical

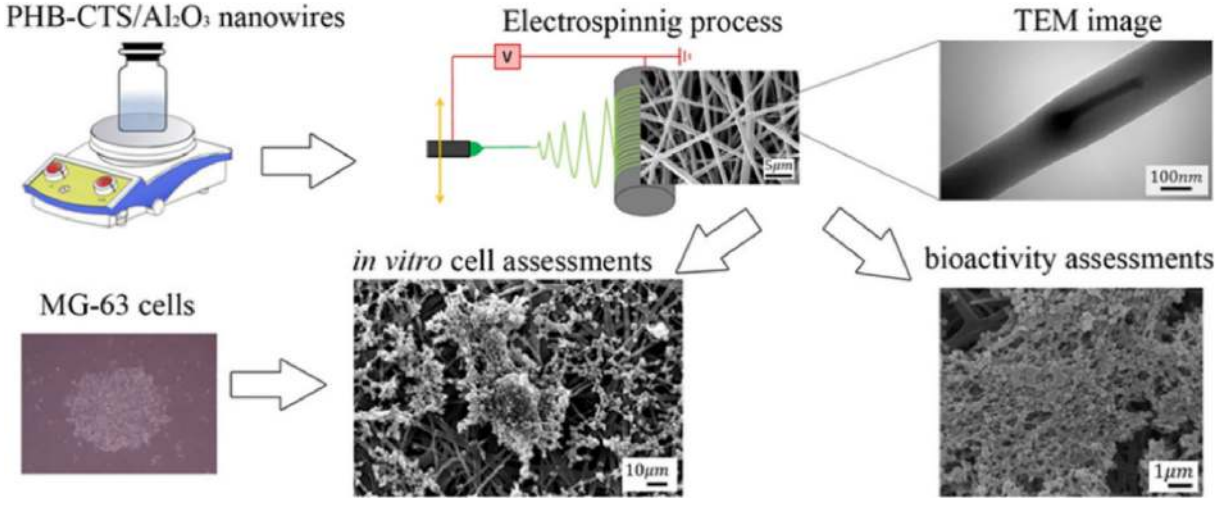

FIGURE 6 Alumina nanowires are added to polyhydroxybutyrate-chitosan (PHB-CTS) alloy solution, and the scaffolds are prepared by electrospinning method. And showed the proliferation and viability of MG-63 cells on scaffolds.
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results and fail to repair the cartilage. Biodegradable polymers nanofibers opened new therapeutic perspectives with their biocompatibility and ability to mimic ECM. PHAs are being applied as scaffolds for cartilage tissue engineering, and PHB has attracted attention due to having favorable properties such as good biocompatibility and relatively high mechanical properties; however, its hydrophobicity and brittleness are not suitable for cartilage tissue engineering scaffold fabrication. The addition of CTS can increase the hydrophilicity of the EPS PHB scaffolds while maintaining the mechanical properties in a suitable range.[181] Chondrocytes attached well to the surfaces of PHB/CTS scaffolds. Studies have demonstrated that the properties of PHB/CTS scaffolds are important for chondrocytes proliferation.[181] Hydrogels have attracted great attention as scaffolds for cartilage tissue engineering due to the similarity between their hydrated structures and the hydrophilic environment of cartilaginous ECM. The PHBV nanofibers as a reinforcement within the hydrogels significantly improve the mechanical properties of the structure due to stress transfer between the matrix and the reinforcement. Meanwhile, the PHBV/hydrogel composite scaffold supported the chondrogenic differentiation of bone marrow mesenchymal stem cells.[182] Therefore, composite scaffolds have become more important with desired biocompatibility, while maintaining high mechanical properties.

4.6 | Skin tissue engineering

Surgical dressings can remove metabolites, inhibit foreign bacterial invasion and improve appearance of human trauma. Standard wound dressing should have the following characteristics:(1) hemostatic action (2) antibacterial (3) absorption of exudates (wound fluid) (4) provide and maintain a humid environment (5) reduce patient pain and ease of removal (6) low prices, source rich. The ideal wound dressing is high porosity and protective film for good isolation.[183] To meet these requirements, it is necessary to select appropriate raw materials for wound dressing and design the support structures with high permeability and isolation effect.

Nanofibers wound dressing can meet the requirements of high permeability, prevention of wound infection and dehydration. Non-woven polymeric nanofibrous scaffolds mimic the morphological, fibrillar, and topographical aspects of the native ECM of the skin. Nanofibers scaffolds can prevent the entry of microbial pathogens because of their small pore size while restoring structural integrity and inhibiting wound contraction.[184]

The structural similarity of pure PHBV nanofibers and the ECM in the skin may performance well for fibroblast cell adhesion and proliferation.[185] Modified PHAs attached with a thioester group in the side chains and PHB co-EPS with antibiotics have exhibited excellent antibacterial properties against potential pathogen like

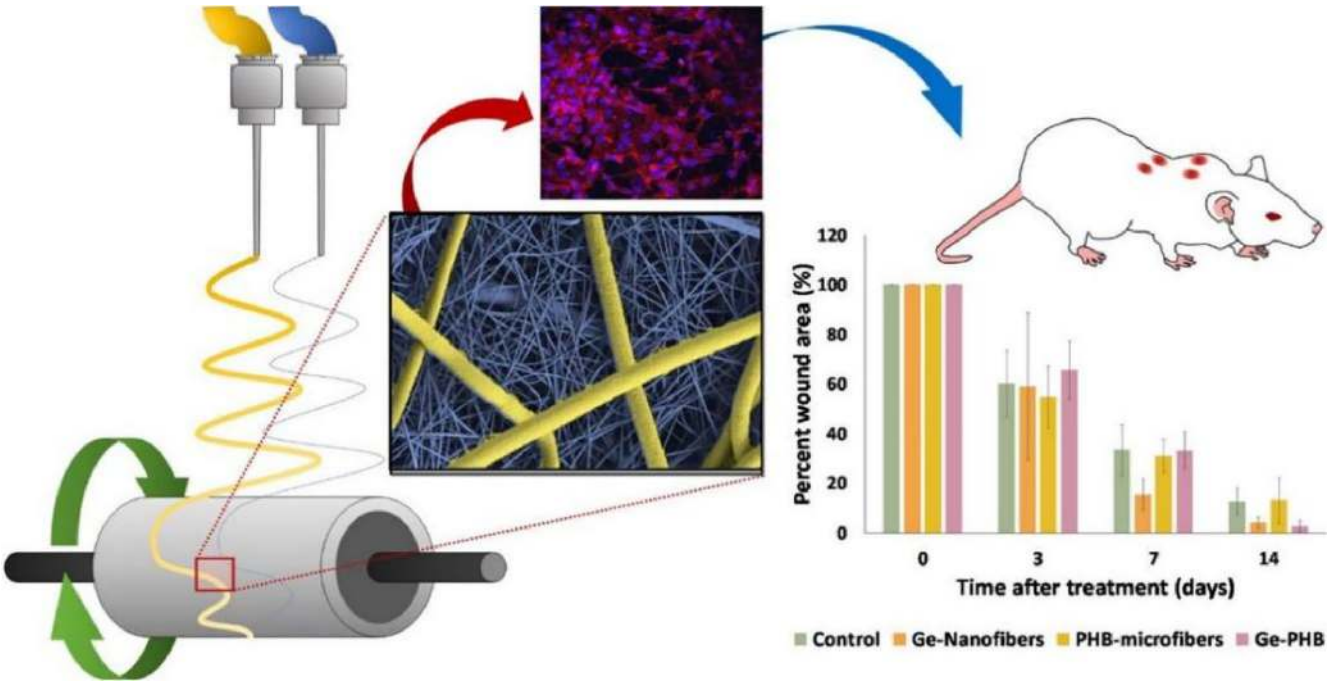

FIGURE 7 Poly-3-hydroxybutyrate (PHB) microfibers and gelatin (Ge) nanofibers of different polymers were simultaneously electrospinning to promoted skin regeneration.
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Staphylococcus aureus.[186,187] PHB scaffold blends of CTS, collagen, GEL, or PLA have been found to promote cell attachment and proliferation[123,188–193] However, the increase of the poly(vinyl alcohol) (PVA) fraction in the PVA/PHB blend had a negative impact on fibroblast adhesion and growth, whereas that of HaCaT cells were increased in PVA/PHB composite nanofibers.[194] Meanwhile, nanomaterials with stem cells have evolved as a promising therapeutic strategy to regenerate various tissues. Sundaramurthi et al. showed the efficacy of PHBV to aid BM-MSCs differentiation and the suitability of this novel scaffold construct for skin tissue engineering. This stem cell-nanomaterial construct can be used as an immediate coverage for third degree burns, traumatic ulcers and diabetic wounds.[110,195] PHB and its copolymers like PHBV and PHBHHx have been used for skin regeneration[171,196] (FIgure 7).

4.7 | Drug delivery from PHA nanofibers

Since the earliest synthetic polymer (polyethylene glycol ester) drug release system has been studied, the design and synthesis of new natural polyester materials have attracted a growing number of scientists, because natural bio-polyester materials need not be removed from the implant after drug release. And natural bio-polyester materials can make drugs achieve controllable release in time and space, improving the bioavailability of drugs and do not need frequent administration, and can maintain the effective concentration of drugs in vivo for a long time. Furthermore, the selection of EPS materials is very flexible, so many drugs (antisepsis and anti-inflammation,[118,120–126] chemotherapy drugs,[127] and others[129,130]) can be added to the appropriate solution for EPS (Table 5). Analysis of the literature on EPS of natural bio-polyester materials for drug release has been found in recent 10 years, and found that the research and development of drug release are particularly active in the last 5 years. These studies cover most areas of treatment, such as neural tissue, cardiovascular, skin, bone, as well as antisepsis and anti-inflammation, cancer treatment, and so forth.

Infections with bacteria have become a serious problem in tissue engineering. The antibiotics (gentamicin sulfate[120] and kanamycin sulphate[121]) loaded PHB nanofibers are synthesized, and research showed their antimicrobial property is proved by the good zone of inhibition tested against *S. aureus*. However, with the outbreaks of infectious diseases caused by pathogenic bacteria and the rise of antibiotic resistance of bacteria, much attention in pharmaceutical and medical fields has been focused on creating new antibacterial agents. Nanosilver has been proven is the highly effective antimicrobial agent. Xing et al.[122] investigated the antibacterial activity of PHBV nanofibrous scaffolds with different amounts of silver against, and results showed that the PHBV nanofiber scaffolds had silver nanoparticles, which completely inhibited the proliferation of *S. aureus* (gram-positive) and *Klebsiella pneumoniae* (gram-negative) bacteria. Furthermore, natural product extracts serve as precious medicinal sources for developing a new drug, among them, black soldier fly,[184] osthol,[124] and phenolic compounds[125] were a natural antimicrobial agents loaded with PHAs. According to the latest researches, the NO donor S-nitroso glutathione was blended with PHB and nanofiber-grade PLA for the fabrication of antimicrobial NO-releasing nanofibers tailored for blood-contacting applications, and showing that these nanofibers exhibit dual antimicrobial and antithrombotic activity.[126] In addition to achieving the slow release of drugs, on demand release of drugs is also important. Li et al.[85] developed a fabricate polymeric nanofibers with a core-shell structure. PHBV/PHBHHx/PES was chosen as the shell layer, while a broad-spectrum potent biocide (dodecyl trimethylammonium chloride) and a carrier polymer PVP were chosen as the core layer. An on-demand release of biocide was achieved from a PHAs-based core-shell nanofibers membrane. This nanofiber can effectively prevent the biocide from an undesirable payload release in physiological environments, and author hypothesized that in the presence of bacterial lipase, the PHAs/PES shell will be hydrolyzed by lipase, and the biocide will be released, subsequently imposing targeted antimicrobial effects on the bacteria. Additionally, PHAs nanofibers can be loaded with a cancer chemotherapy drug (paclitaxel[130]). Interestingly, PHAs nanofibers can also be loaded with graphene oxide (GO). PCL/PHBV core shell nanofibers were employed via the EPS process. GO and CP localized in core and shell parts of nanofibers, respectively.[129] And results confirmed that applying of GO and CP in the structure of PCL/PHBV leaded to the improvement of mechanical properties, wettability, surface free energy and cell activities. More importantly, study illuminated, the nanofibers of PHB have significant potential as retinal tissue engineering scaffold materials. Natural polysaccharide pectin has been grafted with PHB for the first time via ring-opening polymerization of β-butyrolactone,[131] this copolymer was blended with PHB in various proportions and EPS to produce nanofibers. Human retinal pigmented epithelium (ARPE-19) cells which were seeded onto pectin-PHB nanofibers as scaffold and showed good proliferation (Figure 8).

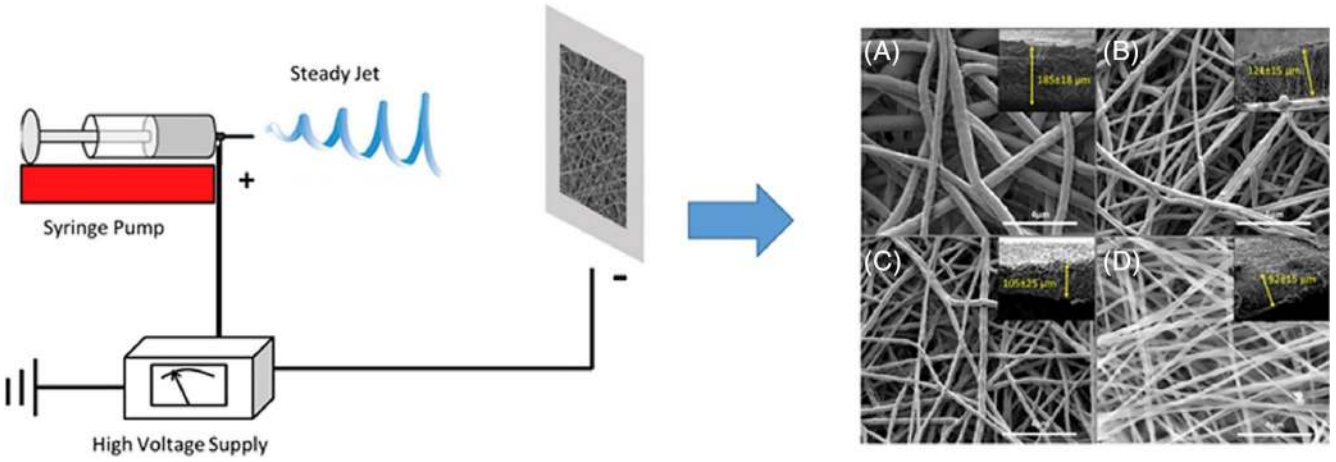

FIGURE 8 Schematic diagram showing curcumin-loaded PHBV nanofibers were successfully produced via electrospinning. Reproduced from Reference 129, with permission from 2017 Elsevier B.V

5 | CONCLUSIONS

Biomedical material is an important branch of materials science and engineering, and its characteristics are extensive interdisciplinary, great application potential. With the continuous emergence of new materials, technologies and applications, many scientists have been attracted into the research of this field, and it has become one of the hottest research fields of materials science. In China, although some remarkable achievements have been made in the research of biomedical materials, innovations are not enough and there still are many follow-up studies that need to be achieved. In terms of industrialization, China's biomedical materials and their products account for less than 2% of the world market share, mainly relying on imports, and the technical structure and level of products are basically in the primary stage. Facing the tide of the great development of biomedical materials research in the world, it is a challenge and an opportunity for China, to vigorously develop biomedical materials research. Medical grade PHAs have excellent biocompatibility, and their degradation products can promote the rapid growth of cells. Many studies at home and abroad have shown that it has a great potential in tissue repair and absorbable medical devices. The EPS technology improves the mechanical properties, biodegradation rate of PHAs and the interaction between PHAs and cells. In addition, it is imperative to study the degradation rates, crystallinity and tissue regeneration of new class of PHAs like PHBVHHx nanofibers. However, high cost is a major obstacle to the development of PHAs research. Therefore, research must be focused on reducing production costs and improving PHAs yield, so that large scale production of the polymer could be realized from cheap substrates. Compared with PLA and PLGA approved by FDA as implant materials, the acidity of PHAs is weaker than that of PLA and PLGA and can be easily excreted from the body within an hour. Moreover, Studies have shown that the cytotoxicity of PHAs is negligible.[197] However, there still exist several issues like in vivo biodegradation rate of PHAs, and is usually much slower than PLA and PLGA, Therefore, PHAs alone are not suitable for applications requiring rapid in vivo degradation. Besides, some of the mentioned medical implant applications including drug delivery, bone, vessels, cardiac, nerve have been obtained, we believe muscles and tendons, dental, medical consumables and cancer chemotherapeutic drugs[110] of PHAs nanofibers will be field that deserved to be paid close attention. To the best of our knowledge, only one papers discussed PHAs nanofibers loaded with cancer chemotherapeutic drugs. Almost all studies on PHAs BMs have shown positive effects on tissue engineering. However, there is currently no commercial medical-grade PHAs products supply on the market. This further illustrated that PHAs EPS has huge potential in the market, especially considering the exponential growth in the demand for plastic surgery. Expecting more PHAs-related medical products with application potential to be developed. Furthermore, PHAs biopolymer materials are expected to have more breakthroughs and applications in medicine by virtue of their own excellent properties combined with the characteristics of fibers. Moreover, its oligomers, as potential drugs for some diseases, are also expected to open new fields for the applications of PHAs.

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