Review Article

Polymers for Fabricating Nerve Conduits

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Peripheral nerve regeneration is a complicated and long-term medical challenge that requires suitable guides for bridging nerve injury gaps and restoring nerve functions. Many natural and synthetic polymers have been used to fabricate nerve conduits as well as luminal fillers for achieving desired nerve regenerative functions. It is important to understand the intrinsic properties of these polymers and techniques that have been used for fabricating nerve conduits. Previously extensive reviews have been focused on the biological functions and *in vivo* performance of polymeric nerve conduits. In this paper, we emphasize on the structures, thermal and mechanical properties of these naturally derived synthetic polymers, and their fabrication methods. These aspects are critical for the performance of fabricated nerve conduits. By learning from the existing candidates, we can advance the strategies for designing novel polymeric systems with better properties for nerve regeneration.

1. Introduction

Peripheral nerve injury is a serious health problem that affects 2.8% of trauma patients annually [1]. There are around 360,000 cases of upper extremity paralytic syndromes in the United States and more than 300,000 peripheral nerve injuries in Europe on an annual basis [2]. These cases can potentially lead to lifelong disabilities although peripheral nerves exhibit the capacity of self-regeneration for less severe injury. Researchers have developed various strategies for better recovery of nerve functions. End-to-end suturing is one effective method for short nerve gaps whereas tubular structures are necessary for bridging longer gaps [3]. Autologous nerve grafts are considered as “gold standard” for bridging long gaps, but they suffer from limited tissue availability, donor site morbidity, and potential mismatch of tissue structure and size [1–3].

Therefore, various bioengineered nerve grafts have been developed from polymeric materials that have well-tailored properties and dimensions to meet the requirements for peripheral nerve regeneration. These materials range from naturally derived polymers to conventional nondegradable and biodegradable synthetic polymers. Generally, an ideal nerve guide should be non-cytotoxic, highly permeable, and sufficiently flexible with suitable degradation rate and products to provide guidance for regenerative axons and to

minimize swelling and inflammatory responses [4]. Inner luminal fillers, offering larger surface area and platform for incorporating bioactive substances, are often used to improve the performance of nerve conduits. The required properties of both tubes and fillers are highly dependent on the intrinsic characteristics of these materials, such as the chemical structure and molecular weight, as well as the fabrication method for making them [5–7]. The polymers for fabricating tubes and their physical properties and manufacturing techniques are summarized in Table 1. Although these materials should have complete information about their molecular characteristics and properties, we only list the information found in the references.

Because of the importance of this topic, there exist a number of review articles on guided nerve regeneration using polymeric materials for constructing nerve conduits and luminal fillers [1–24]. Instead of elaborating on their biocompatibility and *in vivo* regenerative performance, this paper is to focus on the intrinsic properties of these polymeric materials and their specific fabrication techniques. We provide readers with the knowledge about these polymeric biomaterials and fabrication methods that have been investigated for peripheral nerve regeneration, as well as the material design strategies that can be used to control the physical properties and regenerative functions of synthetic nerve conduits.

TABLE 1: Summary of polymers used for fabricating nerve conduits.

Material	Chemical structure	T_g (°C)	T_m (°C)	Molecular weight (g/mol), intrinsic viscosity $[\eta]$, and composition [reference(s)]	Fabrication method [reference(s)]	Mechanical properties [reference(s)]
Alginate/Chitosan blend				Alginate: 57% mannuronic acid; Chitosan: 89%* and 91%*	Mandrel coating [31]	0.38 ± 0.16 N (pull-out force) [37] $\pm 1, 40 \pm 4$, and 61 ± 1 kPa (shear modulus) under normal forces of 3, 10, and 30 N
Chitosan		203		210 k, 93%* 22 k, 92.3%* 400 k, 89%* 85%* 1.8 M, 85.1%*	Dip-coating [25] Injection molding [26] Injection molding [29] Soft lithography and molding [27] Braiding and molding [28]	Unreinforced porous conduits: 0.41 ± 0.17 MPa; Fiber-reinforced conduits: 3.69 ± 0.64 MPa (tensile strength)
Chitosan/PLA blend				Chitosan: 22 k, 92.3%*; PLA: 460 k	Mandrel coating [30]	
Collagen					Dip-coating and crosslinking [32, 33] Injection molding and crosslinking [34–36] Fiber winding [37] Unidirectional freezing and freeze-drying [38–40] Film rolling and crosslinking [41, 42]	Crosslinked: 32.6 ± 0.6 or 22.5 ± 0.7 kPa; Uncrosslinked: 16.7 ± 0.7 kPa. (tensile modulus) [42]
Collagen/Chitosan blend				Chitosan: 150 k, 96.7%*, Collagen: Chitosan = 4 : 1 Collagen: Chitosan = 3:1 Collagen: Chitosan = 4:3	Unidirectional freezing and freeze-drying [43] Freeze-drying and steam-extrusion [44]	87 ± 7 kPa (tensile modulus) 326 ± 11 kPa (tensile modulus) 886 ± 3 kPa (tensile modulus)
Gelatin				bloom number: 300	Injection molding and crosslinking [45–47] Dipcoating and crosslinking [48–50]	Porous: 0.94 ± 0.22 MPa; Nonporous: 7.25 ± 4.1 MPa (tensile stress) [46]

TABLE 1: Continued.

Material	Chemical structure	T_g (°C)	T_m (°C)	Molecular weight (g/mol), intrinsic viscosity $[\eta]$, and composition [reference(s)]	Fabrication method [reference(s)]	Mechanical properties [reference(s)]
Cinnamoyl HA Hyaff					Injection molding and photo-crosslinking [52] Braiding [54]	Dry condition: 10.9 ± 0.3 MPa (maximum fracture strength), 27.7 ± 0.8 g (compressive strength); Wet condition: 5.5 ± 0.4 MPa (maximum fracture strength), 2.5 ± 0.5 g (compressive strength).
SF					Injection molding [55] Electrospinning and film rolling [56]	
PAN-PVC					Wet-phase inversion [57, 58]	
PDMS or silicone					Commercially available [59–63]	
PE					Commercially available [64, 65]	
PHEMA-MMA					Centrifuge casting and crosslinking [66–73]	177 ± 26 kPa, 311 ± 51 kPa (tensile modulus) [71] 263 ± 13 kPa (tensile modulus) [73]
PPy					Electro-plating and molding [74]	
PCD				$[\eta] = 2.09$ dL/g, PCL:PDO = 95 : 5	Injection molding [75]	
PCL		~ -60	~ 60	65 k [76] 80 k	Dip coating [76, 77] Braiding [78] Melt extrusion [79] Wire mesh and mandrel coating [80]	206–345 MPa (tensile modulus) 20–34 MPa (tensile strength)
PCL/CultiSpher					Wire mesh and mandrel coating [80]	0.13 ± 0.1 MPa (tensile modulus) 0.51 ± 0.3 MPa (tensile strength)

TABLE 1: Continued.

Material	Chemical structure	T_g (°C)	T_m (°C)	Molecular weight (g/mol), intrinsic viscosity $[\eta]$, and composition [reference(s)]	Fabrication method [reference(s)]	Mechanical properties [reference(s)]
PCL/gelatin and PCL/PLL grafted gelatin				PCL: 80k; gelatin: bloom number 300; FITC-labeled PLL: 30–70 k; PLL bromide: 150–300 k	Melt extrusion and inner surface treatment [79]	
PCLA		~ -60	39	3.5 k	Injection molding and photo-crosslinking [81]	70.0 ± 31.1 MPa (tensile modulus at 37° C)
PCLF		~ -59	42	9 k	Injection molding and photo-crosslinking [82–84]	138 ± 17 MPa (tensile modulus) 0.42 ± 0.03 N (pull-out force) 73.4 ± 12.7 MPa (flexural modulus)
PDLLA				46.7 k [85]	Dip coating [65, 85, 86]	
PDLCL				LA:CL = 50 : 50; L:D in LA = 85 : 15 LA:CL = 80 : 20	Dip coating [87] Ink-jet microdispensing [88]	
PDO		-16	110	$[\eta] = 1.89$ dL/g	Injection molding [75]	
PGA		45–50 [89]	225–235 [89]	150 k	Braiding and dip-coating with collagen [90–94]	
PGC				$[\eta] = 1.63$ dL/g, GA:CL = 65 : 35	Injection molding [75]	
PGS			5.23, 37.62 [95]		Injection molding and crosslinking [95, 96] Film rolling [97, 98] Commercially available [99]	0.28 MPa (tensile modulus) > 0.5 MPa (tensile strength)
PHB
PHBHHx					Dip coating and leaching [100]	Conduits with non-uniform wall porosity: 2.29 ± 0.37 MPa, with uniform wall porosity: 0.94 ± 0.19 MPa (wet state tensile stress)

TABLE 1: Continued.

Material	Chemical structure	T_g (°C)	T_m (°C)	Molecular weight (g/mol), intrinsic viscosity $[\eta]$, and composition [reference(s)]	Fabrication method [reference(s)]	Mechanical properties [reference(s)]
PHBV/P(L-D,L)LA/PLGA blend				PHBV: 95% PHB;	Solvent casting from micropatterned silicon templates and then film rolling on electrospun mat [101]	Solid film: 1.05 ± 0.23 MPa, Porous film: 0.08 ± 0.02 MPa (tensile modulus)
	P(L-D,L)LA: PLLA-P(D,L)LA = 70:30, $[\eta] = 5.5\text{--}6.5$ g/dL;
	PLGA: 50:50 ⁺ , $[\eta] = 0.32\text{--}0.44$ g/dL		
PLC		60	134	$[\eta] = 1.58$ dL/g, LA:CL = 60:40	Injection molding [75]	
PLGA				113 k, 75:25 ⁺ , 52 k, 50:50 ⁺ , Pluronic F127 (EG ₉₉ PG ₆₅ EG ₉₉ , 12.5 k) added.	Immersion precipitation [102, 103]	7-channel, porosity of 78.6%: 0.8 ± 0.2 kPa; 7-channel, porosity of 78.6%: 510 ± 130 kPa (compression modulus) [108] Porous multiple lumen conduits using 80–120 K (porogen; polymer = 12:1): 134 kPa (compression modulus) [111] Porous conduits: ~8 MPa (tensile modulus)
				$[\eta] = 0.5\text{--}0.79$ dL/g, 50:50 ⁺ ; $[\eta] = 1.2\text{--}1.59$ dL/g, 90:10 ⁺ [104] 51.9 k, $[\eta] = 0.9\text{--}1.2$ dL/g, 85:15 ⁺ [105] $[\eta] = 0.2$ dL/g, 50:50 ⁺	Dipcoating and immersion precipitation [104, 105] Wet phase inversion [106]	
				94 k, 85:15 ⁺ [107] 122 k, 75:25 ⁺ [108] 58.8 k, 50:50 ⁺ ; 92 k, 75:25 ⁺ ; 120 k, 85:15 ⁺ [109] 75 k, 85:15 ⁺ [110] 80–120 k, 11–24 k, 75:25 ⁺ [111] 136 k, 85:15 ⁺ [112, 113]	Injection molding [107–113]	
				37.4 k, 75:25 ⁺ 100 k, 10:90 ⁺ 10:90 ⁺ 64.7 k, 85:15 ⁺	Extrusion [114] Electrospinning [115] Microbraiding [116] Dip coating [117]	

TABLE 1: Continued.

Material	Chemical structure	T_g (°C)	T_m (°C)	Molecular weight (g/mol), intrinsic viscosity $[\eta]$, and composition [reference(s)]	Fabrication method [reference(s)]	Mechanical properties [reference(s)]
PLGA/gelatin blend					Molding [118]	Composition dependent: ~0.25–~3.75 MPa (tensile strength)
PLGC				300 k, LA:GA:CL = 75:8:1	Film rolling [119]	
PLLA		55–60	170–175	46.5 k	Extrusion [114] Braiding [120] Solvent casting, extrusion, and particulate leaching [121, 122] Fused deposition [89] Dip coating [117, 123] Braiding and dip coating with collagen [94]	Porous conduits: ~80 MPa (tensile modulus) 81.7 ± 35.1 MPa (tensile strength), 1.0 ± 0.4 MPa (tensile modulus) [121]
PLLA and PGA				100 k [117] 130 k [94]		
PLLA-PEG-MA				LLA:PEG = 2:1 and 4:1	Centrifuge casting and crosslinking [124]	
PPE, or P(BHET-EOP/TC)				14.9 k and 18.9 k, EOP/TC = 80:20, x:y = 4:1	Dip coating [125–127]	2.68 ± 0.05 MPa (tensile modulus); single-channel conduits: 52.0 ± 1.2 MPa (flexural modulus); seven-channel conduits: 66.0 ± 3.7 MPa (flexural modulus); 0.11 N (pull-out force)
PPF-PCL		–57	17.1	29k, PPF:PCL = 10:90	Injection molding and photo-crosslinking [128]	
PSU		185			Commercially available [129–131]	
PTMC-CL		47		TMC:CL = 30:70, $[\eta]$ = 1.31 dL/g	Dip coating [132, 133]	
PU based on PEG and PCL diol		44		TMC:CL = 15:85, $[\eta]$ = 1.27 dL/g 110 k	Dip coating [134] Rapid prototyping [135]	~8–~15 MPa (tensile strength)
PU based on PHBV-diols and PGC-diols		–35 –35 –30	120 122 123	178 k 105 k 160 k	Extrusion [136]	1.9 MPa (tensile modulus) 8.4 MPa (tensile modulus) 46 MPa (tensile modulus)

* Deacetylation degree; † Lactide:Glycolide (LA:GA) ratio.

2. Tube Materials

2.1. Natural Polymers for Fabricating Nerve Conduits. Natural polymers utilized for fabricating nerve conduits include chitosan [25–31], collagen [32–44], gelatin [45–50], hyaluronic acid (HA) [51–54], and silk fibroin (SF) [55, 56]. These natural polymers offer excellent biocompatibility, support cell attachment and functions, avoid serious immune response, provide appropriate signaling to cells without the need of growth factors and can degrade by naturally occurring enzymes [5–7, 22]. However, natural polymers generally suffer from batch-to-batch variance and need extensive purification and characterization [5–7]. Further, most of them lack adequate mechanical strength and degrade relatively fast *in vivo* [5–7]. Oftentimes natural polymers need to be chemically modified and crosslinked or blended with other structural components such as synthetic polymers to meet the mechanical requirements. Due to their low denaturing temperature and thermal stability, natural polymers are usually fabricated via injection molding, dip-coating, and electrospinning from their solutions at ambient or lower temperatures [5–7]. Although these fabrication methods are mentioned in this section, the detailed descriptions will be elaborated in Section 4.

Chitosan, a copolymer of D-glucosamine and N-acetyl-D-glucosamine, is a well-known biodegradable polysaccharide obtained from N-deacetylation of chitin, which can be extracted from the shells of crabs and shrimps [5, 6, 22]. Chitosan has been used to fabricate nerve tubes and scaffolds because of its excellent biocompatibility and antibacterial activity [5, 6, 22]. Due to its high glass transition temperature (T_g) of $\sim 203^\circ\text{C}$ and relatively low thermal stability, pure chitosan cannot be melted and is usually processed in solutions. In one study, chitosan was dissolved in trifluoroacetic acid (TFA) first and added with methylene chloride (MC) to prepare a solution [25]. This chitosan/TFA/MC solution was electrospun onto a rotating Steel use Stainless (SUS) bar to form macro/nanofibrous scaffolds as the inner layer while chitosan-acetic acid solution is dip-coated on the SUS bar to form an outer layer [25]. Immobilization of laminin peptides to these bilayered chitosan tubes was also achieved [25]. Multichanneled chitosan nerve conduits with more complex patterned designs and precise dimensions have been achieved by molding chitosan/acetic acid solution in polydimethylsiloxane (PDMS) molds prepared through soft lithography [27]. Chitosan is relatively brittle and can degrade rapidly in solutions at high temperatures; therefore, many studies have been conducted to improve the mechanical properties of chitosan scaffolds via crosslinking or blending with reinforcing fibers or other polymers [26, 28–31]. Chitosan dissolved in acetic acid was injected in a tubular stainless-steel mold and crosslinked with formaldehyde into a porous viscous gel [26]. Nerve conduits were formed by subsequent freeze-drying or lyophilization and inserted with longitudinally aligned poly (glycolic acid) (PGA) fibers as luminal fillers [26]. Chitosan tubes prepared using mold casting were strengthened by over 9 times with braided chitosan yarns [28]. In another study, reinforcing poly (L-lactide-co-glycolide) (PLGA) coils were mounted into a mold

before chitosan solution was injected and dried [29]. Poly (lactic acid) (PLA) was also incorporated with chitosan in preparing nerve tubes using the dip-coating method to improve the resistance to tension and compression [30]. Physically crosslinked hydrogel nerve tubes can be formed by adding alginate aqueous solution into chitosan/acetic acid solution because these two polysaccharides are oppositely charged [31].

Collagen is comprised of a group of 28 proteins with a same triple helical structure as an extended rod stabilized by hydrogen bonding [5, 6, 23, 24]. Collagen (types I and III) can be derived from animal tissues such as porcine skin [32] and bovine deep flexor (Achilles) tendon [33–35, 42, 44]. As one major form of extracellular matrix (ECM) protein, collagen provides excellent biocompatibility and weak antigenic activity [5, 6]. Collagen has been extensively employed to form both outer tubular structures and central lumen for nerve regeneration. By crosslinking collagen between amine groups, the relatively low mechanical properties of collagen can be circumvented and the structural stability of fabricated nerve conduits can be achieved. The crosslinking reagents for collagen include formaldehyde, glutaraldehyde, and 1-ethyl-3-(3-dimethylaminopropyl)-1-carbodiimide (EDC)/N-hydroxysuccinimide (NHS) pair for a zero-length crosslinking method. Among several commercially available nerve guides [5, 32, 36], there exists an FDA-approved nerve conduit made from crosslinked bovine collagen (type I). This collagen nerve conduit is known as NeuraGen (Integra) tube [5, 32, 36]. Besides conventional injection molding and dip-coating methods for preparing nerve conduits [32–36], collagen can be extruded in its water solution and coagulated into filaments [37]. These collagen filaments can be wound up around a mandrel to form a tubular structure and also used as longitudinally aligned luminal fillers [37]. Collagen sponge tubes with parallel oriented interconnected pores have been achieved through unidirectional freezing followed by lyophilization [38–40]. Microwave irradiation was also used to crosslink collagen and this method is advantageous because potentially toxic crosslinking agents such as glutaraldehyde can be avoided [41, 42]. The average tensile modulus of microwave-crosslinked collagen tubes was enhanced from 16.7 ± 0.7 kPa for uncrosslinked tubes to 32.6 ± 0.6 kPa [42]. Collagen was blended with chitosan homogeneously in acidic solutions to fabricate nerve conduits [43, 44], which exhibited much higher tensile modulus of 886 ± 3 kPa when the collagen:chitosan ratio was 4 : 3 after crosslinking and freeze-drying [44].

Gelatin is a biodegradable polymer derived from collagen by thermal denaturation of chemical and physical degradation. Gelatin has excellent biocompatibility, plasticity, and adhesiveness. The water solubility of gelatin renders convenient processing in aqueous solutions but the resulting products suffer from poor mechanical properties and handling characteristics [5, 6]. Thus, subsequent crosslinking using proper crosslinking agents is crucial to improve the chemical and physical characteristics of gelatin for preventing toxicity and fabricating suitable tubular structures for nerve regeneration [5, 6]. Gelatin tubes are usually

prepared by injection molding or dip-coating followed by immersing the mold or mandrel into crosslinking agent solutions [45–50]. Styrenated gelatin was synthesized and photopolymerized into nerve conduits and fibers under visible light irradiation in the presence of camphorquinone [45]. Other than chemical modification of gelatin, three commonly used agents, genipin, proanthocyanidin, and EDC/NHS, can be used to crosslink gelatin via primary amino groups along the chain backbone [46–50]. The residue free amino groups are a useful indicator for estimating the crosslinking density [47, 48]. Crosslinking degree has been revealed to be crucial in tuning the degradation rate so as to influence nerve regenerative responses because a too low crosslinking density results in more degradation products to evoke more severe foreign body reaction while a too high crosslinking density impedes the degradation and causes nerve compression with thickened perineurium and epineurium [48].

Hyaluronan (HA or hyaluronate) is a high molecular weight glycosaminoglycan (GAG) that can be found in ECM of humans [22]. HA demonstrates a unique combination of advantages including nonimmunogenic, nonadhesive, bioactive GAG that has been associated with several cellular processes and axonal ingrowth [22, 51–54]. HA has to be modified to be crosslinkable for forming three-dimensional (3D) structures with mechanical strength. HA, conjugated by cinnamic acid to the carboxyl group using aminopropanol as a spacer, can be injected into a silicone mold and cured under ultraviolet (UV) light [51, 52]. Crosslinked HA is so weak for handling that augmentation of an outer layer made from another biodegradable material is required for the operation procedure and during the nerve regeneration period because the nerve conduits should keep their structure with sufficient elasticity and flexibility for the fixation to the nerve stumps [52]. Another crosslinkable HA is glycidyl methacrylate HA or GMHA [53]. Nerve conduits based on an esterified hyaluronan derivative (Hyaff) have been prepared from individually knitted strands and strengthened by coating a thin layer of the same polymer [54]. Although Hyaff nerve tubes demonstrated excellent biocompatibility, a quick degradation, massive ingrowth of cells, and fibrous tissue formation can possibly hamper the ultimate goal of the tubes in peripheral nerve repair [54].

SF, a core structure protein derived from natural silk, can be used as a textile material. SF is also a candidate biomaterial for nerve regeneration applications [55, 56]. Similar to other naturally derived polymers, SF is also water soluble with excellent biocompatibility, but it has a high resilience and a relatively slower degradation rate [55]. Fabrication method is crucial for achieving desired properties from SF. Normal injection molding techniques followed by demolding via lyophilization result in fragile sheets with weak compressive and tensile properties under wet conditions [55]. Tubes woven from electro-spun SF fibers are easily crushed and the degradation is slow *in vivo* although they have an improved tensile strength [55]. Tubes with a unique eggshell-like microstructure have been developed by combining a molded tubular structure with inner oriented SF filaments [55]. Tubes with this eggshell-like

microstructure have a good compressive strength of 10.9 ± 0.3 MPa at the dry state and a lower value of 5.5 ± 0.4 MPa at the wet state [55]. Using electro-spinning, SF nanofibers have been fabricated after blended with poly(ethylene oxide) (PEO), which helps achieve stable and continuous processing [56]. SF membranes decorated with SF nanofibers were hydrated and rolled around a mandrel and glued using cyanoacrylate glue to form a tube, which was further coated with PLGA [56].

2.2. Synthetic Polymeric Tubular Materials. Compared with their naturally derived counterparts, synthetic polymers have advantages such as unlimited supply and tailorable properties via varying their chemical structures [12–22]. The ease of copolymerization facilitates the development of regulating and optimizing material characteristics such as degradation behavior, mechanical performance, thermal properties, and wettability [12–22]. These polymers (Table 1) are generally classified into two categories based on degradability. Non-biodegradable polymers used in fabricating nerve conduits include silicone rubber or PDMS [59–63], polyethylene (PE) [64, 65], polysulfone (PSU) [129–131], poly(acrylonitrile-*co*-vinyl chloride) (PAN-PVC) [57, 58], poly(2-hydroxyethyl methacrylate-*co*-methyl methacrylate) (PHEMA-MMA) [66–73], and polypyrrole (PPy) [74]. Biodegradable polymers used in fabricating nerve conduits include poly(ϵ -caprolactone) (PCL) [76–80], PCL acrylate (PCLA) [81], PCL fumarate (PCLF) [82–84], polypropylene fumarate-*co*-PCL (PPF-PCL) [128], polydioxanone (PDO) [75], PCL-*co*-PDO (PCD) [75], PGA [90–94], poly(glycerol sebacate) (PGS) [95, 96], PLGA [102–118], poly(L-lactic acid) (PLLA) [89, 114, 117, 120–123], poly(D,L-lactic acid) (PDLLA) [65, 85, 86], poly(D,L-lactide-*co*-caprolactone) (PDLLC) [87, 88], poly(L-lactide-*co*-caprolactone) (PLC) [75], poly(glycolide-*co*-caprolactone) (PGC) [75], poly(lactide-*co*-glycolide-*co*-caprolactone) (PLGC) [119], poly(L-lactide-*co*-ethylene glycol) methacrylate (PLLA-PEG-MA) [124], poly(3-hydroxybutyrate) (PHB) [97–99], poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) (PHBHHx) [100], poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)/poly(L-lactide-*co*-D,L-lactide)/PLGA [PHBV/P(L-D,L)LA/PLGA] blend [101], polyphosphoester (PPE) [125–127], poly(trimethylene carbonate- ϵ -caprolactone) (PTMC-CL) [132, 133], and polyurethane (PU) [134–136]. Among these polymers, one of the authors and his colleagues recently developed injectable and photocrosslinkable PCLA [81], PCLF [82–84] and PPF-PCL [128], which have well controlled material properties, slow degradation rates, and nonswelling characteristics in water. Figure 1 demonstrates nerve conduits made from crosslinked PCLF before and after implantation in the rat sciatic nerve for 17 weeks [83].

Nerve guides made from non-biodegradable materials can lead to chronic nerve compression and may damage the regenerating nerves [5–7, 15]. Therefore, a secondary surgery is needed to remove these nondegradable conduits after nerve regeneration is fulfilled. Silicone rubber tubes are the earliest and widely used synthetic nerve tubes because

FIGURE 1: Polymer nerve conduits made from crosslinked poly(ϵ -caprolactone) fumarate (PCLF) before (a) and after (b) implantation in the rat sciatic nerve. (Source: [83], copyright with permission from Elsevier Science).

of their inertness, availability, and flexibility [15, 59–63]. It can be processed directly without the need of a solvent, which may cause problems such as evaporation and toxicity. Because silicone nerve conduits are not biodegradable or permeable for large molecules, they only supply an isolated environment for nerve regeneration [59–63]. Other commercially available PE or PSU tubes were also used to evaluate the role of luminal fillers such as gel rod and aligned filaments or electro-spun fibers in guiding neurite extension and promoting axon growth in long-gap nerve injuries [64, 65, 129–131]. Although PHB conduits are normally prepared using the film rolling method [97, 98], they are also commercially available [99].

PAN-PVC copolymer was used to fabricate nerve guides via a wet-phase inversion technique [57, 58]. Semipermeable membranes can be formed from the polymer solution using an annular spinneret with deionized water as a liquid precipitant [57, 58]. Using different starting polymer solutions, various hollow fiber membranes were fabricated with different wall thicknesses and hydraulic permeabilities [58]. The wall architectures of these membranes were anisotropic and consisted of a fingerlike macrovoid structure [58].

Poly(2-hydroxyethyl methacrylate) (PHEMA) is an elastic and inert polymer. Hydrogel-based tubular structures made from PHEMA are too soft to be handled in implantation [66]. A hydrophobic monomer methyl methacrylate (MMA) was copolymerized with HEMA in the presence of crosslinking agent ethylene dimethacrylate to obtain PHEMA-MMA hydrogel with a higher mechanical strength [66–73]. A biphasic wall structure can be created with an inner porous sponge-like layer and an outer gel-like layer because of phase separation during the polymerization with centrifugal forces [68–73]. Because PHEMA-MMA nerve conduits are still weak, PCL coils have been used to further enhance their mechanical strength and prevent tubes from partial collapse during implantation [72]. Mechanical stability can be also improved by wrapping small PHEMA-MMA tubes in an expanded polytetrafluoroethylene (e-PTEF) membrane [73].

As electrical stimulation has been demonstrated to have a beneficial effect on axonal regeneration, electrically conductive nerve conduits are promising for enhancing restoration

of lost nerve function [74]. Nerve conduits made from PPy could optimally utilize the polymer properties, such as controllable charge density, erodability, and wettability [74]. To fabricate 3D PPy structures, PPy monomer has been oxidized to form a tubular structure on an electrode while subsequent reduction allowed mechanical dissociation from the cylindrical electrode mold to separate PPy from its conductive template [74]. PPy can be also incorporated with PCL network in preparing nerve conduits [84], which will be discussed later.

Biodegradable nerve conduits are generally more promising in bridging nerve gaps as they can degrade away after accomplishing their task. Further, biodegradable nerve conduits offer possibilities of incorporating bioactive chemicals such as nerve growth factor (NGF), laminin, and fibronectin inside the wall and then releasing them in a controlled manner during polymer degradation [5–7, 12–22]. In order to achieve this goal, polymer degradation rate should match the rate for axon growth along the gap. The thermal and mechanical properties of biodegradable polymers can be readily controlled at the molecular level using advanced synthetic routes. These properties are crucial for handling and implantation of conduits and axonal ingrowth. Many biodegradable polymers are semi-crystalline and their thermal properties such as melting temperature (T_m), crystallinity, crystallization rate, and morphology of crystalline domains are important for determining their bulk and surface physicochemical properties. The existence of crystalline regions can enhance mechanical strength and structural stability while it reduces the degradation rate and permeability of the nerve tubes made from these semi-crystalline polymers, consequently affecting cellular and regenerative functions [5–7].

Polyesters such as PGA, PLA, PCL, PDO, and their copolymers are most commonly used biodegradable polymers in constructing tubular structures for peripheral nerve regeneration. These polyesters are usually synthesized via ring-opening polymerization and can degrade via the hydrolysis of ester bonds along the polymer backbone [5–7]. As shown in Table 1, there are many methods to fabricate polyesters into nerve conduits, such as dip-coating, immersion precipitation, injection molding, extrusion, braiding,

and electro-spinning. These polyesters dissolved in solutions can also be electro-spun to fibers or fibrous mats, which can be subsequently braided or rolled into flexible, porous, and highly permeable tubes. There are also commercially available fibers of these polyesters for braiding. Fabrication of nerve conduits using fibers is an advantageous way to overcome the inherent rigidity of polylactides such as PGA, PLA, and their copolymer PLGA with T_g higher than the body temperature [90–94, 115, 116, 120]. In order to improve their processability and the flexibility of the produced conduits, polylactides can be plasticized adding 2% triethyl citrate, a plasticizer [65].

Material properties can be readily tailored by varying the composition and block length in the copolymers such as PCD [75], PLC [75], PGC [75], PDLLC [87, 88], and PLGC [119]. Besides copolymers, PLGA was also blended with gelatin in a co-solvent MC to obtain composition dependent mechanical properties with tensile strength varied from ~0.25 to ~3.75 MPa [118]. Besides making single-component nerve conduits [76–80], PCL was also blended with gelatin, poly(L-lysine) (PLL)-grafted gelatin [79], or porous collagen-based beads (CultiSpheres) [80] for preparing nerve conduits, which have the combination of good processability of PCL and the optimal biocompatibility of natural polymers. Crosslinkable PLLA-PEG-MA was synthesized by the ring-opening polymerization of LLA in the presence of PEG with two hydroxyl end groups as the initiator and then end-coupling PLLA-PEG with methacrylate groups [124]. Porous PLLA-PEG-MA nerve conduits were fabricated using the same centrifugal casting method for preparing PHEMA-MMA nerve conduits [124].

PGS synthesized via polycondensation between glycerol and sebacic acid is a viscous prepolymer that can be further crosslinked in a mold into an elastomeric device with a desired shape and excellent mechanical properties [95, 96]. PGS films with a tensile modulus of 0.28 MPa were fabricated to mimic the mechanical properties of ECM and the biocompatibility evaluation suggested PGS an excellent candidate material for neural reconstruction applications [96].

PCL-derived crosslinkable copolymers such as PCLF, PCLA, and PPF-PCL have been synthesized and nerve conduits have been fabricated via a technique that combines injection molding and photo-crosslinking [81–84, 128]. The synthesis routes of PCLF and PCLA were simplified by reacting the hydroxyl groups in PCL diols or triols that have different molecular weights with acryloyl chloride or fumaryl chloride in the presence of potassium carbonate [81–83, 137] as the proton scavenger other than triethylamine (TEA) [138]. The use of this new proton scavenger can avoid colorization and contamination from the reaction between TEA and unsaturated acyl chloride/anhydride and greatly simplify the purification steps [139]. Using PCL diol or triol precursors with different molecular weights, controllable thermal properties such as T_g , T_m , and crystallinity for both uncrosslinked and crosslinked PCLF or PCLA were obtained and used to further modulate the mechanical and rheological properties of PCL networks [81–83]. When the

molecular weight of PCL diol or triol precursor was low, the resulted PCL network was amorphous at room temperature with low-tensile modulus because the crosslinks completely suppressed the crystalline domains [81–83]. In contrast, a higher molecular weight (>2000 g/mol) PCL diol can result in a semi-crystalline network with significantly higher tensile modulus and strength, and resistance to tear in suturing [81–83]. PCLAs generally exhibited better crosslinking efficiency than PCLFs because of more reactive acrylate segments during the reaction and higher crosslinking densities [81–83].

Well-tuned architecture, crystallinity, mechanical and surface characteristic of crosslinked PCLAs and PCLFs have been shown to support and correlate with nerve cell attachment, proliferation, differentiation, and axon myelination [81–84]. Mechanical properties enhanced by PCL crystalline structures were found to play an important role in controlling Schwann cell precursor line (SpL201) cell behavior [81, 83]. *In vivo* studies of crosslinked PCLF nerve conduits (Figure 1) showed no inflammatory reaction or existence of macrophages [83]. Nerve cable with myelinated axons has been found after 6 or 17 weeks of implantation [83]. Taking advantages of the roughness and flexibility of crosslinked PCLF [82, 83], a conductive PCLF-PPy composite nerve conduit has been prepared recently in the Yaszemski group by polymerizing pyrrole with benzoyl peroxide and naphthalene-2-sulfonic acid sodium salt in a swollen PCLF nerve conduit in MC [84].

In order to achieve a wider range of mechanical properties, PCLF or PCLDA can be blended and crosslinked with PPF [140, 141]. Meanwhile, a series of multiblock PPF-PCL copolymers have been synthesized via a three-step polycondensation between PPF and PCL diol [142]. Through controlling the block size and composition in PPF-PCL copolymers, both uncrosslinked and crosslinked PPF-PCL have a broad range of thermal and mechanical properties that can be used to satisfy the requirements in hard and soft tissue replacements such as bone and nerve repair [128, 142]. Similar to crosslinked PCLF nerve conduits [83], single-lumen and multi-channel PPF-PCL nerve conduits have been fabricated using the molding and photo-crosslinking technique and implanted in the rat sciatic nerve transection model for 4 and 16 weeks to demonstrate biocompatibility and guided axonal growth [128].

PHB is a granular constituent of bacterial cytoplasm, having the advantage of ease of synthesis via microorganisms and its adjustable mechanical properties, biocompatibility and biodegradability. PHB conduits have been fabricated by rolling PHB sheets around a mandrel followed by thermal sealing [97, 98]. PHBHHx was developed with a better flexibility than PHB [100]. Conduits with uniform wall porosity and those with nonuniform wall porosity were fabricated using dip-coating and particulate leaching with NaCl-sized particles as porogen [100]. PHBV containing 95% PHB was blended with P(L-D,L)LA and PLGA to form a porous micropatterned film by solution casting from a silicon template and then the film can be rolled together with a electro-spun PHBV/PLGA aligned fibrous mat inside to prepare nerve conduits [101].

PPE is biocompatible with a controllable rate of degradation via hydrolysis due to their relatively low molecular weight. Porous tubular structure can be easily achieved via dip-coating followed by immersion precipitation [125–127]. The drawbacks of PPE are fast degradation and swelling in water that will reduce its mechanical properties in the duration for axon growth and then may cause tube distortion or even failure [125].

PU has elastic and flexible properties that are favorable for nerve guidance tubes [134–136]. A biodegradable polyurethane has been developed from PCL and PEG with 1,6-hexamethyl diisocyanate as the chain extender and dip-coated into tubes for repairing peripheral nerve injuries [134]. The hydrophilic PEG segment can accelerate the degradation rate of hydrophobic PCL, making the degradation kinetics more compatible with the nerve regeneration rate [134]. Porous nerve conduits can also be processed via rapid prototyping using a double nozzle, low temperature, deposition manufacturing system that combines phase separation and chemical crosslinking simultaneously [134]. PUs made from crystalline PHB segments and amorphous segments of glycolide and ϵ -caprolactone have shown controllable physical properties with varied crystallinity and Young's modulus from 1.9 to 46 MPa when the composition is varied [136].

3. Luminal Fillers

To modify hollow nerve tubes to achieve enhanced performance, luminal fillers have been employed as a structural component [23, 24]. The internal filler substances can provide more surface area and have potentials to incorporate cells and growth factors [17, 23, 24]. Various factors such as composition, mechanical properties, and the permeability of nerve conduits may influence the organization of the inside filler. Fillers may also affect the physical properties of the whole tube and reduce the cross-sectional area for growth of regenerative nerves [17, 23, 24]. Therefore sophisticated design of the filler form should be performed by taking consideration of these factors to achieve optimal enhancement based on the hollow tubes. Widely used structural luminal fillers are summarized in Table 2 and seven major filler forms are demonstrated in Figure 2. Two comprehensive reviews on the roles of luminal fillers in nerve regeneration have been published earlier [23, 24], which also include support cells and neurotrophins. In this section, we focus on the polymeric fillers inside nerve conduits in the forms of gel rod and sponge, gel inner layer, and aligned fibers.

Natural polymers, such as agarose, collagen, laminin, and fibrin, are often used as luminal fillers in the form of solutions, hydrogels, filaments, and porous sponges as platforms for incorporating cells, growth factors, and drugs [17, 23, 24]. Their soft characteristics and biocompatibility can help regenerative guidance for the reconstruction of nerve gaps [17, 23, 24]. Agarose can form hydrogels containing gradients of laminin-1 and NGF molecules in PSU conduits as anisotropic scaffolds [129]. Distributed micro- or nanosized fibers or films in 3D gels are growth permissive

FIGURE 2: Forms of luminal fillers in polymer nerve conduits.

as the gels can serve to distribute the fibers in 3D space, and the fibers would provide a 2D surface for regenerating axons [3]. Collagen has been formed into filaments [37, 63, 90], sponges [90–93], and gel inner layers [135] in PGA, PU, silicone conduits. Collagen sponges were prepared by pouring homogenized collagen aqueous solution into PGA tubes and freezing the solution at -20°C followed by freeze-drying for 3 h [90–93]. The tubes were then subjected to dehydrothermal treatment at 140°C for 24 h to induce crosslinking among the collagen molecules [90–93].

Laminins as major proteins found in basal lamina are important molecules widely investigated for regeneration of nerve tissues [5–7]. Laminins contain various cell binding sites including the Ile-Lys-Val-Ala-Val (IKVAV) sequence, a bioactive peptide that can promote neurite outgrowth [5]. One commercially available laminin-containing gel, Matrigel, and the above-mentioned agarose hydrogels containing laminin have been used as filler materials in nerve conduits [65, 129, 132]. Fibrin, a fibrous protein made from fibrinogen, can be formed into a matrix as structural support for neural tissues [5–7]. In one case, the liquid-state mixture of collagen, laminin, and fibronectin can be injected through a precooled micropipette into the lumens inside silicone rubber chambers prior to crosslinking of collagen *in vivo* [60]. These gel-like luminal fillers can also be used as injectable materials with the capability of carrying support cells, NGF, and drugs for central nerve repair and other degenerative diseases [22].

Synthetic filler polymers are usually inserted into nerve conduits as aligned fibers or filaments. For this purpose, these polymers have been fabricated into fibers using traditional fiber spinning techniques or electro-spinning:

TABLE 2: Summary of structural luminal fillers in polymer nerve conduits.

Filler material	Structure	Filler form	Tube material(s) [reference(s)]
Agarose coupled with laminin		Gel rod	PSU [129]
Alginate with or without fibronectin		Gel rod	PHB [99]
Chitosan immobilized with peptides		Electrospun fiber mesh inner layer	Chitosan [25]
Collagen		Aligned fibrils	Collagen [37], Silicone [63]
		Fiber	PGA coated with collagen [90]
		Sponge	PGA coated with collagen [90–93]
		Gel layer	PU [135]
Collagen-GAG		Gel rod	Collagen and silicone [34]
Fibrin		Gel rod	Silicone [60], PLGC [119], PHB [97]
HA		Gel rod	PE [64]
Gelatin		Fiber or gel rod	Gelatin [45]
Matrigel		Gel rod	PTMC-CL [132], PDLA and PE [65]
SF		Longitudinal aligned fiber	SF [55]
Polyamide		Filament	Silicone [62]
PAN-MA		Electrospun fiber	PSU [130]
PGA		Longitudinal aligned fiber	Chitosan [26]
		Filament	PTMC-CL [133]
PHBV/PLGA blends		Electro-spun mat	PHBV/P(L-D,L)LA/PLGA blends [101]
PLLA		Filament	Silicone and P(L-D,L)LA (75 : 25) [61]
PLGA		Electro-spun fiber mat roll (LA:GA = 85 : 15)	PSU [131]
		PHEMA inner layer embedded with PLGA microspheres (LA:GA = 85 : 15)	PHEMA-MMA [68]
		PCL inner layer embedded with PLGA microspheres (LA:GA = 50 : 50)	PCL [76]
PP		Filament	PAN-PVC [57]

polyamide [62], polyacrylonitrile-*co*-methylacrylate (PAN-MA) [130], PGA [26, 133], PLLA [61], and PLGA [131]. For example, eight polyamide filaments (250 μm , diameter) were placed inside silicone tubes to increase the overall cross-sectional area that can support myelinated axon [62]. Longitudinal PGA filaments (14 μm , diameter) have been inserted into a chitosan conduit to serve as a directional guide for axons [26]. Electro-spun fibers of PLGA with diameters from 100 nm to 3 μm , which can be controlled by the polymer concentration, were aligned on a rotating mandrel and later this electro-spun fiber mat was rolled into a nanofilament “cigar” and inserted into a PSU tube to guide neurite extension; however, the degradation of PLGA fibers was so fast that distortion of fibers reduced the alignment [131]. To overcome this problem, non-degradable PAN-MA electro-spun fibers (~ 400 –600 nm, diameter) were applied in the same group and successfully promoted regeneration of axons over a 17 mm nerve gap [130].

Other than gel rod/sponge and aligned fibers/filaments, an inner layer can be prepared inside nerve conduits. As shown in Table 2, electro-spun fiber mesh [25], collagen gel [135], and an inner PCL layer embedding PLGA double-walled microspheres [76] have been incorporated with a stronger outer tube made from chitosan, PU, and PCL, respectively. These inner layers supply helpful environment and bioactive substances for axon growth while the outer tube is strong enough to endure the implantation period.

4. Fabrication Methods

As mentioned in Section 2, a variety of techniques have been utilized to fabricate different natural and synthetic polymers into 3D tubular nerve guide, depending on their material characteristics. In this section, we supply detailed descriptions about these techniques using schemes demonstrated in Figure 3. There are seven widely-used techniques such as injection molding, mandrel coating or dip coating, centrifuge casting, film rolling and sealing, extrusion, electrospinning, and microbraiding of filaments. Although not included in Figure 3, polymer nerve conduits can also be fabricated using wet phase inversion [57, 58, 106], immersion precipitation [102–105], and advanced computer-aided microfabrication techniques such as fused deposition and soft lithography [27, 88, 89, 135].

Injection molding (Figure 3(a)) is the most commonly used technique for fabricating nerve conduits because it can be applied to most polymers except for very brittle materials such as PHB. Polymers with relatively a high thermal stability and a relatively low T_m , such as PCL ($T_m = \sim 60^\circ\text{C}$), can be melt extruded while alternatively they can be dissolved in an evaporative solvent, referred to as solvent casting. Polymer melts or solutions with appropriate viscosities can be injected into one specific tubular mold to form a desired shape after solidification at $T < T_m$ or T_g or solvent removal. Due to finite length effect, polymer physical properties such as thermal and mechanical properties normally demonstrate sharp molecular weight dependence when the molecular weight is smaller than a critical value. A molecular weight higher than

FIGURE 3: Widely used methods for fabricating polymer nerve conduits.

the entanglement molecular weight (M_e) of a polymer is generally required for injection molding because otherwise the polymer may lack adequate mechanical strength for structural applications. For low molecular weight oligomers or natural polymers, crosslinking or curing is needed. Chemical crosslinking for collagen or gelatin can occur in a mold by adding crosslinking agent prior to injection. Photo-crosslinkable polymers such as PCLFs and PCLAs can be cured in a transparent glass mold by UV light exposure [81–84]. Permeable conduits can be also easily

prepared using particulate leaching, gas foaming, and phase-separation methods [5–7]. Freeze drying or lyophilization is commonly used for natural polymers to dehydrate and demold. Unidirectional freezing followed by freeze-drying has recently been developed to obtain oriented porous structure in the collagen tubes [38–40, 43].

Mandrel coating or dip coating (Figure 3(b)) is another facile technique to fabricate nerve conduits with better controlled thickness and homogeneity. This technique involves a rotating metal or Teflon or water-soluble poly(vinyl alcohol) (PVA) mandrel [80] that can be coated with or dipped into polymer solutions to form a thin polymer layer after drying. The wall thickness depends on the solution concentration and coating cycles. Dip coating is usually followed by solvent evaporation or immersion precipitation in a nonsolvent, allowing quick formation of a polymer membrane that can have a porous structure on the rotating mandrel. Moreover, the potential of this technique exists to incorporate a myriad of features for each individual layer, such as one layer that can be more permeable and porous than the other [125–127]. Preparing conductive PPy nerve conduits also needs an electrode mold although the synthesis of PPy occurs directly onto the electrode via electroplating [74].

Liquid-liquid centrifuge casting method (Figure 3(c)) developed in the Shoichet group has been used for acrylate-based hydrogels such as PHEMA-MMA [66–73]. The centrifugal casting process is based on phase separation of the polymer phase from the monomer phase during polymerization in a centrifuging mold. The polymer phase with higher viscosity and density can be pushed to the outer edges by centrifugal forces to forming a stable tube. PHEMA-MMA conduits prepared using this method are semipermeable, soft and flexible, and with mechanical properties similar to those of nerve tissue [66–73].

Film rolling (Figure 3(d)) around a mandrel is a very simple method to achieve tubular structure using a polymer sheet or an electro-spun mat. It is particularly convenient for a two-dimensional (2D) substrate with surface patterns that can be only fabricated on a surface to be rolled into a 3D nerve conduit [101]. The sealing step is critical in this method and it can be achieved by heating [97, 98], fusing or gluing the overlapping ends with organic chemicals [56, 119], or dipping the roll in a solution containing crosslinking agents [41, 42].

Melt extrusion (Figure 3(e)) is a conventional method for processing thermoplastic polymers with suitable flow temperatures, melt viscosities, and thermal stabilities. A single-screw extruder can be used to fabricate nerve conduits through melt extrusion [79, 114]. The nozzle or die in this extruder and the rod moving together with the piston determine the outer and inner diameters of the nerve conduit [114]. Melt extrusion is often combined with particulate leaching to prepare porous biodegradable conduits [114, 121, 122].

Electro-spinning (Figure 3(f)) has been extensively used to fabricate fibers with submicron size. These fibers can serve as fillers directly or be microbraided into highly permeable and flexible tubes, especially for PGA, PLLA, and PLGA fibers [90–94, 116, 120]. The microbraiding machine (Figure 3(g))

involves a Teflon mandrel with a controlled diameter that allows fiber to be pulled upward from bottom through a convergence point and forming point [116]. The porosity of the tubular structure can be modulated by the braiding angle, number of fibers in a bundle, and the number of fiber bundles [116]. As discussed in Section 3, electro-spun luminal filler fibers and nerve conduits have porous structures, which are advantages for neurite extension and axon growth along the fiber direction [131].

Because of limitations of precise manufacturing processes, techniques aforementioned cannot reproduce tubes with uniform channel diameter and designed patterns at microscale. Soft lithography has been newly developed to manufacture silicon-based structures and replicate them with PDMS for producing chitosan nerve conduit subunits which can be stacked coaxially [27]. Because of its precise capability, soft lithography is well suited for fabricating nerve conduits with complex structures for controlling regenerative pathways and degradation rate [27]. Soft lithography can be potentially applied to manufacture injectable and photo-crosslinkable polymers to achieve precisely controlled networks. Novel microfabrication system also involves rapid prototyping, which is the general term for a manufacturing process used to produce complicated 3D structures automatically based on computer-aided designs (CADs). Several rapid prototyping processes such as fused deposition modeling [89] and ink-jet microdispensing [88] have been utilized for biodegradable polymers to form nerve conduits with precise dimensions and complex internal structures. In one study, polylactides including PLA, PGA, and PLGA were heated up at 200°C and extruded through a fine nozzle as the nozzle traces an XY surface [89]. The process was repeated layer by layer until the microstructure was completed [89]. A double nozzle, low temperature, deposition manufacturing system has been developed to process PU and collagen simultaneously, combining both phase separation and chemical crosslinking to form a double layered tubular structure [135].

5. Conclusions and Perspectives

This paper summarizes natural and synthetic polymeric materials and fabrication methods to produce tubular structures and luminal fillers for guided nerve regeneration and repair. The importance of material properties such as chemical structure, thermal, and mechanical properties have been discussed to correlate with their performance. Understanding the design strategies for developing novel tubular materials and luminal fillers is crucial to further improve the biological performance and regenerative functions of nerve guidance conduits. Nerve cell-material interactions are also important in examining the suitability of a polymer candidate for nerve repair and regeneration [143–147]. Numerous studies have been performed on the differentiation of pheochromocytoma (PC12) cells, dorsal root ganglia, and neuronal stem/progenitor cells on the polymer substrates with controllable mechanical properties [146–151]. It should be noted that surface stiffness plays different roles in regulating neuronal cells and glial cells:

soft substrates can stimulate neurite extension and branching while inhibit glial cell spreading and proliferation [147–151]. In order to meet the requirements in optimizing regenerative conditions *in vivo*, the physical properties, especially thermal and mechanical properties of the material should be characterized extensively prior to fabrication of nerve conduits and animal implantation. Injectable and photo-crosslinkable materials with sufficient mechanical properties and lower degradation rates have demonstrated great promise for feasible and effective treatment to bridge nerve gaps. Novel *in-situ* crosslinkable polymers and their manufacturing methods, particularly microfabrication methods, need to be developed for fabricating nerve conduits with more complicated structures and advanced functions. In particular, heterogeneous conduits that can precisely combine different materials, varied geometric architecture, and bioactive substances will be promising for nerve regeneration and repair.

Abbreviations

2D:	Two-dimensional
3D:	Three-dimensional
CAD:	Computer-aided design
CultiSpher:	Porous collagen-based bead
ECM:	Extracellular matrix
EDC:	1-ethyl-3-(3-dimethylaminopropyl)-1-carbodiimide
e-PTFE:	Expanded polytetrafluoroethylene
FDA:	Food and Drug Administration
GAG:	Glycosaminoglycan
GMHA:	Glycidyl methacrylated HA
HA:	Hyaluronic acid
Hyaff:	Esterified hyaluronan derivative
MC:	Methylene chloride
M _e :	Entanglement molecular weight
MMA:	methyl methacrylate
NGF:	Nerve growth factor
NHS:	N-hydroxysuccinimide
PAN-MA:	Poly(acrylonitrile- <i>co</i> -methylacrylate)
PAN-PVC:	poly(acrylonitrile- <i>co</i> -vinyl chloride)
P(BHET-EOP/TC):	Poly(bishydroxyethyl terephthalate-ethylorthophosphorylate/terephthaloyl chloride)
PC12:	Pheochromocytoma
PCD:	Poly(ϵ -caprolactone)- <i>co</i> -polydioxanone
PCL:	Poly(ϵ -caprolactone)
PCLA:	Poly(ϵ -caprolactone) acrylate
PCLF:	Poly(ϵ -caprolactone) fumarate
PDLLA:	Poly(D,L-lactic acid) or poly(D,L-lactate)
PDLLC:	poly(D,L-lactide- <i>co</i> -caprolactone)
PDMS:	Polydimethylsiloxane
PDO:	Polydioxanone or poly(<i>p</i> -dioxanone)
PE:	Polyethylene
PEO:	Poly(ethylene oxide)
PEG:	Poly(ethylene glycol)
PGA:	Poly(glycolic acid)
PGC:	Poly(glycolide- <i>co</i> -caprolactone)

PGS:	Poly(glycerol sebacate)
PHB:	Poly(3-hydroxybutyrate)
PHBHHx:	Poly(3-hydroxybutyrate- <i>co</i> -3-hydroxyhexanoate)
PHBV:	Poly(3-hydroxybutyrate- <i>co</i> -3-hydroxyvalerate) or poly[(<i>R</i>)-3-hydroxybutyric acid- <i>co</i> -(<i>R</i>)-3-hydroxyvaleric acid]
PHEMA:	Poly(2-hydroxyethyl methacrylate)
PHEMA-MMA:	Poly(2-hydroxyethyl methacrylate- <i>co</i> -methyl methacrylate)
PLA:	Poly(lactic acid) or polylactide
PLC:	Poly(L-lactide- <i>co</i> -caprolactone)
P(L-D,L)LA:	Poly(L-lactide- <i>co</i> -D,L-lactide)
PLGA:	Poly(L-lactide- <i>co</i> -glycolide)
PLGC:	Poly(lactide- <i>co</i> -glycolide- <i>co</i> -caprolactone)
PLL:	Poly(L-lysine)
PLLA:	Poly(L-lactic acid) or poly(L-lactide)
PLLA-PEG-MA:	Poly(L-lactide- <i>co</i> -ethylene glycol) methacrylate
PP:	Polypropylene
PPE:	Polyphosphoester
PPF- <i>co</i> -PCL:	Polypropylene fumarate- <i>co</i> -poly(ϵ -caprolactone)
PPy:	Polypyrrole
PSU:	Polysulfone
PTMC-CL:	Polytrimethylene carbonate- ϵ -caprolactone
PU:	Polyurethane
PVA:	Poly(vinyl alcohol)
SF:	Silk fibroin
SpL201:	Schwann cell precursor line
SUS:	Steel use Stainless
TEA:	Triethylamine
TFA:	Trifluoroacetic acid
T _g :	Glass transition temperature
T _m :	Melting temperature
UV:	Ultraviolet.

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