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Review

Synthetic-based blended electrospun scaffolds in tissue engineering applications

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ABSTRACT

Electrospinning, as one of the most common methodologies in nanofibers production, involves applying high voltages to a polymeric solution that is entrapped in a syringe to obtain biomimetic nanofibrous constructs. These microstructures may render resemblance to the extracellular matrix (ECM) and be used as a tissue engineering scaffold. The electrospun scaffolds can provide properties commensurate with the intended tissue, to be employed as a potential substitute for cell stroma and/or drug delivery applications. It seems that polymeric nanofibrous electrospun scaffolds are to meet indispensable requirements to support cells to grow, proliferate and differentiate; it is mostly because of interconnected porous architecture and tunable mechanical backup. Despite their wide diversity, synthetic polymers individually do not provide enough amenities for tissue regeneration and thus need to be blended with other biological macromolecules and polymeric biomaterials. This review will discuss recent decades' pieces of literature on blend biopolymeric nanofibrous electrospun scaffolds in tissue repair and regeneration.

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Abbreviations

ADSCs	Adipose derived stem cells
ALG-S	Alginate sulfate
ALP	Alkaline phosphatase
AP–g–GA	Aniline pentamer–graft–gelatin
BSA	Bovine serum albumin
ARPE-19	Human retinal pigmented epithelium
BMSCs	(Human) bone-marrow-derived mesenchymal stem cells
B. subtilis	*Bacillus subtilis*
CAB	Cellulose acetate butyrate
CS	Chondroitin sulfate
CHM	Ciprofloxacin hydrochloride monohydrate
Cs-g-PCL	Chitosan-graft-PCL
CSNe	Chitosan nanoemulsion
CS-HOBt	Chitosan-hydroxybenzotriazole
CA	Cellulose acetate
CNC	Cellulose nanocrystals
CNF	Cellulose nanofibers
CMC	Carboxymethyl chitosan
CECS	Carboxyethyl chitosan
CUR	Curcumin
CHX	Chlorhexidine
CIP	Ciprofloxacin
CPs	Conductive polymers
DMECM	Decellularized meniscus extracellular matrix
DP	Date palm
DMF	Dimethylformamide
DPD	Dipyridamole
E. coli	*Escherichia coli*
EGF	Epidermal growth factor
ECM	Extracellular matrix
EC	Endothelial cells
FEK4	Human skin primary fibroblast cell line
GDNF	Glial cell line-derived neurotrophic factor
gMSCs	Gingival mesenchymal stem cells
hMSCs	Human mesenchymal stem cells
HFIP	1,1,1,3,3,3 Hexafluroisopropanol
HFFF-2	Human fetal foreskin fibroblast cell line
HA	Hyaluronic acid/hyaluronan
HAM	Human amniotic membrane
HaCaT	Human epidermal immortalized keratinocyte cell line
HUVEC	Human umbilical vein endothelial cell
HDF	Human dermal fibroblast
HASMCs	Human aorta smooth muscle cells
HCF	Human cardiac fibroblast
HEK293	Human embryonic kidney cells
HEEpiC	Human esophageal epithelial cells
HPG	Hyperbranched polyglycerol
HEC	Hydroxyethyl cellulose
iPSCs	Induced pluripotent stem cells
K. pneumonia	*Klebsiella pneumonia*
K-CG	K-Carrageenan
Lcl-PHA	Long-chain length PHA
LSCs	Limbal stem cells
MRSA	Methicillin-resistant *Staphylococcus aureus*
mcl-PHA	Medium-chain length PHA
NFZ	Nitrofurazone
NGF	Nerve growth factor
O-Chitosan	Organic soluble chitosan
OECs	Olfactory ensheathing cells
PCL	Poly(ε-caprolactone)
PLGA	Poly(lactic-co-glycolic)acid
PEOT–PBT	Poly(ethylene oxide terephthalate)–poly(butylene terephthalate)
PEGMA	Poly(ethylene glycol methacrylate)
PEGDMA	Poly(ethylene glycol dimethacrylate)
PHA	Polyhydroxyalkanoates
P3ANA	Poly(anthranilic acid)
PMMA	Poly(methyl methacrylate)
PDS	Polydioxanone
PTMC	Poly(trimethylene carbonate)
PGS	Poly(glycerol sebacate)
PA-6,6	Polyamide-6,6
PAAc	Poly(acrylic acid)
PLA	Poly(lactic acid)
PEO	Poly(ethylene oxide)
PHMB	Poly(hexamethylene biguanide)
3ABAPANI	Poly(aniline-*co*-3-aminobenzoic acid)
PRP	Platelet-rich plasma
pHMGCL	Poly(hydroxymethylglycolide-*co*-ε-caprolactone)
PPy	Polypyrrole
PBAPCL	Poly[(1,4-butylene adipate)-*co*-(polycaprolactam)]
PEG-b-$(PPy)_4$	Poly(ethylene glycol)-modified polypyrrole

PVCz	Poly(*N*-vinyl carbazole)
PS	Polystyrene
P(3HB-co-4HB)	Poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate)
PLDLLA	Poly[(L-lactide)-*co*-(D, L-lactide)]
PLCG	Poly [(L-lactide)-*co*-(ε-caprolactone)-*co*-(glycolide)]
PES	Polyethersulfone
PAN	Polyacrylonitrile
PVDF	Polyvinylidene fluoride
PBS-DLS	Poly(butylene succinate-*co*-dilinoleic succinate)
PHBHHx	Poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate)
PLCL	Poly[(L-lactide)-co-(ε-caprolactone)]
PC	Phosphatidylcholine
P. aeruginosa	*Pseudomonas aeruginosa*
PEG	Poly(ethylene glycol)
PEDOT/PSS	Poly(3,4-ethylenedioxythiophene)/poly(styrene sulfonate)
PEI	Polyethylenimine
PEII	Polyetherimide
PVP	Poly(*N*-vinyl-2-pyrrolidone)
(T)PU	(Thermoplastic) polyurethane
PLLA	Poly(L-lactic acid)
PDLA	Poly(D-lactic acid)
PDLLA	Poly(D, L-lactic acid)
PF-108	Pluronic-F 108
PHB	Poly(3-hydroxybutyrate)
PHBV	Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)
PPDL	Poly(L-lactic acid)-*co*-poly(pentadecalactone)
PANIS	Polyanisidine
PAni	Polyaniline
PBS	Phosphate buffered-saline
PVA	Poly(vinyl alcohol)
RGD	Arginine–glycine–aspartic acid
Rap	Rapamycin
rhBMP-2	Recombinant human bone morphogenic protein-2
RBCs	Red blood cells
Scl-PHA	Short-chain length PHA
SMPU	Shape memory polyurethane
SPEU	Segmented polyurethane
SF	Silk fibroin
SBF	Simulated body fluid
SS	Silk sericin
SA	Sodium alginate
SPI	Soy protein
TSF	Tussah silk fibroin
TN	Tannin
TCH	Tetracycline hydrochloride
TC	Tigecycline
TGF-b1	Transforming growth factor-beta 1
VICs	Valvular interstitial cells
WBPU	Waterborne polyurethane
WBCs	White blood cells

Introduction

Tissue engineering is likely to be considered as a multidisciplinary approach, which aims to restore, regenerate and/or repair tissues or a part of tissue using a combination of cells, scaffolds and bioenvironmental factors. Indeed, it employs the basic chemistry to manipulate cellular fate in a protective matrix called a scaffold, bringing up mechanical and biological effects on cell migration, attachment, adhesion and proliferation [1]. To put it differently, this bioengineering discipline is associated with biocompatible and biodegradable scaffolds that provide microenvironments for cells to encourage them to proliferate and make a part of tissue viability [2]. An ideal tissue engineering scaffold would not only resemble extracellular matrix (ECM) but may also imitate a range of ECM functions [3]. Over many years, biodegradable polymeric scaffolds have been used to regenerate or substitute for both soft and hard tissues. In other words, their applications in regenerative medicine and tissue engineering have shown a significant influence on tissue repair in many structural tissues such as bone, cartilage, tendon, ligament and muscle. Moreover, polymeric scaffolds with fibrous structures have been employed widely in nervous and cardiovascular systems, both singular and in blend or in combination with other biopolymers [4].

Biopolymers and their applications in tissue engineering have been largely studied over two recent decades. Biopolymers consist of monomeric units binding together to form macromolecules. Fundamentally, there are two categories for biopolymers: natural biopolymers that are obtained from living organisms and natural resources, and synthetic biopolymers that are synthesized using biomolecules

[5]. In 2015, a research was carried out to investigate which biopolymers are mostly used in tissue engineering scaffolds. It illustrated that the most natural biopolymer-based scaffolds are chosen from chitosan, collagen, elastin, alginate (ALG) and silk fibroin (SF) or silk sericin (SS), while the most frequent employed synthetic biopolymers were poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA) and poly(ε-caprolactone) (PCL) [6]. Synthetic biopolymer-based scaffolds are likely to have the capability to be modified or functionalized to represent larger tenability, more pragmatic and also quite more specific. By applying synthetic biopolymer-based scaffolds, it would be possible to control the procedure before and after fabrication. This will help to accomplish the desirable characteristics including fiber diameter, porosity and pore size [7]. Overcoming the confinement in controlling different features in polymeric scaffolds, researchers could fabricate fibrous scaffolds via the electrospinning method, with unique and adjustable properties. These scaffolds also can be used in diverse applications ranging from tissue engineering to encapsulation of drugs and biomolecules. Indeed, electrospinning may be introduced as one of the most tunable and widely used strategies, capable of controlling morphology, porosity and fiber diameter [4].

Generally speaking, a conventional electrospinning system includes a needle, an electrical field generation source, a collector and a pump. The electrospinning process is fundamentally carried out based upon electrostatic forces; electrostatic repulsion forces are employed in a strong electrical field to fabricate nanofibers [8, 9]. Briefly, the subjected solution to electrospinning is applied to a syringe with a needle, and then, an electrical field is created between the needle tip and the collector. As the solution is ejected, its droplets form a cone-shaped area on the needle tip, due to the potential differences between the needle tip and the collector. Dominating the surface tension, droplets, forming a jet, accelerate to a weaker electric field (collector), followed by simultaneously solvent evaporation and nanofibers formation on the screen [8, 10]. Physical characteristics of electrospun nanofibers largely depend on different parameters including solution properties (electroconductivity, viscoelasticity and surface tension), environmental factors (temperature and humidity) and technical variables (the distance between needle tip and collector, applied electrical potential and feed rate) [8].

Employing electrospinning, researchers have used an array of polymers (synthetic, natural and their blends) as tissue engineering scaffolds with nanofibrous structures [11–14]. Electrospun scaffolds represent many advantages for tissue engineering applications including high surface area, high-porosity constructs that highly resemble the ECM as well as better biocompatibility [10]. Fibrous polymeric blend scaffolds illustrate a combination of favorable biological properties of natural polymers along with excellent mechanical and physical features of synthetic ones. In the upcoming review, we broach the recently studied synthetic polymer-based electrospun scaffolds, e.g., PCL, PLA, PU, etc., blended with either synthetic or natural polymers or both, for tissue engineering intentions.

Application of synthetic-based polymeric electrospun scaffolds in tissue engineering

PCL-based electrospun scaffolds

Among synthetic polymers, PCL has been extensively employed as a biocompatible polymer with reasonable price and high mechanical properties for electrospun fibrous scaffolds [15]. Although its hydrophobicity and low water absorption would be associated with some limitations in biomedical applications, incorporation of other polymers such as natural or synthetic, proteins and polysaccharides may offer a way to tackle these limitations [16]. Herein, we present several recent decades' studies concerning the combination of PCL with natural and/or synthetic polymers.

Blend of PCL with natural polymers

To address the shortage in biological properties of PCL, blending with natural polymers would likely have an extreme impact on serving biocompatibility, representing a more hydrophilic surface for cells. Natural polymers including gelatin, collagen, etc., have been widely employed in many electrospinning-based studies in blends with PCL to extend the use of PCL-based scaffolds for tissue engineering intentions. Gelatin, as a collagen-derived polymer, has been largely used for tissue engineering purposes due to its availability, biodegradability and cost-effectiveness [17]. In a research by Semitela et al. [18],

PCL–gelatin electrospun scaffold was assessed for cartilage tissue engineering, using a 50:50 volume ratio of polymers dissolved in acetic acid (0.2% v/v). The electrospinning parameters including flow rate, voltage and working distance were set up on 1.5 mL h^{-1}, 27 kV and 9 cm, respectively. They also incorporated a sacrificial material, a material to enhance the porosity, creating pores after being eliminated from the structure. This in turn leads to quite more cell infiltration as well as cell proliferation and migration within the fabricated matrix. To this end, poly(ethylene glycol) (PEG) particles were electro-sprayed during the electrospinning of the PCL–gelatin blend and made the porogenic scaffolds. According to the results, the mechanical properties of nanofibrous scaffolds showed as high young's modulus value for PCL–gelatin as 26.79 ± 6.60 MPa, more than pure PCL, 12.21 ± 1.15 MPa. However, in the case of porogenic scaffolds, the values dropped to 12.97 ± 6.54 MPa and 9 ± 1.60 MPa for PCL–gelatin–PEG and PCL–PEG, respectively, which were still in the range of cartilage elastic modulus. They indicated that gelatin may rise the infiltration depth of PCL scaffold [18]. Rose et al. [19] employed electrospun gelatin–PCL scaffolds for cornea stromal regeneration. Gelatin–PCL solutions were prepared in several ratios (100:0, 25:75, 50:50, 0:100) using 1,1,1,3,3,3-hexafluroisopropanol (HFIP) solvent and then were subjected to electrospinning, followed by glutaraldehyde cross-linking procedure, producing two groups of scaffolds with and without cross-linking. Electrospinning parameters applied to the device were 0.75–2 mL h^{-1}, 15–20 kV and 15–20 cm, standing for flow rate, voltage and working distance, respectively. The results indicated that blend electrospun scaffolds supported human corneal stromal cells (hCSCs) proliferation and adhesion. It is notable that cross-linking caused less porosity along with high elastic modulus and elongation at break. Overall, according to the gene expression, the higher expression of markers related to quiescent keratocyte phenotype (ALDH3A1, CD34) and less expression of markers related to activated fibroblast phenotype (ACTA2, THY1) were reported in both non-cross-linked 25:75 and 50:50 scaffolds (Fig. 1) than scaffolds without PCL, which made a supportive and favorable matrix for hCSCs and induced corneal repair [19]. In another study, PCL–gelatin electrospun scaffolds were developed, conjugated with epidermal growth factor (EGF). Culturing rat fibroblasts L929, both fibrous scaffolds (with and without EGF) supported L929 proliferation. Nevertheless, cells on EGF scaffolds had a larger distribution than those on scaffolds with no EGF, which remained round [20]. Also, Chong et al. [21] conducted the electrospinning of PCL–gelatin nanofibrous directly on a commercial polyurethane (PU) wound dressing (Tegaderm®). They applied a voltage of 15 kV, a flow rate of 0.7 mL h^{-1} and a distance of 15 cm to the device. This research proved that electrospinning of PCL–gelatin nanofibers on the Tegaderm® represented a

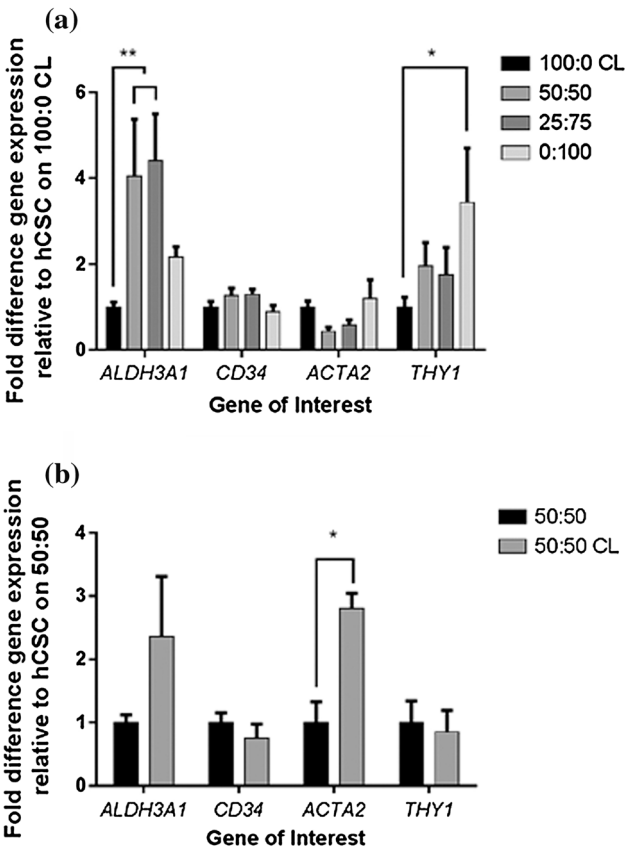


Figure 1 hCSC gene expression in response to electrospun scaffolds measured by qPCR. **a** hCSC gene expression after 12 days culture upon four electrospun scaffolds in K media. All data normalized to GAPDH and displayed relative to 100:0 CL. Data represented by mean relative quantitation ± SEM, (n = 3; triplicate samples); **b** hCSC gene expression after 12 days of culture upon 50:50 scaffolds with and without GA cross-linking. All data normalized to GAPDH and displayed relative to 50:50. Data represented by mean relative expression ± SEM, (n = 3) triplicate samples.*$p < 0.05$, **$p < 0.01$. Adapted with permission from reference [19]. Copyright 2019, John Wiley and Sons, Journal of Biomedical Materials Research Part A.

synthetic wound protection substitute by supporting human dermal fibroblasts (HDF) proliferation and growth [21]. Basar et al. [22] also developed PCL–gelatin hybrid nanofibrous scaffolds loaded with ketoprofen (an anti-inflammation drug) for wound dressing application. They set electrospinning on an applied voltage of 13 kV, flow rate 13 μL min^{-1} and a working distance of 20 cm, at 7:3 ratio. This matrix illustrated a rise in mouse fibroblasts' (L929) growth and proliferation. In other words, the presence of gelatin in the PCL scaffold could prevent the burst release of ketoprofen and brought about an efficient long-lasting release for more than 100 h [22]. In a combined study, both PCL and PU synthetic polymers were used for core–shell electrospinning: PCL–gelatin blend as the shell and PU as the core. The electrospinning device was set at 28 kV, 70 μL min^{-1} and 16 cm. The cell migration and proliferation were promoted, as well as tensile strength and Young's modulus, although physical features such as fiber diameter and porosity were not desirable [23].

According to Powell et al. [24] antecede study, mechanical properties of PCL–collagen electrospun blend surged in comparison with collagen scaffolds. To put it differently, PCL–collagen blends containing as little as 10% PCL exhibited enhanced mechanical properties in vitro. However, scaffolds containing 30% PCL showed the least mechanical features and cell proliferation, as well as growth with poor maturation [24]. Fernandez-perez et al. [25] produced random and radially and perpendicularly aligned PCL–based scaffolds with the incorporation of the decellularized cornea to have corneal native ECM proteins for cornea regeneration applications. Therefore, PCL–ECM was fabricated at 9:1 ratio via electrospinning (15 kV voltage, 2 mL h^{-1} flow rate and 12 cm distance from the needle tip). The results showed that the presence of corneal ECM influenced cellular morphology, but not the cell phenotype. Thereby, the cells offered a round morphology on PCL random fibers, while their shape stretched along the fibers upon culturing on PCL–ECM random fibers. For radially aligned fibers, however, cells could only be stretched along a single fiber in PCL, whereas extended along multiple fibers of PCL–ECM. In the case of perpendicularly aligned fibers, this morphology intensified with some bridge site formation between aligned fibers (Fig. 2). Furthermore, the elongation of keratocytes along with the fibers' direction could in turn increase the migration rate to a great deal (Fig. 3) [25].

Fadaie et al. [26] investigated an electrospun PCL matrix reinforced by chitosan nanofibrils, by adding 1–10 wt% chitosan to 8, 10 and 12 wt% PCL solution. Not only did the addition of chitosan into the PCL scaffold regulate the mechanical stability, but also rose the water absorption and cytocompatibility of PCL. Moreover, the solutions with 1–2 wt% chitosan were electrospinnable, while the addition of 3.5 wt% or higher extent created more viscose solutions without the ability to be electrospun. Furthermore, the incorporation of fibrillated chitosan improved the tensile strength and Young's modulus, while decreased elongation at break. Studying cell culture in vitro, they figured out that the most optimal scaffold in terms of biocompatibility and cytotoxicity was the one containing 10% PCL with 5 and 7.5% chitosan [26]. Regarding nerve tissue engineering, PCL–chitosan (100:0, 95:5, 90:10, 75:25, 0:100) electrospun nanofibers were prepared by applying 25 kV voltage, 0.5 mL h^{-1} flow rate and 15 cm needle distance from the collector. It seemed that the incorporation of chitosan could improve the hydrophilicity and biocompatibility of the fibrous mats. However, In vitro cultured Schwann cells showed higher biocompatibility to lower chitosan content scaffolds [27]. Semnani et al. [28] held a research on the PCL–chitosan blend (70:30 ratio) for liver tissue regeneration, using electrospinning apparatus with a special rotating collector (voltage of 22 kV, flow rate of 0.5 mL h^{-1} and 15 cm working distance). The presence of chitosan led to convenient infiltration of mouse liver epithelial cells' (Hepa 1–6) along with substance exchange [28]. The combination of three components, a polyester (PCL), a polysaccharide (chitosan) and a protein (gelatin), was developed by electrospinning (voltage of 18 kV, a flow rate of 0.3 mL h^{-1} and distance of 25 cm) for skin tissue engineering. PCL–chitosan and PCL–chitosan–gelatin both had the highest values for elastic modulus. While PCL–chitosan–gelatin showed better physical features than PCL–gelatin, the latter blend supported higher human fetal foreskin fibroblast cell line (HFFF2) adhesion than the former. Nevertheless, PCL–chitosan–gelatin could induce the production of collagen type I and fibronectin (two common ECM proteins) in HFFF2 cell line [29].

An approach was introduced making a comparison between PCL–chitosan and PCL–carboxymethyl

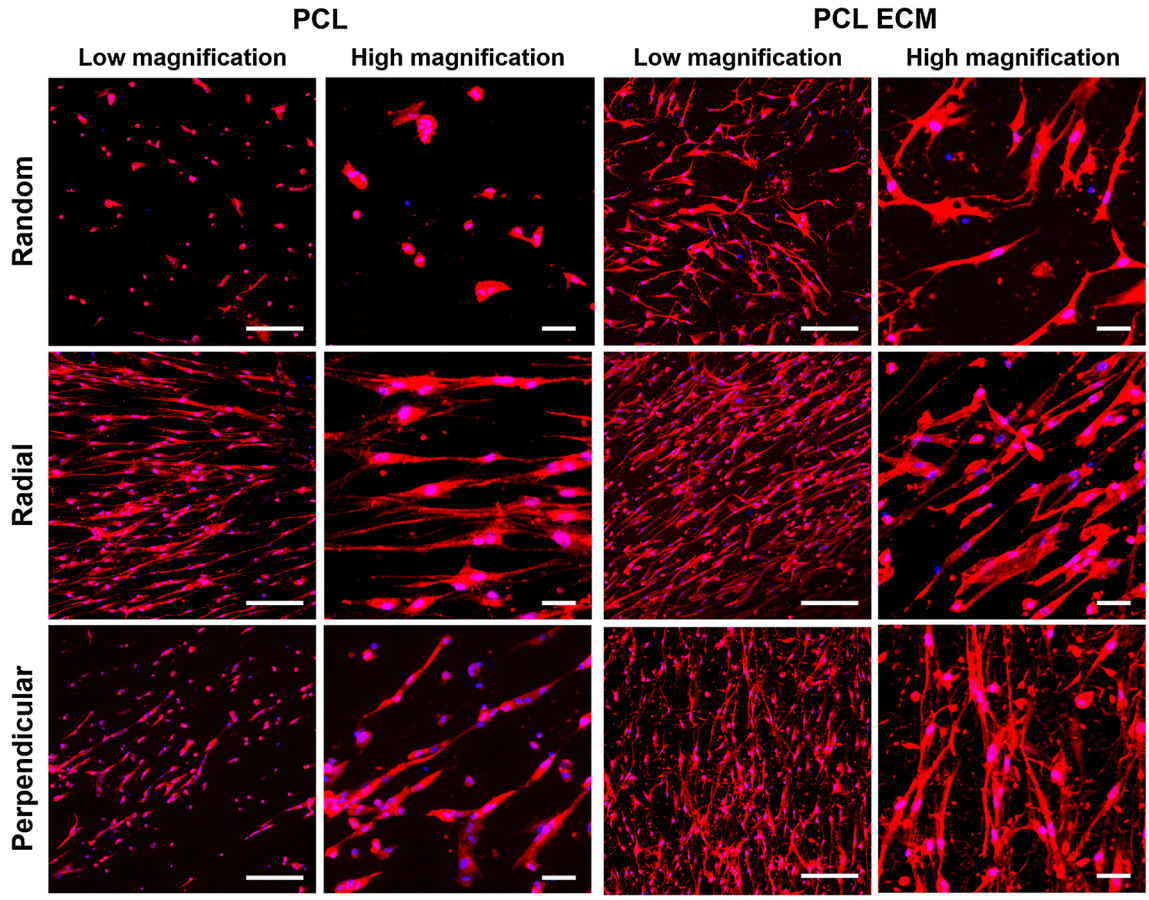


Figure 2 Influence of fiber architecture and presence of ECM on keratocyte morphology. Cytochemical staining of seeded cells after 7 days of culture (blue = nuclei, red = F-actin; low magnification scale bar = 250 μm, high magnification scale bar = 50 μm). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article). Adapted with permission from reference [25]. Copyright 2020, Elsevier, Materials Science and Engineering: C.

chitosan (CMC), to evaluate its suitability for bone tissue engineering. Sharifi et al. [30] prepared both blends by employing 5, 10 and 15% of either chitosan or CMC; they set the electrospinning device at 18–30 kV, 0.1–0.7 mL h^{-1} and 16–20 cm. It is noticeable that PCL–CMC gave the hydrophilicity a rise, by about 70° drop in the contact angle. Moreover, MG-63 osteoblasts attached and proliferated on both scaffolds, although PCL–CMC showed better promoted growth and proliferation than PCL–chitosan [30].

Another approach was conducted based on the electrospun PCL–decellularized meniscus extracellular matrix (DMECM) blends. They were prepared at ratios of 5:0, 4:1, 3:2, 2:3, 1:4 and 0:5, with adjusting parameters at 15 kV, 0.03 mL min^{-1} and 10 cm, to fabricate random and aligned fibers. On the one hand, DMECM incorporation enhanced elastic modulus for aligned nanofibers from 132.27 to 331.40 MPa, suited natural meniscus. Larger yield stresses were also acquired in aligned rather than random fibers. On the other hand, in vitro analysis confirmed non-toxicity and lack of hemolysis, but high proliferation and attachment. Also, gene expression rose in terms of the production of aggrecan, collagen I, collagen II and Sox 9 proteins, in scaffolds with higher DMECM content [31].

In a research, Liao et al. [32] produced wound dressings by the combination of PCL with cellulose acetate (CA) and dextran, to evaluate the improvement in mechanical and biological properties as well as antibacterial activity. In this regard, they prepared the PCL–CA solutions at 1:1, 1:2, 1:3 volume ratios, followed by the addition of 1 wt% dextran. Then, they electrospun the blends by applying 17 kV voltage, 1 mL h^{-1} feed rate and 15 cm working distance. Afterward, the electrospun membranes were embedded into the tetracycline hydrochloride (TCH) as an antibacterial agent. They concluded from

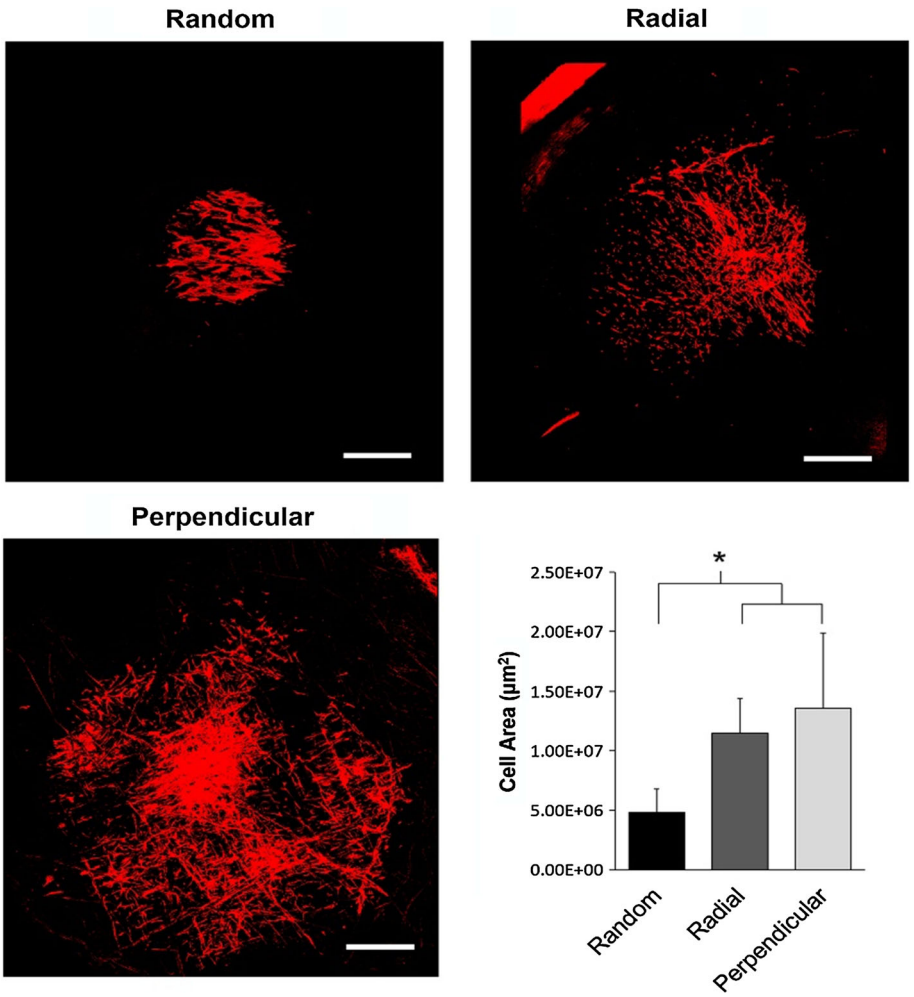


Figure 3 Effect of fiber architecture on cell migration. Area occupied by cells after 24 h of culture on scaffolds, after initial seeding surface of $3 \times 106\ \mu m^2$ (red = F-actin; scale bar = 1 mm; $*p \leq 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article). Adapted with permission from reference [25]. Copyright 2020, Elsevier, Materials Science and Engineering: C.

in vitro studies that nanofibrous blend scaffolds revealed excellent cell growth, proliferation and adhesion and also improved the ability of blood clotting. This survey highlighted that the antibacterial activity against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) may be correlated with the loading of TCH drug, not the blend composition, which created an extended inhibition zone [32]. PCL has been also used in PCL–CA (9:1) scaffolds along with a double layer of chitosan/PEO (1:1), all in one multilayered electrospun membrane by Trinca et al. [33]. They regulated the parameters for electrospinning of PCL–CA (first layer) and chitosan/PEO (second layer) at 20 kV, 30 mL h^{-1} and 15 cm and 25 kV, 2 mL h^{-1} and 15 cm, respectively. They confirmed that these scaffolds are likely to be suitable for wound dressing, due to their non-toxic effect on fibroblast cell line L929. Having said that, however, the less the cells attract to the chitosan layer, the more convenient it would be to change the dressing, without any damage to neo tissue. It appeared that the fibrous multilayered scaffolds had the potential to uptake PBS, with no tangible impact on their mechanical and/or structural properties, which tend to be attributed to their highly porous constructs [33]. De Pinho et al. [34] developed an electrospun hybrid to enhance the ability of electrospinning of ALG for skin tissue engineering. They fabricated scaffolds from PCL–ALG using 20 wt% PCL and 0.5–1 wt% alginic acid solution. The blend solutions were then electrospun at 16 kV voltage, 0.05–4.5 mL h^{-1} flow rate and 15–28 cm working distance. Culturing HDFs on the PCL–ALG nanofibrous matrix showed an initial decrease in metabolic activity in the first culture, while a dramatic rise after the second culture was observed due to the support from attached cells. To assess the formation of tissue in 3D scaffold, collagen I production was evaluated and the results indicated that blend scaffold did not offer any differences in collagen production compared to pure PCL (Fig. 4) [34].

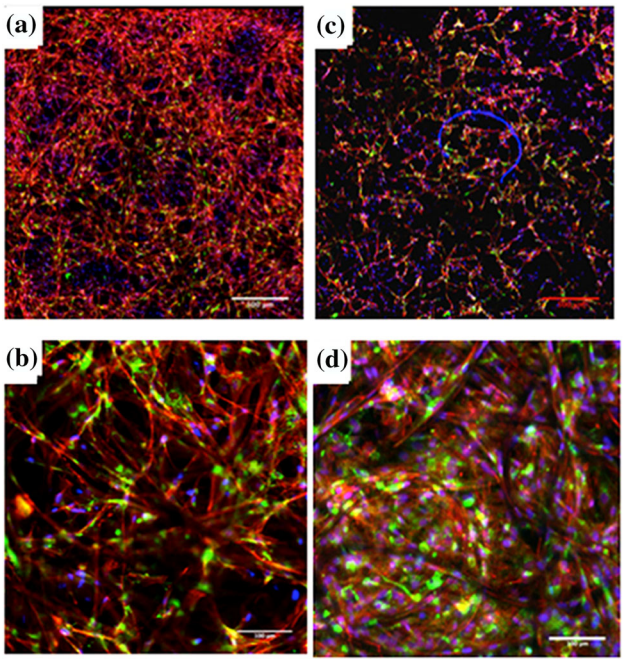


Figure 4 Confocal images of hDF cultured in PCL (**a**, **b**) and PCL/alginate (**c**, **d**) electrospun scaffolds after 14 days in culture showing collagen type I staining (blue—DAPI, red—phalloidin, green—collagen I). Collagen type I is found in both conditions. Scale bar: **a**, **c** 500 μm; **b**, **d** 100 μm. Adapted with permission from reference [34]. Copyright 2019, Frontiers Editorial Office, Frontiers in Bioengineering and Biotechnology.

In another study, Wang et al. [35] made a comparison between PCL–bovine serum albumin (BSA) and PCL–hyaluronan (HA) electrospun blends and investigated the effect of HA on EGF release from the scaffold. Aiming to produce an oil phase (shell), they mixed HA solution into PCL solution (1:10 v/v), along with the incorporation of EGF, employing chloroform as solvent. Also, they dissolved EGF in BSA and prepared PCL–BSA as the aqueous phase (core). Then, the latter was added into the former drop by drop while being stirred. The solutions were then electrospun using a voltage of 18 kV, a flow rate of 1 mL h^{-1} and a working distance of 12 cm. The obtained results explained that fibers containing EGF boosted the HaCaT (human epidermal immortalized keratinocyte cell line) and FEK4 (human skin primary fibroblast cell line) proliferation and also provided a desirable infiltration, by the cooperation of HA and EGF functions. Additionally, in vivo studies confirmed better wound healing in PCL–HA/EGF scaffolds [35]. Martins et al. [36] studied a novel electrospun blend produced from PCL–tannin (TN) at 100:0, 95:5, 85:15 and 78:22 ratios. The electrospinning criteria were set at 15 kV, 1 mL h^{-1} and 12.5 cm. The above ratios were considered to acquire the optimum fiber hydrophilicity along with cytocompatibility. They figured out that surface hydrophilicity and functionalization played a crucial role in adipose-derived stem cells (ADSCs) proliferation and attachment on PCL–TN mats. Furthermore, the nanofibrous scaffolds showed antibacterial activity against Pseudomonas aeruginosa (*P. aeruginosa*) [36]. Salehi et al. [37] produced a hybrid PCL–SF (70:30, 60:40, 50:50) scaffold to improve corneal regeneration. They employed the electrospinning method (applying a voltage of 16 kV, a flow rate of 0.5 mL h^{-1} and a distance of 30 cm), aiming to produce either aligned or random fibers. This group indicated that a rise in the SF content over 30 wt% resulted in a sharp increase in ultimate tensile strength, from 3.34 ± 1.07 MPa and 3.57 ± 0.3 MPa to 4.96 ± 0.4 MPa and 4.67 ± 0.16 MPa for 60:40 and 50:50 blend scaffolds, respectively. Furthermore, hydrophilicity and water uptake surged, associated with better in vitro biodegradation. Culturing human stromal keratocytes, they confirmed the promoted cell adhesion and proliferation on both aligned and random nanofibers [37]. Miguel et al. [38] focused on a hybrid asymmetric two-layer scaffold made of PCL–SF as the upper layer, imitating epidermis, and SF–HA loaded with thymol as the bottom layer, mimicking dermis. The parameters for electrospinning were 28 kV, 1 mL h^{-1} and 10–12 cm. In vivo findings illustrated that human fibroblasts could easily attach and scatter on the electrospun membrane, which confirmed the biocompatibility. Additionally, thymol presence in the bottom layer improved antioxidant and antibacterial properties. Young's modulus and tensile strength were also measured 25.67 ± 6.84 MPa and 23.01 ± 6.73 MPa, respectively, in dry condition, while in wet circumstances the values were calculated 14.70 ± 4.42 MPa and 7.59 ± 1.26 MPa, respectively. Notably, the numbers were quite close to natural skin and the scaffold endured nearly all applied tensions during the wound healing process. Furthermore, the outer layer provided a supportive barrier against bacteria infiltration when compared with the filter paper [38].

In summary, due to the hydrophobic nature of PCL electrospun fibers, cell attachment will be problematic. Thus, one of the approaches that have been used over the years is blending with natural polymers,

which may lead to a better presentation of biological sites for cells to adhere to. Table 1 presents an overview of PCL–natural polymers electrospun blends and their application in tissue engineering, along with some measurement details.

Blend of PCL with synthetic polymers

As it is noted, PCL has limited surface functional groups to attract cellular proteins to set cell attachment. Another promising approach to deal with such a challenge is blending with other esters and copolymers [39]. A study was conducted on PCL–poly(ethylene oxide) (PEO) nanofibrous scaffolds with the volume ratios of 100:0, 75:25, 50:50, 25:75, 15:85, 10:90, 5:95 and 0:100. Kupka et al. [40] electrospun the blend and then covered it using plasma-polymerized cyclopropylamine to amine-functionalize. Electrospun mats with more PCL quantity had larger elongation at break than pure PCL. Functionalization made the PCL–PEO blend scaffolds more cross-linked and enhanced stiffness and water stability, but decreased the ductility. The results showed that an increase in PEO values led to 20 times lower flexibility [40]. Another polyester is PLA that has been used as tendon substitute for years [40]. Directing a study, Baudequin et al. [41] fabricated PCL–PLA core–shell electrospun scaffolds with two different structures, using either PCL–PLA as core or shell and PCL for the other. The osteocyte cell line differentiated from mesenchymal stem cells (C3H10T1/2) on pure PCL scaffolds, while the concurrent incorporation of PCL and PLA—producing fiber diameters of more than 2000 nm—embarked on the differentiation to tendon cell line only within 96 h. [41]. In another study, Aghdam et al. [42] focused on the PCL–PGA blend application in soft tissue engineering at various ratios of 100:0, 80:20, 65:35, 50:50 and 0:100, followed by electrospinning under 17 kV, 2 mL h^{-1} and 10 cm circumstance. The results proved the correlation between PGA content with improved hydrophilicity and mechanical properties [42]. To mimic the construction of cardiac valve, the PCL–poly(L-lactic acid) (PLLA) electrospun blends were studied at 100:0, 90:10, 70:30, 50:50, 30:70, 10:90 and 0:100 ratios. The pulse duplicator and echocardiography test results showed the potential of the nanocomposite blend to be used in heart valve engineering [43].

Recently, Castilho et al. [44] have worked on ultrathin fibers composed of PCL–poly(hydroxymethylglycolide-*co*-ε-caprolactone) (pHMGCL), with 80:20 and 60:40 ratios, in two different styles (rectangular and squared), using melt-electrospinning. This combination would improve cell response to mechanical anisotropy. To put it differently, scaffolds with rectangular shapes showed a more efficient anisotropic behavior on cardiac native tissue than those with squared architecture. Also, the alignment of the cardiac progenitor cells was enhanced on rectangular-shaped mats [44].

A research carried out by De-Paula et al. [45] to assess the antibacterial activity of an electrospun blend of PCL/PEG/GelMA (60:30:10) against *S. aureus*, *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). The group electrospun the blend under 17 kV voltage, 1 mL h^{-1} flow rate and 10 cm needle–collector distance condition, followed by UV cross-linking. They indicated that cross-linked scaffolds decreased the number of bacteria by ten-fold, due to an increase in protein absorption on the surface. Furthermore, in vivo subcutaneous implantation confirmed the mats' biocompatibility, with no necrosis around the implant site [45]. In another study, the electrospun blend of PCL–PEG–GelMA (UV-cross-linked gelatin) was studied by Lobo et al. [46] for bone tissue engineering application. They adjusted the electrospinning parameters at 17 kV voltage, 1 mL h^{-1} feed rate and 10 cm needle–collector distance. The resulted scaffolds presented more desirable hydrophilic properties prior and post-cross-linking, as well as higher mechanical strength for cross-linked mats compared to neat PCL. The findings also revealed that alkaline phosphatase (ALP) activity and calcium deposition rose sharply right after UV cross-linking and stand for a biologic marker for osteoblast differentiation and final stage of osteoblast maturation, respectively (Fig. 5) [46]. It is worth noting that increasing ALP expression quantity could be correlated with bone formation proteins expression during osteogenic differentiation and scaffold-induced mineralization [47].

Han et al. [48] produced PCL–poly(trimethylene carbonate) (PTMC) loaded with shikonin (a herbal drug) at 9:1, 7:3 and 5:5 volume ratios for wound healing application and dermal infections. They used the electrospinning method at 14 kV voltage, 0.8 mL h^{-1} and 18 cm working distance. The researchers declared that scaffolds with 5 wt%

Table 1 A summary of PCL blended with natural polymers and their tissue engineering application

Scaffold	Application	Fiber diameter (FD) and/or pore size (PS)			References
		Composition	FD (μm)	PS (μm)	
PCL–natural polymer blend electrospun scaffolds					
PCL–gelatin–PEG	Cartilage TE	PCL	0.69 ± 0.19	6.23 ± 1.85	[18]
		PCL-GEL-PEG	0.30 ± 0.07	3.97 ± 1.15	
PCL–cartilage ECM		Random PCL-DMECM80%	1.01 ± 0.63	NA	[31]
		Aligned PCL-DMECM80%	0.73 ± 0.44		
PCL–gelatin	Cornea TE	PCL	0.62 ± 0.47		[19]
		GEL-PCL(25:75)	0.63 ± 0.22		
		GEL-PCL(50:50)	0.89 ± 0.58		
PCL–cornea ECM		NA	[25]		
PCL–SF		PCL(aligned)	0.42 ± 0.11	8.94 ± 4.85	[37]
		PCL(non-aligned)	0.44 ± 0.11	7.21 ± 3.23	
		PCL-SF (aligned)	0.38 ± 0.14	10.03 ± 5.20	
		PCL-SF (non-aligned)	0.47 ± 0.07	9.77 ± 2.59	
PCL–gelatin/loaded with EGF	Skin TE	PCL	0.48 ± 0.11	NA	[20]
		PCL-GEL	0.66 ± 0.10		
PCL–gelatin on Tegaderm®		PCL-GEL	0.47 ± 0.12		[21]
PCL–gelatin/loaded with ketoprofen		PCL	~ 0.34		[22]
		PCL-GEL	~ 0.27		
PCL–chitosan–gelatin		PCL-CS	0.89 ± 0.34		[29]
		PCL-CS-GEL	1.23 ± 0.25		
PCL–collagen		PCL	~ 0.2		[24]
		PCL-COL	0.63 ± 0.04		
PCL–ALG		PCL-ALG 0.5%	12.26 ± 2.04–17.2 ± 4.8	12.96 ± 5.19–24.92 ± 12.90	[34]
		PCL-ALG 1%	9.5 ± 2.75–13.83 ± 5.83	13.79 ± 4.79–26.7 ± 17.52	
PCL–HA(shell)/PCL–BSA(core) loaded with EGF		PCL	0.27 ± 0.03	0.56 ± 0.19	[35]
		PCL-HA	0.18 ± 0.006	0.16 ± 0.02	
		PCL-HA-EFG	0.14 ± 0.004	0.17 ± 0.03	
PCL–SF(upper layer)/SF–HA–Thymol (bottom layer)		PCL-SF(pre-CR)	0.47 ± 0.15	NA	[38]
		PCL-SF(post-CR)	0.61 ± 0.19		
		SF-HA(pre-CR)	0.27 ± 0.08		
		SF-HA(post-CR)	0.30 ± 0.08		
		SF-HA-THY(pre-CR)	0.29 ± 0.08		
		SF-HA-THY(post-CR)	0.41 ± 0.10		

Table 1 continued

Scaffold	Application	Fiber diameter (FD) and/or pore size (PS)			References
		Composition	FD (μm)	PS (μm)	
PCL–gelatin (core)/PU (shell)	TE	PCL-GEL/PU (coaxial)	0.53 ± 0.05		[23]
		10%PCL-10%GEL (uniaxial)	1.24 ± 0.11		
PCL–chitosan (nanofibrils)		PCL10-CS5	0.85 ± 0.20		[26]
		PCL10-CS7.5	0.80 ± 0.25		
PCL–TN		10%PCL-5–15% TN	~ 0.19 to 0.15		[36]
PCL–chitosan	Nerve TE	PCL	0.24 ± 0.04		[27]
		PCL-CS	0.12–0.15 ± 20		
PCL–chitosan	Liver TE	PCL-CS	0.24 ± 0.03	12 ± 5	[28]
PCL–CA–dextran/loaded with TCH	Wound dressing	PCL	1.22 ± 0.31	NA	[32]
		PCL-CA-DEX	0.79 ± 0.34		
		PCL-CA-DEX-TCH	0.72 ± 0.30		
PCL–CA (first layer)/chitosan–PEO (second layer)		PCL	1.6 ± 0.7		[33]
		PCL-CA	4.4 ± 1.0		
PCL–CMC versus PCL–CTS	Bone TE	PCL-CTS15%	~ 0.43		[30]
		PCL-CMC15%	~ 0.35		

NA not available, *CR* cross-linking

shikonin tended to enhance the antibacterial effect. Also, they proved that by the addition of PTMC to PCL electrospun membranes, fiber diameter decreased [44, 45].

In an investigation, Kim et al. [50] blended PCL with poly(*N*-vinyl-2-pyrrolidone) (PVP) at different volume ratios (100:0, 90:10, 80:20, 60:40, 50:50, 40:60 and 0:100) and electrospun to optimize and regulate the surface morphology and degradation rates. They set the electrospinning device at 3–20 kV voltage and 10 cm working distance. Not only did these nanoporous scaffolds facilitate the fibers' degradation, but they also promoted the cells' dispersion and adhesion on the mat surface. In terms of mechanical properties, the scaffold Young's modulus increased by a rise in PVP content, while elongation at break decreased dramatically. The results introduced the 50:50 ratio as the best-fitted quantity responsible for the most efficient morphology for ADSCs, with the highest cells' dispersion among the others [50].

Electrospinning of PCL–poly(methyl methacrylate) (PMMA) was performed by Munj et al. [51] with 25:75, 50:50 and 75:25 volume ratios. They applied 20 kV, 10–12 mL h^{-1} and 20–22 cm for voltage, feed rate and working distance, respectively. The elastic modulus increased for the blend membrane since PMMA has a fragile nature with poor tensile strength and in contrast, PCL shows high ductility and tensile strength, and as a result, the combination of these synthetic polymers led to a more balanced feature than neat PCL [51].

Research was carried out focusing on electrospinning of PCL–poly(glycerol sebacate) (PGS) blend, using 15 kV voltage, 0.4 mL h^{-1} flow rate and 11 cm distance between the needle and collector. The mechanical properties of this blend were more than cardiac native tissue. Moreover, after dissolving PGS

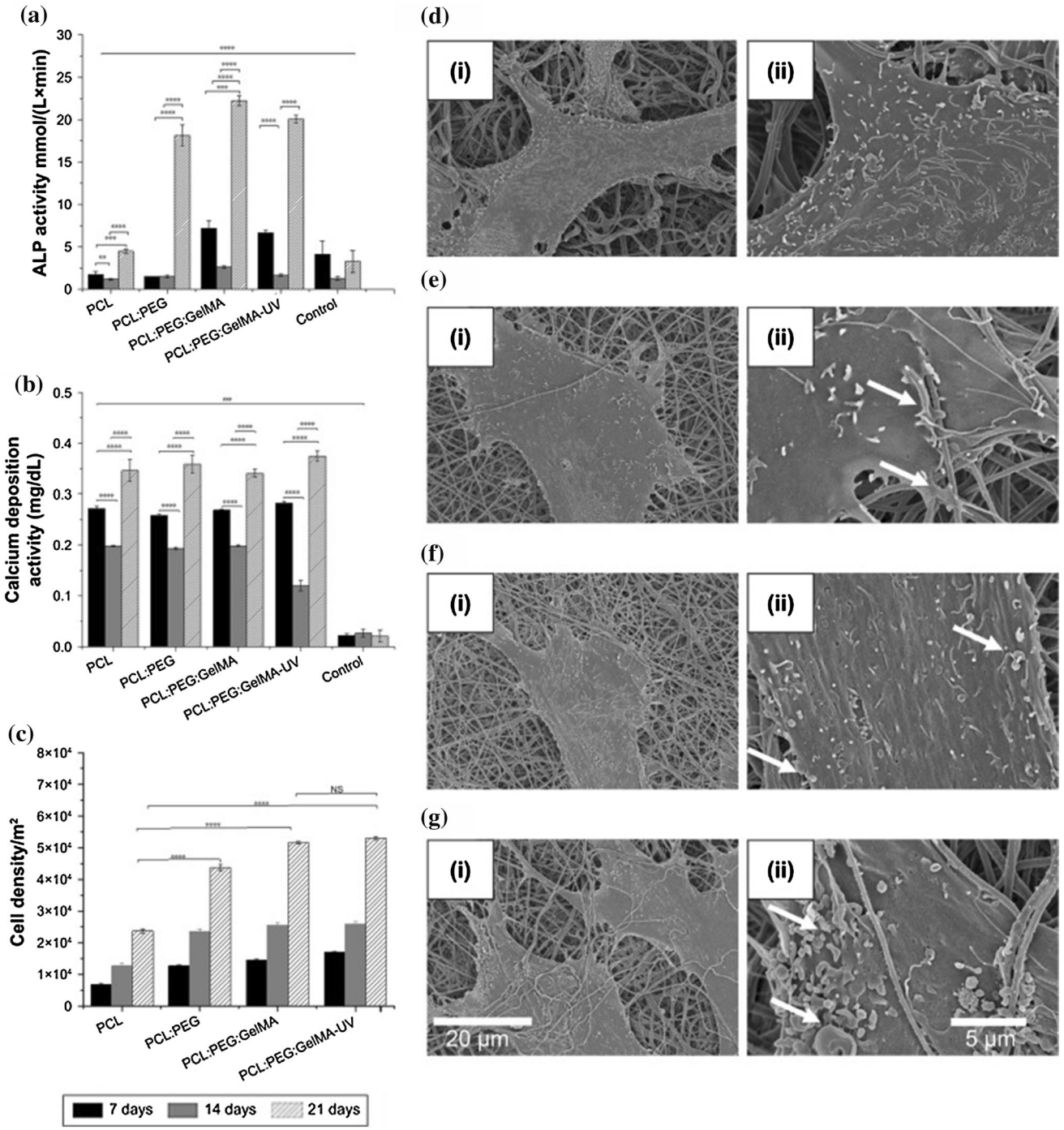
in acetic acid as a less toxic solvent, the remained pores in fibrous scaffolds resulted in enhanced cell adhesion and infiltration. Vogt et al. [52] confirmed that PCL–PGS can play a favorable role in cardiac tissue engineering, due to its mechanical and degradation characteristics [53]. This may be contributed to the hydrophilic behavior of the PCL–PGS blend, caused by hydroxyl groups in PGS backbone structure [49, 50, 54]. A comparative study focused on the comparison between the blend electrospun PCL–polydioxanone (PDS) and the co-electrospun PCL–PDS. The addition of PDS improved the scaffolds' mechanical properties in both groups. However, features including hydrophilicity, biodegradability, human umbilical vein endothelial cells (HUVEC) proliferation and vascularization were much higher in the co-electrospun fibers than the blend [55].

Polyaniline (PAni) seems to be an excellent optical and conductive polymer with high stability. But its poor hydrophilicity makes it hard to be used in tissue engineering applications. To address this limitation, researchers functionalized it with carboxyl groups to enhance hydrophilicity [56]. Recently, the produced poly(anthranilic acid) (P3ANA)—PAni derivate—was blended with PCL in different mass ratios for bone regeneration study. Applying 15 kV voltage, 1 mL h^{-1} flow rate and 15 cm working distance, the researchers electrospun the blend, followed by functionalization with RGD (arginine–glycine–aspartic acid) peptides. The results showed that the incorporation of higher amounts of P3ANA led to enhancing Young's modulus, tensile strength, surface area, cell–cell (Saos-2) and cell–scaffold interactions. Also, an improvement was observed in cell adhesion and proliferation, along with the ALP activity and calcium deposition, which indicates the osteogenic activity of cultured cells [57]. Balu et al. [58] carried out an investigation on PCL–poly[(1,4-butylene adipate)-*co*-(polycaprolactam)] (PBAPCL) blend nanocomposite, fabricated via electrospinning at 3:1, 1:1 and 1:3 weight ratios. In vitro degradation tests suggested better biodegradability for the blend scaffolds compared to neat PCL. Cellular cultivation, on the other hand, provided data on fibroblasts' high viability and non-toxic mats. The osteoblasts also could perfectly adhere to the blend nanocomposite with a great extent proliferation [58].

Xue et al. [59] developed a novel blend composed of poly[(1,3-diamino-2-hydroxypropane)-*co*-(glycerol sebacate)]-*co*-poly(ethylene glycol) (APS-*co*-PEG) (with 15, 25, 40 molar ratios of PEG) and PCL employing electrospinning (17 kV voltage, 1 mL h^{-1} flow rate and constant 10 cm working distance). They corroborated that PEGylation in ASP-*co*-PEG resulted in inhibition of platelet adhesion on the electrospun membranes, thus playing an indispensable role in thrombogenicity mitigation in vivo. To put it differently, ASP-25PEG/PCL mimicked the human cardiac valve and supported aortic valve cell adhesion, which introduces these blend scaffolds applicable for soft tissue regeneration [59]. Developing PCL-based scaffolds with the incorporation of PMMA–lignin copolymer, Kai et al. [60] electrospun PCL/PMMA–lignin blend under 12 kV, 0.5 mL h^{-1} and 15 cm circumstances. The blend represented an increment in tensile strength and elastic modulus, associated with a rise in copolymer percentage, but a decrease in elongation at break. In vitro studies on HDFs also showed biocompatibility along with a great extent of proliferation and attachment [60].

Gene delivery was studied in either PCL/polyethylenimine (PEI) or PCL/PEG-*co*-PEI blends with 3:1, 5:1, 10:1 and 20:1 different ratios, using electrospinning set up at 20 kV, 1 μL min^{-1} and 20 cm. The resultant blend showed over 65% and 40% transfection efficiency in human embryonic kidney 293 cells and MSCs, respectively. When it came to comparison with PCL–PEI, the PCL/PEG-*co*-PEI composition ameliorated the biological compatibility as well as gene transfection. This may result from PEG covering PEI, which in turn led to shortening DNA-PEI agglomerations [61].

Aiming to an improvement in biological characteristics of PCL, de Cassan et al. [62] produced chitosan-grafted PCL (CS-*g*-PCL) and blended it with PCL in different ratios. The blend was electrospun at 20 kV, 4 mL h^{-1} and 20 cm. The nanocomposite blend ameliorated cell proliferation and attachment as well as viability while preserving mechanical characteristics [62]. A study reported the use of three different polyesters in combination with PCL to make a comparison which one is the most suitable blend for retinal regeneration. Therefore, PCL–PGS, PCL–PLLA and PCL–PLGA were blended at a 1:2 ratio, and the nanocomposites were fabricated via electrospinning under 15 kV, 1 mL h^{-1} and 18 cm condition. Among all three blends, PCL–PGS represented more desirable properties as a carrier for retinal progenitor cell delivery, largely due to its perfect surface characteristics [39]. Arbade et al. [63]


(a)
ALP activity mmol/(L×min)
PCL
PCL:PEG
PCL:PEG:GelMA
PCL:PEG:GelMA-UV
Control
(b)
Calcium deposition activity (mg/dL)
(c)
Cell density/m²
NS
7 days
14 days
21 days
(d)
(e)
(f)
(g)
(i)
(ii)
20 μm
5 μm

◀**Figure 5** **a** ALP activity showed an increase in calcification of the extracellular matrix after inclusion of GelMA. **b** Calcium deposition demonstrated a further influence of GelMA to enhance the functions of osteoblasts. **c** MTS assay showing that osteoblastic cells were further influenced by hydrophilic properties after inclusion of PEG and GelMA. Data plotted in mean and SD ($N = 5$). Values of $p < 0.01$ were considered significant. Data were normalized by the cells, and the y-axis was multiplied by 104. For the ALP and calcium deposition, the data were compared with control (cells) and between each time. For cellular proliferation assays, the data were compared with pure PCL. $N = 5$. $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$ mean statistical differences. SEM of human osteoblasts cultivated on scaffolds after 7 days. **d** (i) PCL and (ii) magnified view. **e** (i) PCL–PEG and (ii) magnified view. **f** (i) PCL–PEG–GelMA without UV cross-linking and (ii) magnified view. **g** (i) PCL–PEG–GelMA after UV cross-linking and (ii) magnified view. The cells are spreading on all produced scaffolds presenting filopodium and cytoplasmic extension. Adapted with permission from reference [46]. Copyright 2018, DOVE Medical Press, International Journal of Nanomedicine.

developed a blend composed of PCL–PEG–poly[(L-lactide)-*co*-(ε-caprolactone)-*co*-(glycolide)] (PLCG) to give a rise to PCL biological features. They subjected the blends to electrospinning by applying 13.5 kV, 1 μL min^{-1} and 12 cm. In vitro assessment confirmed viability and growth in gingival mesenchymal stem cells (gMSCs) while cultured onto the blend. In fact, the quantity of PEG and PLCG in the PCL matrix could provide better biodegradability [63]. Multilayer hybrid scaffolds were also studied, consisted of an inner layer of PCL–gelatin, a middle layer of PLGA–gelatin and an outer layer of PLGA–chitosan, for vascular tissue engineering application. Nguyen et al. [64] electrospun each blend separately at 27–30 kV and 0.5 mL h^{-1}. The tensile stress value reported for synthetic blood vessels was 2.3 MPa. The study findings revealed good compatibility of the hybrid, enduring great pressures along with excellent cell growth and proliferation [64].

Overall, the combination of PCL with either natural or synthetic polymers or even both will provide the chance for biomaterials to be biologically receptive to cells. Table 2 summarizes the studies performed on PCL-based polymeric blends with synthetic polymers that were subjected to electrospinning. It is categorized by tissue application and scaffold composition along with the results for fiber diameter and pore size which are reported in comparison with pure PCL.

PU-based electrospun scaffolds

PUs are multifunctional macromolecules with cytocompatibility, high oxygen permeability and supreme resistance to the thrombus. They also represent biocompatibility, biodegradability and wide tunable mechanical properties comparable to native tissues, which provide them with the opportunity of being used in different biomedical applications. There are three main components involved in the PU synthesis procedure: (1) polyol, (2) diisocyanate and (3) cross-linker, which are combined to produce –NHCOO- urethane bond and forms PU backbone structure [61, 62]. Polyols might be either polyester, polyether, polycarbonate polyols or PCL. There likely are more than 500 different types of polyols commercially available [63, 64].

By selecting specific ratios for these three factors, researchers can make it possible to fabricate PU with proper biological activity. Characteristics such as flexibility, biodegradability, hydrophilicity or hydrophobicity and chemical cross-linking would be controlled, to meet every tissue engineering requirements [65–67]. As with other synthetic polymers, PU also needs to be blended with synthetic and/or natural polymers to best fit the properties of the target tissue [68, 69]. Therefore, herein we will introduce the PU-based electrospun polymeric blends as the following.

Blend of PU with natural polymers

The biostability of PU electrospun scaffolds while turning into a highly porous structure is a fundamental problem in tissue engineering. Nevertheless, a few studies have been conducted to address this issue through the incorporation of natural polymers [70, 71]. Gostev et al. [72] compared the stability of two different commercially available PU as vascular grafts, Tecoflex EG-80A (Tec-80A) and Pellethane 2363-80A (Pel-80A), when blended with gelatin. They used 3% Tec-80A with 15% gelatin and 3.5% Pel-80A with 10% gelatin to prepare electrospun mats, with parameters set at 18.5–24 kV, 1–1.15 mL h^{-1} and 19–20 cm. They reported that Pel-80A-gelatin was stable for the whole 6-month period, while Tec-80A-gelatin showed some changes after 3 months of implantation in rat aorta, but both grafts induced neointima and vascular tissue formation as it is obvious in Fig. 6. Nevertheless, the tensile strength

Table 2 A brief overlook of studies regarding PCL–synthetic polymer electrospun blends

Scaffold	Application	Fiber diameter (FD) and/or pore size (PS)			References
		Composition	FD (μm)	PS (μm)	
PCL–synthetic polymer blend electrospun scaffolds					
PCL–PEO	TE	PCL	0.15 ± 0.05	NA	[40]
		PCL-PEO	0.25–0.45		
PCL–PVP		PCL	~ 1.2		[50]
		Blend	~ 1.27 to 1.88		
PCL–PMMA		NA			[51]
PCL/Cs-*g*-PCL			0.84 ± 0.20–2.04 ± 0.41	2.69 ± 0.35	[62]
PCL–PLA(core or shell)/ PCL(core or shell)	Tendon substitute	PCL	~ 0.5 to 1	NA	[41]
		Coaxial blend	≥ 2		
		Blend PLA out	2.46 ± 0.35		
PCL–pHMGCL	Cardiac TE	PCL	~ 4 to 12	NA	[44]
		PCL blend 40	~ 3 to 7		
PCL–PGS		PCL	0.8 ± 0.3		[52]
		PCL-PGS	1.3 ± 0.7		
PCL–PLLA		PCL	2.4 ± 0.43		[43]
		PCL-PLLA	2.3 ± 0.21		
PCL–PEG–GelMA	Skin TE	PCL	1.53 ± 0.74		[45]
		PCL-PEG-GelMA	0.24 ± 0.10		
PCL/PMMA-*co*-Lignin		PCL	1.05 ± 0.26		[60]
		PCL-copolymer	0.37 ± 0.10		
PCL–PTMC/loaded shikonin	Wound healing and antibacterial effects		0.20 ± 0.07–0.30 ± 0.10		[49]
PCL–PEG–GelMA	Bone TE	PCL	2.63 ± 0.78		[46]
		PCL-PEG	0.39 ± 0.14		
		PCL-PEG-GelMA	0.42 ± 0.17		
PCL–P3ANA		NA			[57]
PCL–PBAPCL			~ 0.4	NA	[58]
PCL–PDS	Vascular TE	PCL	~ 8	~ 23	[55]
		PCL-PDS blend	~ 5	~ 19	
		PCL/PDS coelectrospun	~ 6	~ 21	
PCL–gelatin/PLGA–gelatin/ PLGA–chitosan		PCL	~ 5	NA	[64]
		PLGA-CS	~ 0.5 to 1		
		PLGA-GEL	~ 0.2 to 0.5		
		3-Layer hybrid	~ 1000		
PCL/APS-*co*-PEG	Soft TE		~ 0.3		[59]
PCL–PGA		NA			[42]
PCL/PEG-*co*-PEI	Kidney TE and Gene delivery		~ 0.5 to 0.8	NA	[61]
PCL–PEG–PLCG	Gingival TE	PCL	0.41 ± 0.97		[63]
		PCL-PEG	0.61 ± 0.11		
		PCL-PLCG	0.72 ± 0.23		
		PCL-PEG-PLCG	0.75 ± 0.31		

Table 2 continued

Scaffold	Application	Fiber diameter (FD) and/or pore size (PS)			References
		Composition	FD (μm)	PS (μm)	
PCL–PGS, PCL–PLLA, PCL–PLGA	Retinal TE	PCL	1.62 ± 0.19	PA:104.2 ± 9.4	[39]
		PCL-PGS	2.30 ± 0.25	PA:73.2 ± 5.1	
		PCL-PLLA	3.17 ± 0.56	PA:68.7 ± 4.3	
		PCL-PLGA	1.23 ± 0.09	PA:79.9 ± 2.4	

NA not available, *PA* pore area

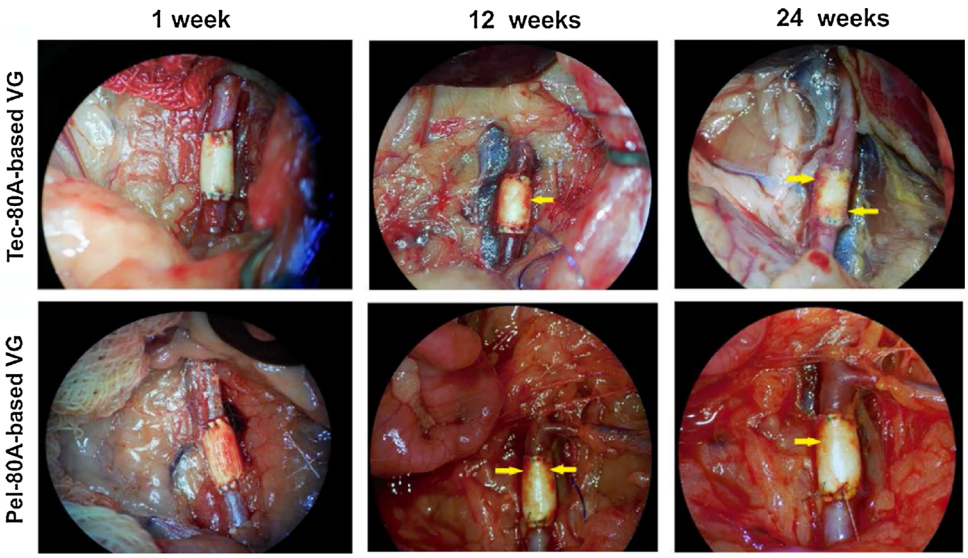


Figure 6 The vascular graft (VG) view during explantation at different points of observation (Carl Zeiss OPMI Pico surgical microscope). The arrows demonstrate the ingrowth of tissues from the outer VG side. Adapted with permission from reference [72]. Copyright 2020, MDPI, Polymers.

was not affected for up to 6 months in neither grafts [72].

Chao et al. [73] conducted a report on PU-based electrospun membrane, blended with grapeseed oil and honey/propolis, to find out the role of grapeseed oil polyphenols in cell response and also its capability in bone tissue regeneration. They electrospun the scaffolds under 10.5 kV voltage, 0.5 mL h^{-1} flow rate and 20 cm distance. When it came to hydrophilicity, it appeared that either the PU/grapeseed oil/honey/propolis (7:1:1) or PU/grapeseed oil (7:2) blends were conductive for cell adhesion and osteoblasts proliferation. Having said that, however, PU/grapeseed oil was more hydrophobic, which in turn resulted in longer coagulation time, more blood compatibility and irreversible plasma proteins adhesion compared with the other. According to hemolytic studies (hemolytic index of under 1%; substances with under 2% values known as non-hemolytic materials), these blends provided a biocompatible, non-toxic surface for red blood cells (RBCs) and HDF [73]. A similar study was performed by the addition of castor oil to PU solution to obtain a nanocomposite electrospun scaffold for cardiovascular engineering. The blend PU–castor oil (8:2) was electrospun applying 10 kV voltage, 1 mL h^{-1} flow rate and 16 cm working distance. Jaganathan et al. [74] observed that when castor oil was incorporated, the nanocomposite water contact angle and thermal stability enhanced. Furthermore, lower amounts of hemolysis (given in Table 3) and thus higher RBCs security were suggested [74]. Mani et al. [75] appraised an electrospun membrane composed of PU–ginger extract (8:1) for wound healing application. They fixed all the three parameters, a voltage of 10.5 kV, a flow rate of 0.2 mL h^{-1} and a needle–collector distance of 15 cm, at the electrospinning apparatus. The presence of ginger extract enhanced hydrophilicity and surface roughness. The assay findings showed a more rapid coagulation time for the blend than pure PU scaffolds. To put it differently, not only did the hemolytic index and biocompatibility evaluations revealed a non-toxic effect on RBCs, but also the proliferation rate increased for HDF (159 ± 5.57%), which can be

Table 3 A brief overview of the electrospun blends consisted of PU with natural polymers

Scaffold	Application	Fiber diameter (FD), hemolytic index (HI) and pore size (PS)				References
		Composition	FD (μm)	HI (%)	PS (μm)	
PU–natural polymer blend electrospun scaffolds						
PU–gelatin	Vascular TE	NA				[72]
PU–proteins (collagen, gelatin, fibrinogen, BSA)		PU-Coll	~ 0.35	NA	NA	[78]
		PU-GEL	~ 0.32			
		PU-Fib	~ 0.30			
		PU-BSA	~ 0.28			
PU–ECM	Nerve TE and Vascular TE	TPU-Col-CS (aligned)	0.25 ± 0.14	NA	0.10 ± 0.01	[79]
		TPU-Col-CS (Random)	0.36 ± 0.22		0.24 ± 0.14	
PU–grapeseed oil/honey propolis	Skin TE	PU	0.89 ± 0.11	2.48	NA	[73]
		PU-grapeseed oil	0.81 ± 0.15	1.28	NA	
		PU-grapeseed oil-honey propolis	0.60 ± 0.15	0.86	NA	
PU–castor oil	Cardiovascular TE	PU	1.18 ± 0.10	2.7	NA	[74]
		PU-castor oil	0.76 ± 0.14	1.15		
PU–ginger extract	Wound healing	PU	1.15 ± 0.14	2.56	1.08 ± 0.06	[75]
		PU-ginger Ex	0.61 ± 0.15	0.96	0.70 ± 0.09	
PU–grape extract		PU	0.89 ± 0.11	2.48	1.06 ± 0.07	[76]
		PU-grape Ex	0.73 ± 0.12	1.20	0.87 ± 0.05	
PU–murivenna oil		PU	0.96 ± 0.21	2.73	NA	[77]
		PU-murivenna oil	0.74 ± 0.16	0.86		

NA not available

considered as a good candida for engineered skin [75]. In another research held by the same group, the grape extract was used instead of ginger extract in combination with PU. Grape extract incorporation showed anti-thrombogenicity and cytocompatibility (with 173 ± 1% viability) upon HDF along with enhanced thermal and tensile strength; 19.55 MPa resulted from hydrogen bonds between the components. Also, they reported a hemolytic index of under 2%, which represented the non-hemolytic nature of the blend [76]. Another research was conducted based on using murivenna oil as the reinforcing phase in the PU matrix to determine its wound repair functions. PU–murivenna oil (8:2) was electrospun under 7 kV voltage, 0.5 mL h^{-1} flow rate and 16 cm distance. Manikandan et al. [77] showed that this blend was largely blood compatible, with a 0.86% hemolytic index, and largely increased thermal stability and hydrophilicity [77].

A comparative study on four different proteins, collagen, gelatin, fibrinogen and BSA, combined with PU (75:25 ratio for each) was carried out to determine its functionality in vascular tissue engineering. The parameters for electrospinning were set at 15 kV, 1 mL h^{-1} and 12 cm. Culturing human aorta smooth muscle cells (HASMCs), Jia et al. [78] showed the maximum proliferation on PU–collagen, 42% more than PU–fibrinogen nanocomposite. Both PU–collagen and PU–gelatin could align cells and showed more cell adhesion. Also, these cell-rich scaffolds expressed smooth muscle proteins including alpha-actin and heavy-chain smooth muscle myosin, to a greater extent [78]. In another approach, the combination of collagen–chitosan–PU with 60:15:25 ratio was electrospun, either random or aligned, to imitate the ECM composition and construct, setting at 18 kV voltage, 1 mL h^{-1} flow rate and 12–15 cm needle–collector distance. Huang et al. [79] showed high ductility and tensile strength in the blend nanocomposites. Moreover, in vitro studies reported good viability for endothelial and Schwann cells, accompanied by induction of cell alignment and morphology. This research represented a novel blend commensurate to be used either for nerve conduits or for vascular substitutes [79].

As summary, to create scaffolds mimicking the native ECM, PU has been blended with natural polymers such as collagen and chitosan. This results in better biocompatibility, while maintaining mechanical characteristics. In regards to the PU–natural polymer blends, a summary is presented in Table 3, describing different parameters and their applications.

Blend of PU with synthetic polymers

Serving better biocompatibility than other synthetic polymers, PU, however, is introduced as a not-hemocompatible polymer and requires other components to be involved to lessen the blood coagulation and platelet adhesion. Moreover, the combination of PU with other synthetic polymers will bring about better mechanical performance where it is needed. To this end, many studies have been carried out to evaluate the effect of synthetic polymers in blend with PU, when subjected to electrospinning.

For vascular tissue regeneration, a two-layer hollow tube of PU–PCL blend was fabricated by the electrospinning technique. Le et al. [80] employed PU–PCL–poloxamer as the inner layer and PU–PCL as the outer, incorporating poloxamer to boost biological properties [80]. Poloxamer is a copolymer with two PEG hydrophilic tails and a PPG hydrophobic tail, arranged linearly and used commonly to avoid protein absorption and platelet adhesion and to enhance blood compatibility [81]. The findings revealed that the surface behavior was altered due to the presence of poloxamer and made the tubular scaffolds more hydrophilic with good mechanical support, followed by cell adhesion and proliferation, with the simultaneous effect of platelet adhesion inhibition [80].

Shape memory polyurethanes (SMPUs) composed of PU–PLGA and PU–PLLA/PEG were studied as drug delivery systems to evaluate biodegradability, memory-related features and also the ability of controllable release. Being electrospun at 5 kV voltage, 0.5 mL h^{-1} flow rate and 10 cm needle–collector distance, the scaffolds were then loaded with rapamycin (Rap) drug. PU–PLGA nanofibrous scaffolds seemed to have more mechanical stability over the degradation period compared with PU–PLLA/PEG. Also, human cardiac fibroblasts (HCF) in vitro cultivation confirmed a controlled release of Rap from both systems, which in turn inhibited cell growth on the surface of the scaffolds [82].

Caracciolo et al. [83] accomplished research on PU–PLLA (50:50) blend electrospun scaffold that was surface-modified by heparin to provide substitutes for small-diameter vessels. The setup for electrospinning was based upon the following: an applied voltage of 13 kV, a feed rate of 1 mL h^{-1} and a working distance of 15 cm. The results suggested that heparin-immobilized scaffolds largely could hinder the platelet adhesion and no hemolysis was seen. Moreover, hydrophilicity and water uptake were promoted, led to higher adhesion and proliferation of ADSCs [83]. Wang et al. [84] produced PU–PEG blend electrospun scaffolds with 90:10, 80:20, 70:30, 60:40 and 50:50 weight ratios for vascular tissue regeneration; they fixed voltage, feed rate and distance at 20 kV, 0.6 mL h^{-1} and 20 cm, respectively. Incorporating PEG, they improved hydrophilicity along with the formation of a highly porous interconnected structure. HUVEC were adhered and proliferated on the blend scaffolds extensively with the least coagulation possibility [85]. This group also worked on poly(ethylene glycol methacrylate) (PEGMA) blended with PU for the same weight ratios and application. The PU–PEGMA blend was reported as a blood-compatible hybrid scaffold for small-diameter vessel substitute. It also indicated strong mechanical strength and hydrophilicity as well as excellent biocompatibility for HUVEC [84]. According to another research, two blends of PU–PEG and PU–phosphatidylcholine (PC) were developed to assess their potential as a substitute for small-diameter vascular graft. PU–PEG and PU–PC were separately electrospun either random or aligned by applying 23 kV, 0.01 mL h^{-1}, 15 cm and 22 kV, 0.01 mL h^{-1}, 15 cm, respectively. The resultant mechanical properties changed considerably in PU–PC scaffolds. Both hybrids showed greater hydrophilicity and cytocompatibility with a small amount of hemolysis, provided higher attachment and proliferation in HUVECs [86].

Another approach was based on the nanofibrous fabrication of thermoplastic polyurethane (TPU) with PGS using electrospinning. The parameters were set at 18 kV, 0.5 mL h^{-1} and 20 cm for vocal fold tissue engineering. The final sheet presented a resemblance of the vocal fold lamina propria ECM along with greater cellular proliferation and extension in comparison with neat TPU [87].

As it is obvious, almost all the studies in cardiovascular tissue engineering achieved good blood compatibility together with better mechanical properties. It can be concluded that blending with synthetic polymers could hinder the direct effect of PU on platelet adhesion and promoted hemocompatibility. Table 4 represents a compendium application of PU–synthetic polymer electrospun mats in tissue engineering along with the reported details on fiber diameter, pore size and hemolytic index.

PLA-based electrospun scaffolds

PLA is a synthetic linear polymer, with three stereochemical forms: PLLA, poly(D-lactic acid) (PDLA) and poly(D, L-lactide) (PDLLA). PLA electrospun composites have been employed in bone, cartilage, blood vessels, nerves, liver, kidney stromal and drug delivery applications [88]. However, poor mechanical properties and hydrophilicity could weaken cell adhesion and differentiation [89]. Furthermore, its electrospun fibers have small diameters with a less porous structure, which may limit cell infiltration and migration into the construct [85, 86]. Studies have illustrated that the incorporation of other polymers could have an impact on the entire properties and bolster them to a large extent [90]. Here, we will elaborate on the PLA-based scaffolds, blended with synthetic and natural polymers.

Blend of PLA and its derivatives with natural polymers

As said before, the drawbacks of singly using PLA, PLLA or PDLA in electrospun scaffolds make scientists take blending with natural polymers into consideration, creating a more tunable matrix suitable for target tissue engineering. In the perspective of determining PLA–gelatin structural properties along with biocompatibility, Hoveizi et al. [91] prepared the scaffolds, dissolving 7:3 and 3:7 weight ratios in HFIP, followed by electrospinning at 10–16 kV voltage and 0.5 mL h^{-1} feed rate. The study findings demonstrated that gelatin-modified PLA scaffolds enhanced fibroblasts viability to a great extent. Also, the scaffold with 7:3 weight ratio appeared appropriate for ECM mimicking. On top of that, histological studies confirmed the neo-tissue formation including dermis and epidermis after 21 days of culturing [91]. Recently, the blend of PLA–

Table 4 A brief overlook of studies regarding PU-based electrospun blends with synthetic polymers

Scaffold	Application	Fiber diameter (FD), hemolytic index (HI) and pore size (PS)				References
		Composition	FD (μm)	HI (%)	PS (μm)	
PU–Synthetic polymer blend electrospun scaffolds						
PU–PCL–poloxamer(inner layer)/PU–PCL(outer layer)	Vascular TE		< 1	NA	NA	[80]
PU–PLLA/modified by heparin		PU-PLLA PU-PLLA-hep	NA	0.45 ± 0.03 0.28 ± 0.44–0.78 ± 0.02	NA	[83]
PU–PEG		PU PU-PEG	1.02 ± 0.18 0.39 ± 0.10	> 4 1.23	NA	[85]
PU–PEGMA			0.54 ± 0.07–0.62 ± 0.11	NA	NA	[84]
PU–PEG/PU–PC		PU PU-PEG PU-PC	0.54 ± 0.18–0.57 ± 0.14 0.68 ± 0.12–0.75 ± 0.19 0.44 ± 0.14–0.64 ± 0.16	~ 2 to 2.5 0.48 ± 0.5 NA	NA	[86]
TPU–PGS	Vocal fold TE	TPU TPU-PGS	~ 0.22 to 0.95 ~ 0.25 to 1.06	NA	NA	[87]
PU–PLGA/loaded with Rap	Drug delivery and Cardiac TE	NA				[82]

NA not available

hydrosoluble collagen with multilevel construct was investigated using 5, 10 and 15% collagen. Setting voltage, feed rate and distance at 15 kV, 0.5 mL h^{-1} and 20 cm, respectively, Kang et al. [92] designed structures using patterned grids to fabricate multilevel structures. According to observations, mechanical properties (with 15 wt% amount of collagen, tensile strength rose to 8.1 ± 0.7 MPa) and hydrophilicity (72.4 degree) improved. Also, great extent of L929 fibroblasts infiltration into the scaffolds resulted in more cell adhesion and proliferation. In vivo studies, on the other hand, showed desirable biocompatibility as well as enhanced repair behavior [92].

Cellulose nanocrystals (CNC) was blended with PLA (10:1, 10:2, 10:4) to highlight the effect of CNC on PLA osteogenic and biocompatible potential. Electrospinning was performed to produce blend nanocomposites, set at 16 kV and 15 cm. Due to the strong CNC–polymeric chain interactions, mechanical features boosted to a great degree. Furthermore, an increase in mineralization was observed as well as higher cell extension, proliferation and adhesion on the scaffolds. Also, osteogenic genomic markers were expressed for the most part, correlated with human bone marrow-derived mesenchymal stem cells (BMSCs), which witnessed the high osteogenic ability. Moreover, in vivo findings showed osteoinductivity in nanocomposite mats [93]. In another research, Huan et al. [94] fabricated random and aligned PLA–CNC blend scaffolds, employing 0, 5, 10, 15 and 20 wt% CNC in 10 wt% PLA solution, via electrospinning. Nanofibrous microstructure surface altered from smooth to nanoporous by changing in CNC values, regardless of its random or aligned structure. Furthermore, organized aligned mats resulted from PLA tension transmission to CNC. Tensile properties also increased in the case of aligned PLA–CNC to the maximum tension of 15.3 MPa for composites with 5 wt% CNC, while a rise in CNC percentage decreased mechanical properties, caused by less crystallinity [94]. Zadeh et al. [95] discussed the combination of PLA/polyphenol extracted from date palm fruit (DP) with weight ratios of 100:0, 99:1, 95:5 and 90:10, produced by electrospinning (setting at 13 kV, 0.8–1.5 mL h^{-1} and 15 cm). They indicated that the addition of DP rose the scaffold hydrophilicity, while decreased the tensile strength and Young's modulus due to increased polyphenol concentration. However, cellular behavior was promoted when DP was involved. Findings of the Scratch test proved that 20% of scratched sites diminished, which could be related to 3T3 cell migration to improve the healing process [95]. Gao et al. [31], in another study, subjected the PLA–Tussah silk fibroin (TSF) blend to electrospinning to investigate the effect of mineralization on biological and mechanical properties, applying 18 kV, 0.9 mL h^{-1} and 17.5 cm to the electrospinning apparatus. According to the results, only 10 wt% of TSF led to hydroxyapatite nucleation onto the mat surface, when soaked in simulated body fluid (SBF). Furthermore, compressive mechanical properties enhanced considerably by 32.8- and threefold for mineralized membranes, which was more than those of non-mineralized. This mineralization also can be associated with larger cell adhesion and proliferation along with better mesenchymal stem cell differentiation to osteoblasts [96].

As mentioned beforehand, one of the most applicable PLA derivatives is PLLA, a biodegradable and biocompatible polymer, whose degradation by-product is lactic acid, a substance that could be involved in biochemical cycles [99]. The electrospun nanofibers of PLLA have been extensively utilized in diverse tissues, including bone, nerve, skin and dental tissue engineering and also drug delivery [97]. Having a large hydrophobic surface area and strong mechanical properties, PLLA scaffolds, however, are not comparable to natural biomaterials because of their hydrocarbon backbone with no specific site to interact with ECM components [94, 95, 98]. Therefore, the blend of PLLA with different natural polymers has been investigated to control the biological properties. Zhao et al. [100] carried out an investigation to obtain a blend double-layer wound repair dressing, employing PLLA–SS (4:1, 2:1, 1:1 ratios) loaded with 0.2, 0.5 and 1% nitrofurazone (NFZ). They fabricated the blends under electrospinning conditions of 18 kV voltage, 1 mL h^{-1} feed rate and 15 cm working distance. PLLA–SS/NFZ was considered as the first layer and PLLA/NFZ as the second. In vivo wound healing indicated a more reduced wound size for double-layer blend, approximately 97%, compared to commercial dressings, 84%, after 12 days [100]. This could be because of the gradual dissolution of SS, leaving larger space for cells to migrate and proliferate [101]. Overall, the fabricated mats seemed antibacterial, biologically non-toxic and biocompatible [100]. Recently, PLLA/Cs-*g*-PCL electrospun

blend was produced in weight ratios of 8:2, 6:4, 4:6 and 2:8 to make chitosan electrospinning much more convenient. The device was adjusted at 20 kV, 0.8 mL h^{-1} and 15 cm. The obtained results represented an abated fiber diameter accompanied by Cs-*g*-PCL addition. Although the mechanical properties declined in nanocomposite scaffolds, they showed more values than the pure polymer. In vitro investigation indicated promoted cell adhesion and proliferation with wide dispersion in the blend [102]. In another report, Fiqrianti et al. [103] electrospun PLLA with chitosan and collagen in different compositions to mimic the shape of vascular grafts (Fig. 7): sample A: PLLA, sample B: PLLA–collagen–chitosan 0.5%, sample C: PLLA–collagen–chitosan 0.6%. The electrospinning was performed under 15 kV, 0.5 mL h^{-1} and 12 cm conditions. In vitro assessment demonstrated enhanced cell viability along with hemocompatible properties, with a hemolytic index of 1.04%. Furthermore, the tensile strength reached 2.13 by the incorporation of chitosan and collagen. The most suitable properties for vascular conduit application were accrued to nanocomposite with 10% PLLA, 0.5% chitosan and 1% collagen [103]. Li et al. [104] prepared blend scaffolds composed of PLLA–gelatin and PLLA–chitosan by applying 10–13 kV voltage and 15–20 cm needle–collector distance. The results interestingly confirmed a 2-h attachment of WI-38 fibroblast cells in blend scaffolds, while only 15% of the cells could attach to pure PLLA. Growth and proliferation also improved in the presence of natural polymers [104].

Three-dimensional constructs consisted of PLLA–gelatin blend with different gelatin compositions, which were fabricated in random and aligned orientation via electrospinning. The parameters of electrospinning were set at 13 kV, 0.4 mL h^{-1} and 10 cm. Higher viability and proliferation were observed in HUVECs and SMCs with different quantity of gelatin. To put it differently, aligned fibers could provide a helpful environment for cells to successfully elongate in the direction of fibers [105]. Another study focused on the employment of aniline pentamer–graft–gelatin (AP-*g*-GA) in a PLLA matrix at different weight ratios of 1:10, 3:10 and 5:10. The final blends were then subjected to electrospinning, applying 1.5 kV, 30–40 μL min^{-1} and 24 cm. The results illustrated that electroactivity, thermal stability and

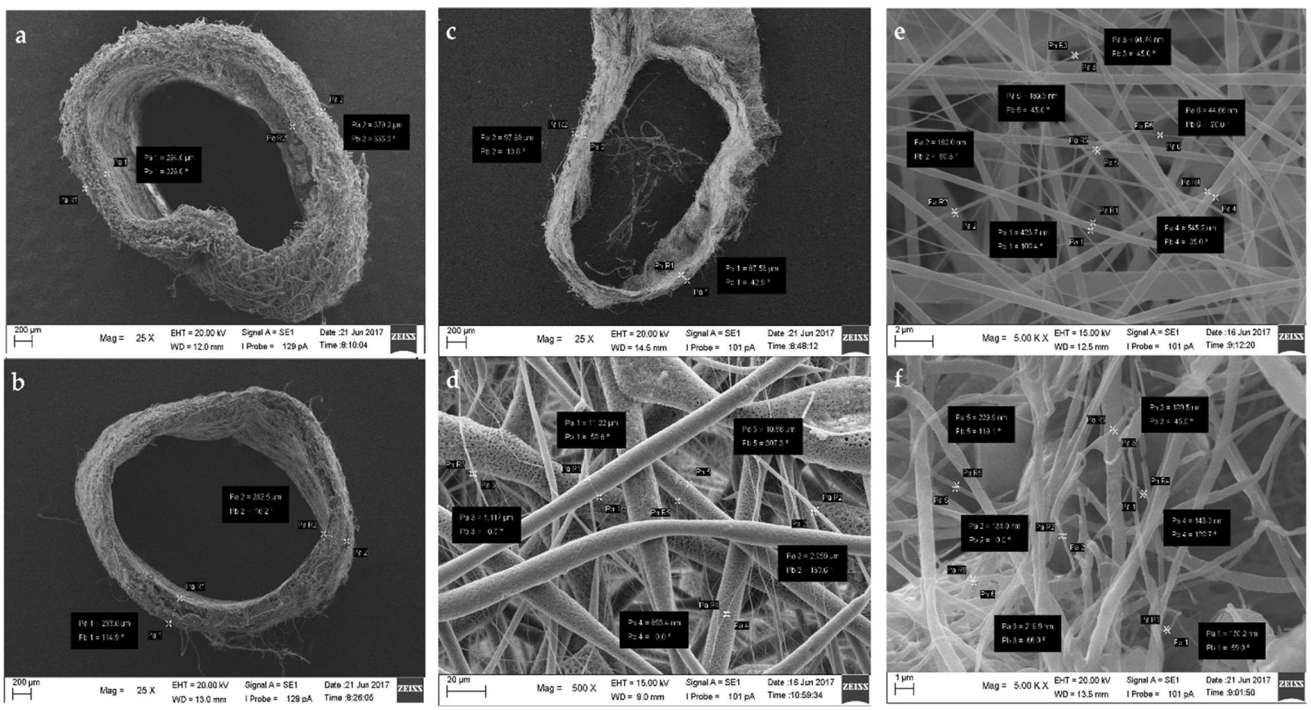


Figure 7 Cross section (25 × magnification) of **a** Sample A; **b** Sample B; **c** Sample C. Nanofiber diameters of **d** Sample A (500 × magnification); € Sample B; **f** Sample C (5000 × magnification), Pa is the nanofiber diameter, Pb is the inclination of the measuring line. Adapted with permission from reference [103]. Copyright 2018, MDPI, Journal of Functional Biomaterials.

biodegradability improved by the addition of AP-*g*-GA. Culturing pre-osteoblastic MC3T3-E1 cells on the nanocomposites, Liu et al. [106] could lead the cells orientation to be aligned along with the direction of fibers, quite more than neat PLLA. To put it differently, applied electrical signals had the potential to promote cell differentiation to an osteoblastic morphology [106]. Zhao et al. [107] conducted a project based on the absorption of plasmid DNA onto the surface of PLLA–collagen electrospun scaffolds to transfer the recombinant human bone morphogenetic protein-2 (rhBMP-2) for its potential in osteogenesis stimulation. The study findings represented that either mRNA or protein of rhBMP-2 was expressed highly, along with gene-induced ectopic bone formation [107]. Intending to evaluate the PLLA–collagen blend as a potential release system, Salehi et al. [108] developed a bilayer scaffold by encapsulating aloe vera gel in chitosan as the outer layer of the blend, for skin dressings in burn injuries. They electrospun PLLA–collagen at 18 kV and 1 mL h^{-1} condition. The results revealed that although the porosity declined, other properties improved including mouse fibroblasts attachment and proliferation [108].

These studies have opened an avenue for taking advantage of PLA and its derivatives in combination with natural polymers to mimic the bio-environment of subjected tissue. To review the whole PLA and PLLA electrospun blends with natural materials, Table 5 is presented, describing their application and fiber diameter of the final products.

Blend of PLA and its derivatives with synthetic polymers

Being introduced as a product of agricultural crops fermentation, PLA-based materials have rapid degradation, poor mechanical properties and thermal performance; thus, it is strongly suggested to make blending with other synthetic polymers to bolster the noted characteristics and studies have been conducted to assess the results. Reviewing recent studies, Bertuoli et al. [109] made biocompatible nanofibrous scaffolds via either uniaxial or coaxial (core–shell) electrospinning, using PLA–PAni and PLA/PEG/PAni5% for the former and PLA/PAni (core) and PLA/PEG (shell) for the latter. PLA/PAni solutions were prepared by adding 2.5–10 wt% PAni to PLA, and PLA/PEG weight ratios were 0.7:0.3 and 0.9:0.1 in composition. The voltage of 15–20 kV and distance of 25 cm were applied for both electrospinning, while the feed rate differed as 5 mL h^{-1} and 1.2 mL h^{-1} for uniaxial and coaxial, respectively. The results revealed that the incorporation of PEG in uniaxial fibers could increase cell mortality, correlated with its rapid dissolution in cell medium and release of PAni, while covering PAni in a core–shell system would show better biocompatibility [109]. In order to discuss the properties of a potential scaffold for skin tissue engineering, PLA–PEO (3:1) electrospun membranes were studied, using 1 wt% cellulose nanofibers (CNF) as the reinforcement phase. To this aim, 15 kV voltage, 1.19 mL h^{-1} flow rate and 10 cm needle–collector distance were fixed for the electrospinning device. Ghafari et al. [110] reported extremely boosted mechanical properties (500% toughness, 400% tensile strength and 350% stiffness), along with higher water uptake compared with PLA–PEO blend [110]. In the frame of a study based on the effect of electrospinning parameters on fibers diameter, Herrero herrero et al. [111] evaluated PLA–PCL electrospun mats. They showed that solvent ratio and voltage had a great influence on fibers diameter, which is important when it comes to producing scaffolds with especial diameter values. As regards BSA delivery, it was confirmed that blend scaffolds with micron-sized fibers would be efficient for BSA release [111].

Based on a report by Perumal et al. [112], a wound dressing composed of PLA–hyperbranched polyglycerol (HPG), with the addition of curcumin (CUR) as an antibacterial natural agent, was investigated. Using the electrospinning method, they set the device at 13–15 kV, 500 μL h^{-1} and 12 cm. The findings showed a promoted hydrophilicity along with good drug absorption behavior, also boosted cell proliferation and growth associated with higher adhesion in comparison with PLA–CUR. The scratch test, besides, confirmed good cell migration in the scratch area, within 3 days of implanting PLA–HPG–CUR blend membrane [112]. The combination of PLA–poly(3-hydroxybutyrate) (PHB) reinforced by 1 and 5 wt% of CNC was electrospun using 10.7 and 10.8 kV, 1 mL h^{-1} and 14 cm. CNC could enhance thermal and mechanical resistance in blend membranes. According to the results, nanocomposite scaffolds with 1 wt% of CNC performed better properties than that of 5 wt% [113].

Jiang et al. [114] produced a skin-engineered substitute using PLLA blended with TN-grafted PCL with the presence of Pluronic F-108 (PF108), at weight

Table 5 A concise overview of electrospun PLA-based polymeric blends with natural polymers

Scaffold	Application	Fiber diameter (FD)		References
		Composition	FD (μm)	
PLA and its derivatives–natural polymer blend electrospun scaffolds				
PLA–gelatin	Skin TE	PLA	~ 0.65	[91]
		PLA-Gel	~ 0.25 to 0.35	
PLLA/Cs-*g*-PCL		PLLA	0.82 ± 0.28	[102]
		PLLA/CS-g-PCL	0.46 ± 0.22–0.76 ± 0.24	
PLLA–chitosan		~ 0.20		[104]
PLLA–gelatin				
PLLA–collagen		PLLA-Col	0.68 ± 0.04	[108]
PLA–collagen	TE	NA		[92]
PLA–CNC		NA		[94]
PLA–CNC	Bone TE	PLA	~ 0.33	[93]
		PLA-CNC	~ 0.19 to 0.14	
PLA–TSF		PLA	~ 1.02	[96]
		PLA-TSF	~ 0.51	
PLLA/AP-*g*-GA		PLLA	~ 0.9	[106]
		Blend	~ 0.2 to 0.35	
PLLA–collagen		NA		[107]
PLA–polyphenol	Wound healing	PLA	~ 1.8	[95]
		PLA-DP10	~ 0.5	
PLLA–SS/loaded by NFZ		PLLA-SS/NFZ	0.41 ± 0.01–1.09 ± 0.03	[100]
PLLA–chitosan–collagen	Vascular TE	PLLA	0.13 ± 0.20	[103]
		PLLA-Col-CS	0.08 ± 0.24–0.13 ± 0.22	
PLLA–gelatin		PLLA-Gel	0.10- 0.50	[105]

NA not available

ratios of 90:10, 85:15 and 80:20. They directed electrospinning through an applied voltage of 8 kV, a flow rate of 0.2 mL min^{-1} and a distance of 15–20 cm. The membranes with 15 wt% of TN-grafted PCL showed higher and better tensile strength and elongation at break. Although this combination dropped the hydrophilicity, it increased sharply again after the addition of 1 wt% PF108 [114]. A bilayer PLLA-segmented polyurethane (SPEU) was studied to imitate the outer and inner layers of vascular grafts. Employing electrospinning at 13 kV, 0.5 and 1 mL h^{-1} and 15 cm, Montini Ballarin et al. [115] fabricated the blends at 50:50 and 90:10 ratios for the inner and outer layer, respectively. The physical, thermal and surface properties of electrospun blends were improved. The blend nanocomposites also presented faster hydrolytic degradation due to lower crystallinity [115]. Aiming to study the effect of PLLA–poly(vinyl alcohol) (PVA) electrospun membrane on differentiation potential of ADSCs to pancreatic cells, Ojaghi et al. [116] provided documents that cells cultured on the blend membranes could respond to various glucose concentrations and secreted different amounts of insulin. From the genetic point of view, the cells had the potential of expressing tissue-specific biomarkers, when they were cultivated on PLLA–PVA scaffolds [116]. Another research was conducted with an objective of chondrogenic differentiation of induced pluripotent stem cells (iPSCs) on PLLA–PVA electrospun scaffolds. The scaffolds were prepared under 23 kV, 1 mL h^{-1} and 18 cm circumstances. The genetical assessment showed an increment in collagen type I and X and also aggrecan expression on the blend nanocomposite. This blend could as a result provide a large capacity for chondrogenic differentiation [117]. In another report, the combination of PLLA–poly(3hydroxybutyrate-*co*-3hydroxyvalerate) (PHBV) was electrospun at 10:0, 8:2, 7:3, 6:4 and 0:10 weight ratios in room temperature. Wagner et al. [118] showed that the higher the PLLA content presents, the more porous structure would it make. Therefore,

the blends with 8:2 and 7:3 ratios resulted in the best and non-bead constructs with enhanced mechanical and thermal properties [118]. To determine the shape memory potential of the scaffolds for bone tissue engineering, a similar study was conducted on PLLA–PHBV blends. Wang et al. [119] prepared the blends in mass ratios of 10:0, 9:1, 8:2, 7:3, 6:4 and 0:10 and then electrospun under 15–17 kV, 2 mL h^{-1} and 18 cm circumstances. The incorporation of PHBV up to 30% led to an increment in Young's modulus. The findings revealed that the 7:3 formulation was the most desirable composition for osteogenic differentiation of BMSCs associated with the effect of osteoinductive factors and excellent shape memory properties. In fact, the PLLA–PHBV (7:3) was able to induce osteogenesis in BMSCs, regardless of the osteoinductive condition [119]. Poly(L-lactic acid)-*co*-poly(pentadecalactone) (PPDL) was blended with PLLA in a different study, producing PLLA–PPDL electrospun nanocomposites for nerve tissue engineering. The fabricated blend represented a larger fiber diameter than pure PLLA. Also, the surface nanotopography increased and together with higher fiber diameter led to neurite outgrowth on the nanocomposite scaffold [120]. Research on the PLLA–poly(ethylene glycol dimethacrylate) (PEGDMA) blends as vascular stent coating was carried out to investigate re-endothelialization improvement. Boodagh et al. [121] fabricated the blends at 1:1, 1:2 and 1:4 compositions via electrospinning. The PEGDMA/PLLA nanocomposite with 1:1 ratio could mitigate the platelet and SMCs attachment, but ameliorated stem cell secretion factors that are associated with endothelial proliferation and growth [121].

In a study on PDLA, an isomer of PLLA, its blend with PAni was produced at 83:17, 80:20 and 75:25 ratios by electrospinning method to investigate its conductive potential. According to the results, the current of 5 mA could only pass through the 75:25 ratio. Cultivation of rat SMCs showed the potential of outgrowth and proliferation accompanied by simultaneous scaffold degradation over time. Conductivity and cellular compatibility introduced PDLA–PAni as a desirable blend for nerve conduit substitute [122].

PLLA-*co*-PCL known as P(LLA-CL) has been employed in various tissue engineering applications, due to its excellent mechanical characteristics and tunable degradation rates [123]. However, synthetic polymers and their copolymers might show hydrophobic features, which is not favorable for cell proliferation and attachment [124]. A study by Kijenska et al. [125] reported an electrospun blend, based on P(LLA-CL), by adding collagen I and collagen III in different compositions (P(LLA-CL)–collagen III; 90:10, P(LLA-CL)–collagen I/collagen III; 75:15:10). The voltage of 12 kV, a feed rate of 1 mL h^{-1} and a working distance of 11 cm were all applied to an electrospinning apparatus. They calculated the tensile strength for P(LLA-CL)–collagen I/collagen III about 11.59 ± 1.68 MPa, along with the average fiber diameters of 253 ± 102 nm. They also illustrated that cell attachment and proliferation surged by 22% compared with the neat copolymer, as a result of neurofilament protein expression induced by the concurrent impact of two kinds of collagen. Scaffolds with collagen III showed more extended cells, whereas C17.2 cells proliferation was much higher on membranes with both collagen compared with others. The research findings also confirmed that P(LLA-CL)–collagen I/collagen III could resemble the nerve ECM, and it may present good qualities for nerve regeneration [125]. Blend mats composed of poly[(L-lactide)-*co*-(D, L-lactide)] (PLDLLA)/poly(acrylic acid) (PAAc) were prepared in a different study via electrospinning, at 20 kV, 0.5 mL h^{-1} and 15 cm. The results confirmed that an increment in PAAc extent led to an enhancement in hydrophilicity and degradation rate. Additionally, in vitro culture of SNL 76/7 fibroblast cells on the scaffold with 10 wt% PAAc brought about non-toxic and biocompatible features suited for tissue engineering applications [126].

All in all, the combined effect of PLA-based materials with synthetic substances will promote the final product's physical, mechanical and even biological behavior in contact with cells and make it balanced. Table 6 provides an overview of the researches on PLA-based polymeric blends concerning their intended tissue.

PLGA-based electrospun scaffolds

PLGA copolymer is made of two kinds of saturated poly(α-hydroxy esters), PLA and poly(glycolic acid) (PGA), with combined attributes. This copolymer can be degraded through de-esterification, and the degradation by-products easily may be removed from the body by especial pathways [127]. As regards tissue regeneration applications, PLGA has been widely used in scaffolds and drug delivery systems,

Table 6 An overview of electrospun PLA-based polymeric blends with synthetic polymers

Scaffold	Application	Fiber diameter (FD)		References
		Composition	FD (μm)	
PLA and its derivatives–synthetic polymer blend electrospun scaffolds				
PLA–PAni	Cardiac TE	PLA/PAni	3.47 ± 0.20–5.20 ± 0.08	[109]
PLA–PEG–PAni				
PLA–PAni (core)/PLA–PEG (shell)		PLA/PEG//PLA/PAni	1.01 ± 0.06–1.77 ± 0.02	
PLLA–PU	Vascular TE	PLLA	0.51 ± 0.16	[115]
		Adventitia layer	0.32 ± 0.11	
		Media layer	0.57 ± 0.16	
PLLA–PEGDMA		NA		[121]
PLA–PEO/CNF	Skin TE	NA		[110]
PLLA–TN-*g*-PCL/PF108		PLLA	1.66 ± 0.15	[114]
		PLLA/TN-*g*-PCL	1.38 ± 0.20–1.45 ± 0.17	
PLA–HPG/CUR	Wound dressing	PLA-Cur	~ 0.51	[112]
		PLA-HPG-Cur	~ 0.60	
PLA–PCL/BSA	TE	PLA-PCL	~ 0.8 to 1.8	[111]
PLA–PHB/CNC		PLA-PHB	0.30 ± 0.05	[113]
		PLA-PHB-ATBC	0.35 ± 0.05	
		PLA-PHB-ATBC-CNC	0.25 ± 0.05–0.30 ± 0.02	
PLLA–PHBV		PLLA	0.99 ± 0.32	[118]
		PLLA-PHBV	1.21 ± 0.41–1.51 ± 0.36	
PLLA–PPDL		PLLA	1.75 ± 0.74	[120]
		PLLA-PPDL	2.20 ± 0.80	
P(LLA-CL)/collagen I and III		P(LLA-CL)-Col I, III	0.25 ± 0.10	[125]
PDLA–PAni		PDLA-PAni	0.94 ± 0.65–1.19 ± 1.04	[122]
PLDLLA–PAAc		NA		[126]
PLLA–PVA	Pancreatic TE	NA		[116]
PLLA–PVA	Cartilage TE	NA		[117]
PLLA–PHBV	Bone TE	PLLA	2.96 ± 0.46	[119]
		PLLA-PHBV	2.16 ± 0.73	

NA not available

in combination with other polymers, which will be discussed as follows.

Blend of PLGA with natural and synthetic polymers

Although the ratio of PGA and PLA in this polymer can be adjusted to create better properties, measures should be taken to present more adaptable features of PLGA-based nanofibrous scaffolds to have a range of possible properties, from osteoinductivity in the field of bone regeneration to desirable functionalities in skin tissue applications.

Aiming to highlight the effect of PLGA–gelatin on wound healing and skin regeneration, Vazquez et al. [128] electrospun (10 kV, 0.3 mL h^{-1} and 20 cm) different weight ratios, 9:1, 7:3 and 5:5, of the blend to evaluate physical and biological properties. The results showed that scaffolds with 7:3 and 5:5 ratios increased swelling, hydrophilicity and degradability rate compared to 9:1 nanocomposites. This could be efficient for wound therapy with exudates. Higher gelatin incorporation made the nanocomposite stiffer, with larger elastic moduli in dry conditions. However, it decreased dramatically up to 91% in wet conditions. Scaffolds with 7:3 ratio had the most cell proliferation with fortified viability when MSCs were cultured [128]. Having said that, however, this blend was also studied for the cardiac patch to protect the myocardium after infarction, using electrospinning at 14 kV, 1 mL h^{-1} and 12 cm working distance. Gelatin incorporation attenuated the tensile strength and elongation at breakdown to 1.6 MPa and 70%,

respectively, though it was still desirable for cardiac tissue. The results put into evidence that biocompatibility increased due to an integrated cardiomyocyte extension as well as enhanced cytoskeletal functional proteins expression [129]. In order to develop a substitute for vascular tissue, tri-component electrospun blend was studied composed of PLGA/gelatin/elastin (PGE) at different weight ratios of 1:2:1, 2:2:1, 3:2:1, 1:3:1, 2:3:1, 3:3:1, 1:4:1, 2:4:1 and 3:4:1. The study findings revealed that the composition with 3:2:1 ratio acquired the smallest fiber diameter, as well as the greatest Young's modulus of 770 ± 131 kPa and tensile strength of 130 ± 7 kPa. From the biological point of view, PGE scaffolds with all values could support the attachment and metabolism of human endothelial cells (EC) and bovine aortic SMCs. Interestingly, the blend nanocomposites could provide an environment in which the cells can separately be distributed onto and within the scaffolds to form different organ cell populations [130]. The co-electrospinning of PLGA and chitosan/PVA solutions were carried out at a voltage of 15 kV, feeding rate of 0.2 mL h^{-1} and distance of 10 cm. Duan et al.[131] observed a sharp reduction in tensile strength and Young's modulus before cross-linking, while these variables escalated to 3.8 ± 0.4 and 106.2 ± 32.9 MPa, respectively, right after glutaraldehyde cross-linking. Additionally, fibroblasts could adhere and proliferate to a great extent on the scaffold, showing a good perspective for skin regeneration [131].

In the case of bone tissue engineering, PLGA–collagen blends at 80:20, 65:35 and 50:50 compositions were electrospun applying 8–10 kV voltage, 0.1–0.3 mL h^{-1} feed rate and 15 cm needle–screen distance. In both wet and dry conditions, the scaffolds showed an increment in hydrophilicity, contrary to declined mechanical properties. Moreover, elastic modulus multiplied to 83 MPa for wet and cross-linked PLGA–collagen scaffold with 80:20 ratio. It is also associated with a less impact on tensile strength, which seemed to be an appropriate stroma for bone regeneration. However, in other compositions, collagen dissolution resulted in poor structural properties [132]. An approach involving the use of PLGA–SF–collagen in nerve regeneration was conducted with different compositions of 50:25:25 and 30:35:35. Wang et al. [133] fixed electrospinning parameters at 10 kV, 4 mL h^{-1} and 10 cm. They reported an increase in hydrophilicity and porosity in both blends, although scaffolds with 30:35:35 composition showed more adhered Schwann cells. However, the assay findings elucidated that 50:25:25 was likely the best fit composition for nerve tissue engineering [133]. Evrova et al. [134] introduced PLGA–PEO blend with 100:0, 70:30, 50:50, 30:70 weight ratios and electrospun by applying 11 kV voltage, 0.7 mL h^{-1} flow rate and 15 cm needle–screen distance. With the perspective of using in muscle tissue engineering, the present blend scaffold (mostly 50:50 content) supported C2C12 myoblasts growth and proliferation, which led to a more myotube formation and spontaneous alignment in comparison with neat PLGA. Notably, the more the PEO was added, the more hydrophilic the scaffold became, which in turn decreased Young's modulus but made an increment in tensile strength [134]. Another research was held assessing the combination of PLGA/PCL; fabricated via electrospinning, by applying a voltage of 25 kV, a flow rate of 0.5 mL h^{-1} and needle–screen distance of 20 cm. Hiep et al. [135] observed that biocompatibility for the most part was obtained in the scaffolds with higher PLGA extent, whereas the 20:80 composition showed the best mechanical features [135]. Intending to highlight the effect of heparin immobilization on vascular mats for absorbable suture application, the PLGA–PEI blend was electrospun. Heparin loading on PLGA–PEI surface together with its release profile suggested that an increment in PEI concentration led to quantitatively higher heparin loaded values along with the more sustained release than pure PLGA, caused by PEI–heparin electrostatic interactions. Furthermore, the strength of final mats with heparin increased and was suited to analogous synthetic sutures [136].

To summarize, the blending will establish the situation in which features and functionalities would be adjusted to provide better interactions with biological compounds and the environment. Table 7 provides data concerning the application of PLGA polymeric blends in tissue engineering.

PHB-based electrospun scaffolds

Polyhydroxyalkanoates (PHA) are a family of synthetic polymers that are produced by a group of bacteria, as carbon and energy sources. Being under food constraints, including nitrogen, phosphorous or oxygen, for the most part, PHAs are synthesized within the cytoplasm of microorganisms [94, 95]. The

Table 7 An overview of the antecede studies based on PLGA-based polymeric blends

Scaffold	Application	References
PLGA–natural polymer blend electrospun scaffold		
PLGA–gelatin	Wound healing	[128]
PLGA–chitosan/PVA	Skin TE	[131]
PLGA–gelatin	Cardiac patch	[129]
PLGA–gelatin–elastin	Vascular TE	[130]
PLGA–collagen	Bone TE	[132]
PLGA–SF–collagen	Nerve TE	[133]
PLGA–synthetic polymer blend electrospun scaffold		
PLGA–PEO	Muscle TE	[134]
PLGA–PCL	TE	[135]
PLGA–PEI/heparin	Wound healing	[136]

chemical structure of PHA largely depends on its chain length and is categorized into short-chain length (scl-PHA), medium-chain length (mcl-PHA) and long-chain length (lcl-PHA). Speaking of their features, scl-PHA shows poor mechanical properties and fragility, while mcl-PHA has improved mechanical characteristics, therefore higher elongation at break [137].

PHA are linear aliphatic polyesters composed of monomeric units of R-hydroxyalkanoic acids [138]. There are several kinds of PHA monomers with a variety of mechanical and biological properties. PHB, a PHA important derivate, is known as a hydrophobic synthetic biopolymer with a natural resource, which also presents biodegradability and biocompatibility. PHB also has been introduced as scl-PHA, a prolific polymer composed of 3-hydroxybutanoic acid units. It can be used, either alone or in blend with other polymers, in tissue engineering through extrusion, molding, electrospinning, etc. [139]. Many studies have been carried out, regarding PHB combination with natural and synthetic polymers to enhance its biological and also mechanical properties [140, 141]. The upcoming section provides information regarding PHB-based polymeric blends, fabricated by electrospinning for a broad range of tissue engineering applications.

Blend of PHB-based materials with natural polymers

Despite the advantages of PHB and its copolymers, however, some constraints may be accompanied, because of PHB insufficient cellular affinity. Therefore, a blend with natural polymers is proposed. To this end, the copolymer of poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate) (P(3HB-*co*-4HB)) was blended with corn protein, Zein, with different compositions of 80:20, 60:40, 40:60 and 20:80. Zhijiang et al. [142] used electrospinning at 26 kV, 0.2 mL h^{-1} and 20 cm to prepare the nanocomposites. Increasing the quantity of P(3HB-*co*-4HB) from 20 to 80% led to an improvement in tensile strength, double in number and promotion in elongation at break by 400%. Furthermore, nanofibrous scaffolds had interconnected pores, which provided excellent biocompatibility and good extension when it came to NIH3T3 fibroblast cells and MG-63 osteoblast cell cultivation [142].

PHB–organic soluble chitosan (O-chitosan) blend was fabricated in different weight ratios via electrospinning at 20 kV, 20 mL min^{-1} and 15 cm. Ma et al. [143] provided data on cytocompatibility, so that when mouse fibroblasts (L929) were cultured, it could enhance the proliferation, attachment and growth in great measure [143]. A fundamental study was also performed by Sadeghi et al. [144] based on the combination of PHB-chitosan scaffolds. They used 5, 10, 15 and 20 wt% chitosan and 7–10 wt% PHB, to create scaffolds with higher hydrophilicity and biodegradability for cartilage tissue engineering. The electrospinning method was employed with the voltage of 9, 13 kV, feeding rate of 0.5 mL h^{-1} and needle–collector distance of 7, 14 cm. The addition of chitosan could render the blends with reduced water contact angle and declination in tensile strength by about a third. Cultivated chondrocytes, on the other hand, revealed a perfect attachment and well-dispersed pattern on the scaffold surface. Furthermore, 15 wt% and 20 wt% of chitosan were introduced as the best-fitted ratios in this blend [144]. To obtain an improved architecture for nerve tissue regeneration, a blend consisting of PHB–chitosan (85:15, 80:20) was electrospun by the former research group, both random and aligned, applying 21 kV, 1 mL h^{-1} and 20 cm. The results put into evidence that by adding chitosan, surface porosity ameliorated, along with a rise in hydrophilicity. Being degraded in vitro, the blends illustrated slower degradation in aligned scaffolds than random ones. Besides, rat neuronal-like cells (B65 cell line) could better disperse along with the direction of fibers in aligned scaffolds than random [145]. Karbasi et al. [146] developed novel nano–microstructure scaffolds, via electrospinning of

PHB–chitosan on a silk sheet. They adjusted the parameters at 210 kV, 10 mL h^{-1} and 15 cm, to prepare a construct suited mechanically for cartilage tissue engineering. The tensile strength and elongation at break rocketed, unaccompanied by any impact on neither fiber diameter nor porosity [146].

Naderi et al. [147] developed PHB–keratin nanocomposite scaffolds to use as an alternative for bone tissue. According to the data, 5–15 wt% of keratin was added to PHB and the final solution was electrospun under 13 kV, 0.016 mL min^{-1} and 25 cm. The mechanical and biological evaluations represented that adding up to 10 wt% keratin caused a slight increase in tensile strength and the degradation rate. MG-63 cells also proliferated vastly, along with enhanced viability and ALP production. It seemed that 10 wt% keratin in this blend could be considered as the best performance composition for bone application [147].

In a late study, PHB was blended with collagen type I at weight ratios of 100:0, 70:30 and 50:50 and subsequently electrospun at 12–16 kV, 0.03 mL min^{-1} and 12–24 cm. Collagen presence brought about an accelerated hydrolytic degradation rate and thus promoted hydrophilicity. Although 70:30 composition showed the least stiffness, 50:50 demonstrated a Young's modulus as high as 100:0, which may be due to the locking collagen chains down by cross-linking. Furthermore, PHB–collagen was biocompatible enough to keep cells alive and represented higher proliferation and attachment [148]. In a very recent study, PHB (2, 5, 8%w/v) and gelatin (10, 20, 30%w/v) were blended and then electrospun under different conditions (15, 20, 25 kV, 0.5, 1, 1.5 mL h^{-1} and 15 cm) to form micro-and nanofibers for diabetic wound treatment. The results of in vitro fibroblasts cultivation showed high proliferation and attachment. Also, in vivo results indicated an accelerated diabetic wound healing, when gelatin was incorporated [141]. PHB–gelatin blend was studied in another research for skin tissue engineering, with weight ratios of 85:15, 70:30 and 50:50, employing electrospinning followed by cross-linking. The mentioned blend could support the proliferation and growth of HDFs and keratinocytes. Also, promoted degradation rate and tensile properties were observed associated with gelatin incorporation [149].

An approach was investigated on electrospun PHBV–gelatin nanocomposites, developed as an alternative for human amniotic membrane (HAM) in ocular tissue regeneration. For comparison purposes, Limbal stem cells (LSC) were cultured on either blend nanocomposite or HAM. The results showed a perfect dispersion and proliferation on the blend nanocomposite substrates, as so on the HAM, maintaining the corneal stem cells phenotype. Also, no considerable change was noticed in gene expression in PHBV–gelatin substrates compared to HAM [150]. Studying electrospun PHBV–gelatin, Kuppan et al. [151] also illustrated higher tensile strength and Young's modulus compared with neat PHBV. Interestingly, human esophageal epithelial cells (HEEpiC) on pure PHBV showed better stability and proliferation than the blend. Having said that, however, ECM and phenotype-specified proteins were expressed in PHBV–gelatin blend to a larger extent more than neat PHBV [151].

Nanofibrous membranes were made using electrospun PHB–CA blends at 100:0, 90:10, 80:20, 70:30, 60:40 and 0:100 weight ratios. The parameters for electrospinning were set at 24–30 kV, 0.2 mL h^{-1} and 25 cm. The resulted scaffolds represented an increase in tensile strength, yield strength and elongation at break, from 3.3 ± 0.35 MPa to 5.05 ± 0.52 Mpa, 2.8 ± 0.26 Mpa to 4.6 ± 0.82 Mpa and $8 \pm 0.77\%$ to $17.6 \pm 1.24\%$, respectively. Additionally, these scaffolds were biocompatible and bioactive with high hydrophilicity, which could be suggested for wound healing [152].

An investigation was performed based on the combination of PHB or PHBV with κ-carrageenan (κ-CG), an anionic polysaccharide, via electrospinning (set at 20 kV, 3–3.5 mL h^{-1} and 15 cm) to study its osteogenic effect. The survey findings revealed that in PHBV/κ-CG blend, κ-CG was positioned on the fibers' surface to a great extent, than PHB/κ-CG in which the polysaccharide content was mainly dispersed thoroughly throughout the blend. Also, NIH3T3 cells could grow with a large density on the blend mats. On the other hand, SaOS-2 cells showed an osteogenic potential within a fortnight. Furthermore, PHBV/κ-CG increased the bioactivity and osteogenicity through the high capability of hydroxyapatite formation along with hydroxyapatite nanoparticles deposition [153].

As the reports reveal, the intrinsic features of natural polymers including gelatin [139, 147–149], collagen [148], chitosan [141–144], etc., will have a significant effect on the PHB-based materials in an electrospun stroma to emerge improved

Table 8 A brief overview on PHB-based electrospun polymeric blends with natural polymers

Scaffold	Application	Fiber diameter (FD), elastic modulus (EM) and tensile strength (TS)				References
		Composition	FD (μm)	EM (MPa)	TS (MPa)	
PHB–natural polymer blend electrospun scaffold						
P(3HB-*co*-4HB)-Zein	Bone TE	P(3HB-*co*-4HB)	0.35 ± 0.16	NA	7.74 ± 1.13	[142]
		P(3HB-*co*-4HB)/Zein	0.21 ± 0.08–0.31 ± 0.15		7.09 ± 0.85	
PHB–keratin		PHB	0.35 ± 0.04	100.42 ± 10.00	2.29 ± 0.23	[147]
		PHB-10% K	0.76 ± 0.01	77.93 ± 6.00	2.99 ± 0.07	
PHB–κ-CG		PHB	2.00 ± 0.50	NA	NA	[153]
		PHBV	2.00 ± 0.50			
		PHB- κ-CG	1.80 ± 0.50			
		PHBV-κ-CG	1.60 ± 0.50			
PHB–O-chitosan	Skin TE	NA				[143]
PHB–gelatin		PHB85-Gel15	0.44 ± 0.01	~ 4.3	~ 6.63	[149]
		PHB50:Gel50	0.23 ± 0.07	~ 4.2	~ 14.56	
PHB–gelatin	Wound healing	Wet	NA	1.2–5.01	2.49–6.54	[141]
		Dry		4.2–6.2	6.63–14.56	
PHB–CA		PHB	0.67 ± 0.22	867.50 ± 201.20	7.44 ± 0.58	[152]
		PHB90-CA10	0.16 ± 0.05–0.45 ± 0.12	854.20 ± 187.60	7.86 ± 0.67	
PHB–chitosan	Cartilage TE	PHB 9%	0.98 ± 0.11	74.45 ± 2.88	87.00 ± 3.02	[144]
		PHB-CS 15%	1.08 ± 0.17	57.80 ± 4.02	49.06 ± 3.12	
PHB–chitosan/SF		PHB-SF	0.98 ± 0.22	NA	NA	[146]
		PHB-CS-SF	0.58 ± 0.07			
PHB–chitosan	Nerve TE	PHB-CS 15% (random)	0.77 ± 0.28	NA	NA	[145]
		PHB-CS 20% (random)	0.86 ± 0.29			
		PHB-CS 15% (aligned)	0.74 ± 0.15			
		PHB-CS 20% (aligned)	0.87 ± 0.18			
PHB–collagen	TE	PHB	0.59 ± 0.01	258.30 ± 7.90	7.70 ± 0.30	[148]
		PHB50-Col50	0.80 ± 0.01–0.86 ± 0.00	225.40 ± 42.50	7.70 ± 1.40	
PHBV–gelatin	Ocular TE	NA				[150]
PHB/PHB–pectin	Retinal TE	PHB	0.49 ± 0.09	0.15 ± 0.00	4.72 ± 0.71	[154]
		PHB-Pec	0.33 ± 0.04–0.42 ± 0.07	0.08 ± 0.01–0.23 ± 0.01	3.03 ± 0.04–7.80 ± 0.16	
PHBV–gelatin	Esophagus TE	PHBV	0.58 ± 0.09	84.53 ± 2.75	1.31 ± 0.05	[151]
		PHBV-Gel	0.43 ± 0.06	236.9 ± 26.37	2.37 ± 0.18	
		PHBV-PEO	1.3 ± 0.2–2.6 ± 0.6	30 ± 4–50 ± 10	0.4 ± 0.2–0.8 ± 0.2	

NA not available

biocompatibility. Table 8 renders a succinct description of these studies, along with a report of elastic modulus, tensile strength and fiber diameter in each case.

Blend of PHB-based materials with synthetic polymers

Many attempts have been made to create a perfect suit for nerve or skin tissue engineering, through the application of PHB-based substances. Thus, the inclusion of synthetic polymers or their copolymers with natural ones has been proceeded to obtain the required properties, such as improved electrical signal conduction.

In a research conducted by Asran et al. [155], PHB was blended with PVA at 95:5, 90:10, 70:30 and 50:50 mass ratios, followed by electrospinning at 16–20 kV, 100 μL h^{-1} and 15 cm, regarding skin regeneration. PVA addition gave a rise to hydrolytic degradation of PHB. Cell culture results yielded higher growth and proliferation of HaCaT and HDFs on neat PHB than PHB–PVA blend. To put it differently, only 5 wt% of PVA in the PHB matrix could hinder HaCaT cells' growth, excluding HDFs. Nevertheless, HaCaT cells' growth surged on PHB–PVA (50:50) blends, while inhibited HDFs to grow [155]. As regards developing a substitute for wound dressing, research was held on the PHB–PF-108 fabrication, with 0.5 and 1 wt% of PF-108, via electrospinning (20 kV, 2 mL h^{-1} and 20 cm). In this blend, doxycycline antibiotic was also encapsulated within the blend to determine the antibacterial impact. Bhattacharjee et al. [156] demonstrated a rise in water uptake and hydrophilicity properties. Although the tensile modulus decreased due to the presence of PF-108, the blend showed resistance to break to a large extent. Furthermore, this system improved blood clotting rate compared to neat PHB, along with supporting in vitro fibroblasts adherence and antibacterial features [156]. Regarding nerve tissue engineering, Daranarong et al. [157] investigated poly[(L-lactide)-*co*-(ε-caprolactone)] (PLCL) copolymer in a blend with PHB, at different compositions (100:0, 75:25, 50:50, 25:75, 0:100), using electrospinning at 15 kV, 4 mL h^{-1} and 15 cm. The findings revealed a reduction in tensile strength, from 5.8 to 1 MPa, but 4–6 times improvement in elongation at break. Moreover, an increment in PLCL extent in PHB–PLCL nanocomposites led to better adhesion and proliferation of olfactory ensheathing cells (OECs), as well as quite more mitochondrial activity. They also promoted the cell cycle progression, which led to necrosis alleviation [157].

Cheng et al. [158] investigated the physical and mechanical properties of poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) (PHBHHx)/PDLLA at mass ratios of 100:0, 75:25, 50:50, 25:75 and 0:100 using electrospinning. They adjusted the voltage of 18 kV, feeding rate of 0.5–1 mL $^{-1}$ and 25–28 cm at the electrospinning apparatus. The researchers illustrated an increase in tensile strength and modulus with the addition of more PDLLA quantity in the blend [158].

Recent research was carried out on double-layer scaffolds composed of PHB/chitosan as the first layer with 90:10, 85:15 and 80:20 weight ratios, electrospun on polyvinylidene fluoride (PVDF) as the second layer. The layers were electrospun by applying different electrospinning parameters: 18 kV, 7 mL h^{-1} and 15 cm for PVDF and 21 kV, 8 mL h^{-1} and 15 cm for PHB/chitosan. The latter scaffold was also loaded with 1, 2, 3% gentamycin drug. The addition of PVDF values rose mechanical strength significantly. Moreover, the degradation rate augmented, associated with a raise in chitosan amounts. The drug release also showed a sustained pattern [159]. Another research was directed based upon the combination of PHB with PHBV copolymer in the presence of collagen type I (45:45:10), to figure out the effect of this composition on myelin regeneration in nerve tissue engineering. Fabricating random and aligned nanofibers, Masaeli et al. [160] used the electrospinning strategy at 16 kV, 1.5 mL min^{-1} and 15 cm. Schwann cells could orient in the direction of aligned fibers, while their morphology on random nanocomposite fibers was multi-directed (Fig. 8). The incorporation of collagen within the PHB–PHBV blend increased Glial cell line-derived neurotrophic factor (GDNF) gene expression as well as nerve growth factor (NGF) secretion, also bringing about good cell differentiation [160].

Pectin, a natural polysaccharide, was copolymerized with PHB, and the obtained copolymer was mixed with PHB to prepare PHB/PHB–pectin mixture at various ratios of 98:2, 95:5, 90:10 and 80:20. The final solutions were then electrospun at 10 kV, 1 mL h^{-1} and 7.5 cm. Chan et al. [154] observed that the nanocomposite could reduce the fiber diameter and provided a more hydrophilic stroma. Moreover, elongation at break boosted with the presence of

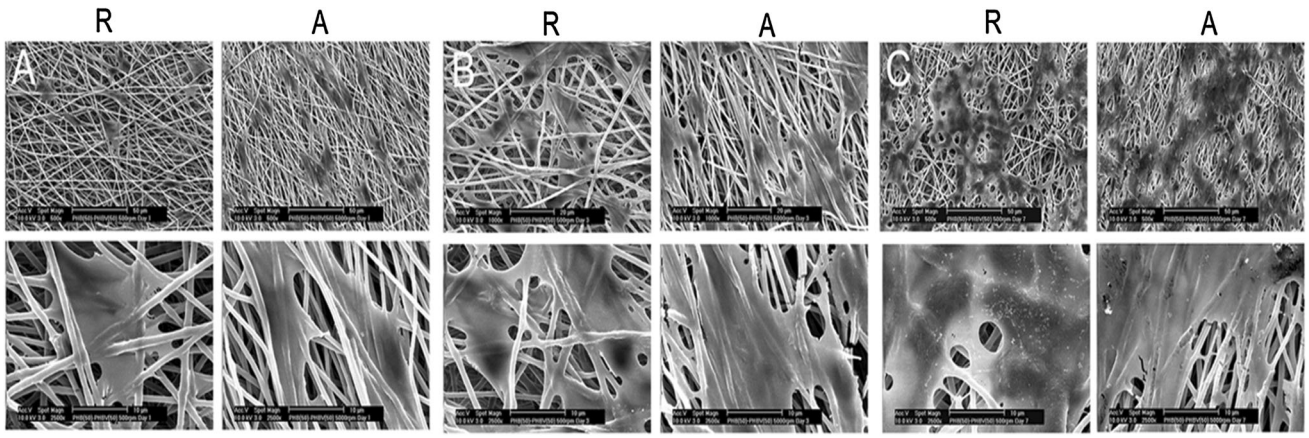


Figure 8 SEM images of SCs on PHB(50)/PHBV(50) random (R) and aligned (A) nanofibers. **a** 1 day, **b** 3 days, and **c** 7 days after cell seeding. Scale bars represent 50 μm for top and 10 μm for button pictures, respectively. Adapted with permission from reference [160]. Copyright 2011, Public Library of Science, PLoS One.

pectin. Human retinal pigmented epithelium (ARPE-19) showed bigger viability and compatibility on nanofibers with 90:10 and 80:20 ratios, along with a higher density of cellular population [154]. In a different study, polymeric blend of PLA–PHBV was electrospun in different ratios of 100:0, 80:20, 60:40, 50:50, 40:60 and 0:100, followed by dip-coating using poly(3,4-ethylenedioxythiophene)/poly(styrene sulfonate) (PEDOT/PSS). The study results indicated that the scaffold could support in vitro HDFs culture, showing great viability and biocompatibility. Having said that, however, coated nanocomposite with 50:50 composition provided a far more beadless uniform fibers distribution, as well as higher hydrophilicity and cytocompatibility compared to its non-coated counterparts [161]. In another research, Hassan et al. [162] produced PHBV–PLGA nanocomposites at weight ratios of 25:75, 50:50 and 75:25, employing electrospinning at 20 kV, 3 mL h^{-1} and 10 cm. Their investigation resulted in perfect fibroblasts viability and proliferation along with high fibers uniformity, especially at 50:50 ratio, despite the hydrophobic nature of the blend [162]. The blends of PHBV and PEO were also prepared at different weight ratios of 100:0, 80:20, 70:30, 50:50, 0:100, through applying 12 kV, 0.4 mL h^{-1} and 12 cm at the electrospinning device. The results demonstrated well-dispersed uniformity in random fibers with mechanical improvement and acceptable porosity [163].

Overall, the last decade studies showed that blending PHB-based materials with other synthetic polymers will produce features adjusted to the target tissue, especially in terms of fabricating aligned electrospun fibers for nerve regeneration and enhanced porous structure for wound healing [142]. An overview is provided in Table 9, regarding PHB-based polymeric blends with synthetic polymers based upon their application and also detailed information on fiber diameter and mechanical properties.

PVA-based electrospun scaffolds

PVA is a widely known synthetic, biodegradable, biocompatible and non-toxic polymer. PVA scaffolds indeed tend to be known to have large mechanical stability, including great tensile strength and elongation at break, which gives rise to endure enormous strains, both in cardiac, muscle and bone tissue engineering, and also its perfect alignment in nerve tissue regeneration [162, 163]. To put it differently, nanofibrous electrospun PVA-based scaffolds may have been represented an extended variety of physical and biological properties, meeting the entire requirements for almost every tissue [164]. Being less electrospinnable, however, it is suggested that PVA should be blended with other natural and synthetic polymers to overcome this confinement [165].

Blend of PVA with natural polymers

Excellent hydrophilicity, structural stability and biocompatibility make PVA one of the synthetic polymers that can be blended with natural substances with weak features to boost the final properties as well as PVA's ability to be electrospun [167]. To this

Table 9 A brief overview on PHB-based electrospun polymeric blends incorporating synthetic polymers

Scaffold	Application	Fiber diameter (FD), elastic modulus (EM) and tensile strength (TS)				References
		Composition	FD (μm)	EM (MPa)	TS (MPa)	
PHB–Synthetic polymer blend electrospun scaffold						
PHB–PVA	Skin TE	PHB	~ 0.68	NA	NA	[155]
		PHB-PVA	~ 0.61			
PHB–PF-108			1.4–1.7	100–200	4.2–4.5	[156]
PHBV–PLA		PHBV	1.90 ± 0.2	NA	NA	[161]
		PHBV-PLA	0.48 ± 0.2			
PHB/chitosan–PVDF/gentamycin		PVDF	0.20 ± 0.05	~ 6.60	~ 0.57	[159]
		PHB-CS-PVDF	0.10 ± 0.02–0.14 ± 0.04	4.97–5.31	0.47–0.50	
PHB–PLCL	Nerve TE	PHB	0.65–0.7	NA	~ 1 to 1.25	[157]
		PHB-PLCL	0.20–0.25		~ 1 to 1.25	
PHB/PHBV-Col I		PHB (random)	NA	67.8 ± 23.5	1.7 ± 0.30	[160]
		PHBV (random)		254.0 ± 24.5	4.9 ± 0.5	
		PHB-PHBV-Col (random)		59.3 ± 11.3	3.4 ± 0.3	
		PHB-PHBV-Col (aligned)		45.4 ± 4.7	1.3 ± 0.1	
PHBHHx–PDLLA	TE	$PHBHH_X$ (random)	NA	110 ± 10	6 ± 0.9	[158]
		$PHBHH_X$ (aligned)	NA	1200 ± 200	113 ± 20	
		$PHBHH_X$-PDLLA (random)	0.5–0.6	130 ± 20–150 ± 20	6.5 ± 0.5–8.3 ± 0.5	
		$PHBHH_X$-PDLLA (aligned)	0.2–0.4	500 ± 100–700 ± 100	20 ± 3–33 ± 5	
PHBV–PLGA			0.41 ± 0.12–0.67 ± 0.14	NA	NA	[162]
PHBV–PEO		PHBV	2.8 ± 0.1	80 ± 15	1.8 ± 0.2	[163]
		PHBV-PEO	1.3 ± 0.2–2.6 ± 0.6	30 ± 4–50 ± 10	0.4 ± 0.2–0.8 ± 0.2	

NA not available

aim, a series of studies have been performed, which will be elaborated on here.

A nanofibrous mat composed of PVA–alginate sulfate (ALG-S) was reported for determining its capability in support of chondrogenic differentiation from BMSCs. Irani et al. [168] prepared PVA/ALG-S blends, adding 10, 20 and 30 wt% of ALG-S to PVA. After that, they directed electrospinning under applying a voltage of 22 kV, feeding rate of 1.1 mL h^{-1} and needle–screen distance of 25 cm. The researchers showed that PVA/ALG-S with 30 wt% sulfated ALG could improve the biocompatibility, extension and attachment of the cells, as well as boosting their differentiation to chondrocyte-like cells. In addition, collagen type II expression was enhanced due to the ALG-S presence, which could be a cause behind chondrogenic differentiation [168]. A similar study was also carried out on the same blend to investigate the effect of sulfation on delivering heparin-like growth factor and transforming growth factor-beta 1 (TGF-β1). With considering 30 kV, 18 mL h^{-1} and 12 cm, PVA/ALG-S blend was electrospun. Sulfation of ALG could lead to much more affinity sites for hydrogel. The findings revealed that the binding of TGF-β1 to sulfate groups of alginate could promote the growth factor delivery system. Moreover, the biocompatibility of the final scaffold was confirmed through the in vitro cultivation of hMSCs [167].

Another investigation was based on developing a wound dressing made of PVA-SS loaded with tigecycline (TC-SS/PVA) to study its antibacterial activity. Nanocomposite scaffolds were prepared using electrospinning at 15 kV and 20 cm. The resultant membranes presented improved mechanical and physical properties. Studying drug release, the researchers showed as large as 75% tigecycline release from the TC-SS/PVA within only 10 min. Besides, the encapsulated tigecycline in fibers indicated antibacterial performance against *E. coli* and *Bacillus subtilis* (*B. subtilis*). In vivo transplantation results also elicited faster wound healing [169]. In a current effort, a similar blend was evaluated for wound healing application with different sources of SS. Employing the electrospinning method, Gilotra et al. [170] fabricated PVA–SS blend at 8:1 ratio, applying 12–15 kV, 1 mL h^{-1} and 10 cm. The blends represented an extended morphology for cells, in contrast with pure PVA with round cells. On the other hand, SS incorporation could create antioxidant properties, with no inhibition of cell viability over the oxidative stress period. In vitro and in vivo assessments also provided data on biocompatibility without inflammation reactions [170].

Chahal et al. [171] developed a nanostructured blend scaffold for bone tissue engineering via electrospinning, using hydroxyethyl cellulose (HEC) and PVA at weight ratios of 60:40, 50:50, 30:70 and 10:90. They demonstrated that with different ratios of HEC, very disparate mechanical results were obtained, so that the maximum elastic modulus and tensile strength for 60:40 HEC-PVA were reported, by 349 ± 69 MPa and 10.54 ± 1.2 MPa, respectively, while the least elastic modulus extent was for neat PVA, 188 ± 50 MPa, dropped significantly by half. The same was observed in cellular behavior, in which a higher percentage of HEC was accompanied by more extended and proliferated osteosarcoma cells on the scaffolds [171]. This research group also developed modified cellulose blended with PVA at 50:50 and 60:40 weight ratios, through electrospinning at 25 kV, 1 mL h^{-1} and 10 cm. They confirmed that from the physical and thermal point of view, this scaffold has the properties, which suit bone tissue [172]. In another study, Lee et al. [173] interrogated the mechanical properties of a single electrospun fiber consisted of PVA–cellulose nanowhiskers blend. The Young's modulus of electrospun neat PVA fibers was reported 2.1 GPa, while for the blend with 20 wt% nanowhiskers was 7.6 GPa, which increased linearly with an increment in nanowhiskers [173]. PVA–CA electrospinning was also discussed at 100:0, 90:10, 80:20 and 70:30 weight ratios, altering different electrospinning parameters, to reach a uniform and beadless fibrous construct. The final parameters for well-structured fibers were reported 29 kV, 0.8 mL h^{-1} and 17 cm, for voltage, feeding rate and needle-screen distance, respectively [174].

Electrospun chondroitin sulfate (CS)–PVA–collagen (1:1.5:1.5, 1:2:1 and 1:1:2) and collagen–PVA–HA (1:1.5:1.5 and 1:2:1) blends were obtained, followed by non-toxic cross-linking. Mechanical properties improved in either wet or dry conditions, with higher elongation at break in the wet state. The resulted scaffolds indicated pH-sensitive behavior, which might be employed for drug delivery intention. The mats also improved human embryonic kidney cells (HEK293) proliferation and attachment [175]. Sundaramurthi et al. [176] added chitosan to PVA solution to prepare 2:8, 3:7, 4:6, 5:5 and 9:1 solutions and

electrospun the blend as alternatives for skin tissue dressing. Culturing fibroblasts 3T3 illustrated large growth and proliferation. In vivo assessment of chitosan–PVA blend was associated with the usage of growth factor R-Spondin 1, on open wounds in rats. It resulted in wound closure within a fortnight by 98.6%. In fact, R-Spondin 1 incorporation led to a boosted anti-inflammatory behavior in the wound healing procedure. Moreover, enzyme activity including catalase and super-oxidase dismutase was promoted in rats treated with growth factors [176]. In another study, carboxyethyl chitosan (CECS) was blended with PVA to investigate its effect on fibroblasts (L929) in skin regeneration. Zhou et al. [177] prepared pre-electrospun CECS–PVA blends at weight ratios of 100:0, 80:20, 60:40, 50:50, 30:70, 20:80, 10:90 and 0:100, followed by electrospinning at 25 kV and 12 cm. They demonstrated that these mats provided great biocompatibility on L929 cells with improved adherence and proliferation [177]. The effect of chitosan in blend scaffold of PVA–chitosan was investigated; different ratios of 50:50, 60:40, 70:30, 75:25, 80:20, 85:15 and 100:0 were prepared with subsequent electrospinning, at 15 and 20 kV, 0.5 mL h^{-1} and 12 cm. Comparing two voltages, fibers produced at 15 kV were more uniform and without bead structure. The mechanical assay proved that the incorporation of chitosan made the scaffold far more brittle and less ductile. PVA-rich scaffolds, however, showed maximum ductility [178]. Besides, PVA–chitosan (80:20) blend was combined with the TCH drug to study the drug release and delivery profile. The electrospinning factors were set at 15 kV, 0.1–0.35 mL h^{-1} and 10 cm. A burst release was found in the first 2 h, which could act as an antibacterial factor on either gram-positive or gram-negative bacteria. Furthermore, the scratch test showed excellent cell compatibility and viability [179]. In another approach, chitosan nano-emulsion (CSNe) was employed as a reinforcement phase of PVA (low and high molecular weight) in different compositions. The blend solution was electrospun at 15 kV, 0.025 mL min^{-1} and 15 cm. Membranes with low molecular weight PVA produced higher tensile strength and vice versa for high molecular weight PVA. Furthermore, in vivo assay confirmed the greater influence of PVA–CSNe blend membrane on wound healing, even rather than its commercial counterparts [180].

On the other hand, PVA–chitosan (90:10) blend was used as the nerve matrix to support neural tissue regeneration. The electrospinning was performed under 20 kV, 0.6 mL h^{-1} and 15 cm conditions. Culturing PC12 nerve cells on the electrospun scaffolds, Alhosseini et al. [166] showed higher proliferation and viability on the PVA–chitosan matrix than pure

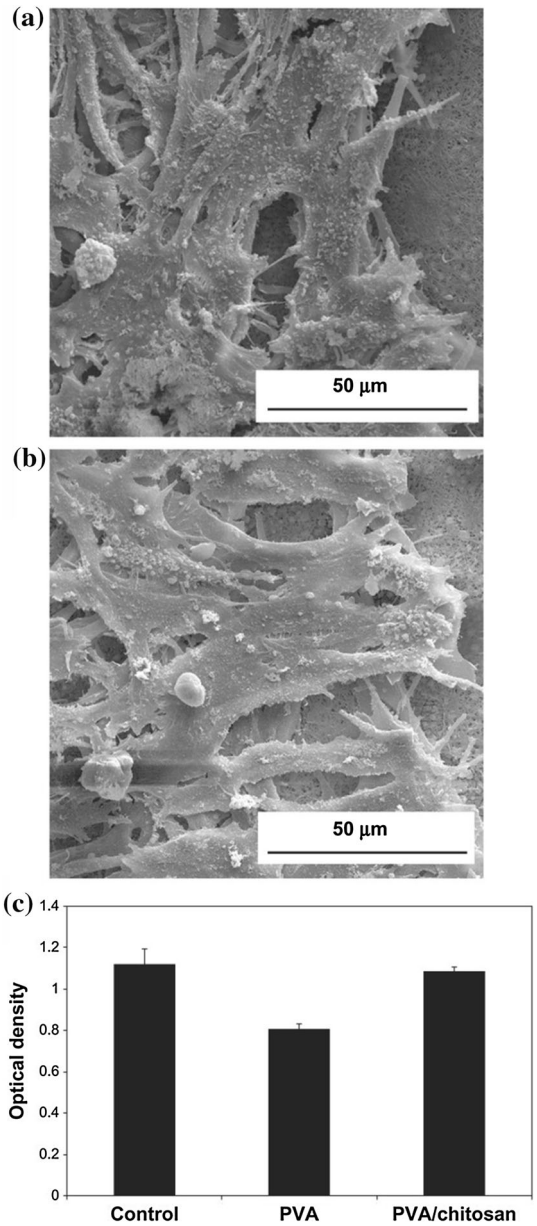


Figure 9 a and **b** Attachment of PC12 nerve cells into PVA/chitosan nanofibrous scaffolds; **c** MTT analysis of PVA and PVA/chitosan samples. PVA, polyvinyl alcohol; MTT, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. Adapted with permission from reference. Copyright 2012, DOVE Medical Press, International Journal of Nanomedicine.

PVA scaffold, in which the chitosan played as an accelerator to enhance the proliferation rate. Figure 9 shows the nerve cells' behavior onto the scaffold surface along with their viability [166]. A different study focused on the mixture of chitosan–hydroxybenzotriazole (CS-HOBt) in PVA matrix. Adding 2 wt% of CS–HOBt into 10 wt% of PVA at various ratios of 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80 and 10:90, the blends were electrospun at 15 kV voltage and 15 cm working distance. Charernsriwilaiwat et al. [181] figured out that a rise in CS–HOBt extent led to fiber diameter reduction. The blend, also, provided a non-toxic environment for human fibroblasts to proliferate and grow [181]. As regards wound dressing, PVA–chitosan solutions were prepared in 90:10 and 50:50 weight ratios, plus the addition of 5, 10 and 15 wt% starch. Then, they were electrospun employing parameters of 25 kV, 0.5 mL h^{-1} and 13 cm. This blend could provide a dump environment, in which it can also control the wound exudates. The resulted mechanical properties brought about a large capability of wound site protection against external factors over the treatment period. Moreover, the scaffolds were preponderantly antibacterial with cytocompatible properties, proved by scratch test findings [182]. Tri-component electrospun nanofibrous mats of PVA–chitosan–gelatin were developed in three different compositions (2:2:2, 3:3:3 and 2:2:4) for tissue engineering intention. The parameters for electrospinning were adjusted at 15–30 kV, 0.15–0.3 mL h^{-1} and 15 cm. The 2:2:4 weight ratio illustrated the most optimum values for fibers diameter. Moreover, cross-linked mats had better stability with good mechanical properties as well as excellent MSC growth and proliferation [183].

Having poor mechanical properties, collagen electrospun scaffolds could be analogous to cornea tissue, but may not bear up against suturing. To deal with the limitation, PVA–collagen blends containing 7% and 9% collagen solution were obtained and then were electrospun to both random and aligned fibers. Human corneal epithelial cells and keratinocytes cultivation showed promoted growth and proliferation in both forms of scaffolds. Scaffolds with 9% collagen represented as large tensile strength as the natural cornea, about 2.252 MPa and 3.581 MPa in random and aligned membranes, respectively [184]. Aiming to highlight the influence of both soy protein (SPI) and pH on mechanical properties and degradation behavior of PVA-based scaffolds, Cho et al. [185] fabricated PVA–SPI blends at 100:0, 85:15, 75:25, 65:35 and 50:50 mass ratios. According to the results, the higher the SPI quantity, the less the tensile strength was yielded. To put it another way, basic pH led to protein denaturation and resultant thinner fibers, which in turn caused extremely poorer tensile strength. However, the degradation rate could be controlled by altering SPI content as well as its dispersion within the PVA matrix to avoid its immediate digestion by microorganisms [185].

Generally speaking, the studies indicate that PVA with inherent strong physical and mechanical properties has gained approval as scaffolding support for tissue regeneration when accompanied with natural polymers. A brief overview is given in Table 10, regarding the application of PVA with natural substances.

Blend of PVA with synthetic polymers

Aiming to enhance mechanical and physical properties, PVA has been studied in blends with synthetic polymers including polyethersulfone (PES) [186], PEI [187], PVP [186–188], PU [191], PLLA [192] and PGS [193], which will be discussed in detail as follows.

Kashef-saberi et al. [186] employed platelet-rich plasma (PRP), as a prolific source of essential osteogenesis growth factors, in combination with PVA and co-electrospun with PES. The parameters of 20 kV, 0.2 mL h^{-1} and 22 cm were adjusted at the electrospinning device. ADSCs could differentiate into osteogenic cells in the presence of PRP. To put it differently, results from measuring ALP activity and calcium content confirmed the effectiveness of involving PRP. In fact, the findings revealed that 5% PRP in PVP–PES electrospun scaffolds directed to the most osteogenic differentiation [186]. Ultrathin fibers consisting of PVA–PEI, in another effort, were blended with PLA via co-electrospinning, adjusted at 10 kV, 0.1 mL h^{-1} and 10 cm. PVA incorporation in PVA–PEI combination triggered higher capacity of PEI of being electrospun. Also, the blend nanocomposite showed a more hydrophilic surface due to PEI presence [187]. From the physical aspects, PVA–PVP blended with 5 and 10% of chitosan was electrospun. Although the viscosity may be involved in fiber diameter, blends with more chitosan content caused a smaller diameter. Also, the combination of PVA–PVP was more hydrophilic than the chitosan-containing blend, as a result more biocompatible [188]. Another

Table 10 A summary of studies on PVA-based polymeric scaffolds in blend with natural polymers divided by the target tissue

Scaffold	Application	Fiber diameter (FD)		References
		Composition	FD (μm)	
PVA–natural polymer blend electrospun scaffold				
PVA–ALG-S	Cartilage TE	PVA	0.18 ± 0.00	[168]
		PVA-ALG-S	0.44 ± 0.00	
PVA–HEC	Bone TE	PVA	0.59 ± 0.02	[171]
		PVA/HEC60%	0.37 ± 0.03–0.52 ± 0.03	
PVA–cellulose		Blend	0.25–0.3	[172]
PVA–ALG-S/loaded with TGF-β1	TE	PVA	0.63 ± 0.05	[167]
		PVA-ALG	0.27 ± 0.05	
		PVA-ALG-S	0.23 ± 0.04	
PVA–cellulose nanowhiskers		PVA	0.29 ± 0.01	[173]
		Blend	0.22 ± 0.02	
PVA–CA		Blend	0.70 ± 0.17–0.92 ± 0.15	[174]
PVA–chitosan		PVA-CS at 15 kV	0.12 ± 0.04–0.18 ± 0.06	[178]
		PVA-CS at 20 kV	0.12 ± 0.08–0.18 ± 0.08	
PVA–chitosan/gelatin		Blend	~ 0.15	[183]
PVA–CS–HOBt		CS-HOBt-PVA	0.19 ± 0.05	[181]
PVA–SPI		PVA	~ 0.64	[185]
		PVA-SPI	~ 0.67 to 0.77	
PVA–collagen, PVA–collagen–HA	Kidney TE	PVA	0.02–0.15	[175]
		PVA-CG-HA	0.07–0.53	
PVA–chitosan/loaded by R-Spondin 1	Skin TE	PVA-CS	0.15 ± 0.01	[176]
PVA–CECE		Blend	0.13–0.45	[177]
PVA–chitosan/loaded by TCH	Wound healing	PVA	0.19 ± 0.03	[179]
		PVA-GA-CS	0.19 ± 0.04	
		PVA-GA-CS-TCH	0.30 ± 0.06	
PVA–CSNe		PVA	0.19–0.26	[180]
		PVA-CSNe	0.14–0.23	
PVA–chitosan–starch		Blend	0.30 ± 0.13–0.42 ± 0.13	[182]
PVA–SS/loaded by TC		SS-PVA	0.43 ± 0.02	[169]
		Drug-SS-PVA	0.35 ± 0.00	
PVA–SS		PVA	0.16 ± 0.05	[170]
		PVA-B. mori SS	0.16 ± 0.04	
		PVA-A. assama SS	0.13 ± 0.06	
PVA–chitosan	Nerve TE	PVA	~ 0.74	[166]
		PVA-CS	~ 0.22	
PVA–collagen	Cornea TE	PVA random	0.30 ± 0.03	[184]
		PVA aligned	0.20 ± 0.05	
		PVA-COL7% random	0.21 ± 0.14	
		PVA-COL7% aligned	0.18 ± 0.09	
		PVA-COL9% random	0.26 ± 0.19	
		PVA-COL9% aligned	0.16 ± 0.10	

approach was based upon PVA–PVP cross-linked nanocomposite blends prepared in 100:0, 90:10 and 75:25 compositions and electrospun at 12 kV, 2 mL h^{-1} and 15 cm. The addition of PVP led to an increment in hydrophilicity and continuous degradation. Shankhwar et al. [189] confirmed biocompatibility of the blend, by in vitro fibroblast L929 and HaCaT cultivation, presenting its ability to mimic the ECM for native skin. Besides, ciprofloxacin hydrochloride monohydrate (CHM) controlled

release was observed, which caused an inhibition zone against *S. aureus*, which provided a barrier for pathogen microbes [189]. PVA–PVP also was electrospun at 25:75, 50:50, 75:25 and 80:20 ratios. Membranes' biocompatibility was confirmed through fibroblasts NIH 3T3 attachment and proliferation [190].

Regarding the physical and mechanical assessment of the combination of PVA–waterborne polyurethane (WBPU), Yang et al. [191] prepared the blend at 10:0, 9:1, 7:3, 5:5, 3:7 and 1:9 weight ratios and then exposed to electrospinning. Tensile strength and thermal stability of nanofibers were affected by different WBPU compositions. The best ratios suggested to be optimum were 7:3 and 5:5 and, as a result, were responsible for higher elasticity and strength. Also, the blend membranes showed greater water uptake than pure PVA, which could be a perfect suit for wound dressings [191].

Nanofibrous membranes were fabricated from PVA–PLLA at 9:1 ratio via electrospinning apparatus, adjusted at 15 kV, 0.35 mL h^{-1} and 12 cm. Water uptake for neat PVA declined after the addition of PLLA. Cytocompatibility studies represented enhanced biocompatibility, hydrophilicity as well as cell attachment and proliferation in NIH 3T3 fibroblasts and fitted to tissue engineering applications. Moreover, CUR release from PVA–PLLA reaches out up to 80% within 4 days and showed a sustained release profile [192]. In an approach, Saudi et al. [193] worked on the effect of different lignin percentages (0, 1, 3, 5 wt%) on physical, mechanical and biological features of PVA–PGS blend in nerve regeneration. Lignin-containing blend solutions were electrospun applying 19 kV, 0.5 mL h^{-1} and 30 cm. The results showed that the greater the lignin percentages, the smaller the fiber diameter became and the higher was elastic modulus. Moreover, genes encountered in nerve tissue development were assessed and lignin incorporation indicated a significant influence on P12 nerve cell differentiation. However, 5 wt% lignin was known as the most effective content in nerve tissue engineering in PVA–PGS nanocomposites [193].

It is clear from the reports that regardless of the target tissue, synthetic polymers incorporation in PVA-based nanofibers may trigger major positive changes in the blend scaffolds. Developed approaches in PVA blending with synthetic polymers are summarized in Table 11, divided into the intended tissue engineering, along with the resultant fiber diameter, mostly reported in comparison with pure PVA.

PGS-based electrospun scaffolds

PGS may be introduced as a biocompatible, non-cytotoxic biopolymer and consisted of glycerol and sebacic acid, which has been extensively used in tissue engineering applications, basically due to its strong mechanical properties that resemble cardiac tissue. Nevertheless, its rapid degradation would be a drawback, and to tackle with, synthetic and natural polymers can be involved [194]. The following part of this review will discuss the different applications of PGS-based polymeric blends.

Blend of PGS with natural and synthetic polymers

Lack of capability of being electrospun, PGS seems to render better functionality in blend with natural and synthetic polymers. Having this in mind, many studies have been conducted to evaluate the effect of different polymers in blend with PGS.

Regarding analogizing the myocardium, PGS–gelatin nanofibrous blends were produced at ratios of 2:1, 1:2 and 0:1, via electrospinning set at 18 kV, 2 mL h^{-1} and 10 cm. The findings represented well-attached and aligned cardiac fibroblasts along with protein expression and increased cardiomyocyte contraction functions on the nanocomposite blends. To put it differently, nanofibers with 33 wt% of PGS directed much better simultaneous contractions in cardiomyocytes, associated with promoted alignment [195]. The evaluation of drug release from this blend also was conducted in another study. Shirazaki et al. [196] used PGS/gelatin (1:3) and ciprofloxacin (CIP) drug regarding skin dressing under electrospinning condition (18 kV, 0.5 mL h^{-1} and 12 cm). The results of the assay suggested a controlled release from the blend, which can be used for wound injury [196]. An approach focused on PGS–(PMMA-*co*-gelatin) at 75:25 and 50:50 weight ratios, employing 10 kV, 1 mL h^{-1} and 15 cm for the electrospinning process. The results were associated with great hydrophilicity and biocompatibility, due to PC12 rat cells cultured on the blend. Additionally, aligned and extended cellular phenotype on the mats represented differentiation from nerve stem cells, induced by PGS–PMMA/gelatin scaffold [197]. Another study was held by mixing Zein protein with PGS at 6:1, 3:1 and

Table 11 A summary of studies on PVA-based polymeric scaffolds blended with synthetic polymers divided by the target tissue

Scaffold	Application	Fiber diameter (FD)		References
		Composition	FD (μm)	
PVA–synthetic polymer blend electrospun scaffold				
PVA–PRP *co*-electrospun with PES	Bone TE	PVA	0.5 ± 0.18	[186]
		Blend	0.62 ± 0.18	
PVA–PEI *co*-electrospun with PLA	TE	PVA-PEI	0.22 ± 0.04	[187]
PVA–PVP–chitosan		PVA-PVP	~ 0.24	[188]
		PVA-PVP-5%CS	~ 0.16	
PVA–PVP		PVA	~ 0.09	[190]
		PVA-PVP	~ 0.21	
PVA–PLLA/CUR		PVA	0.05–0.30	[192]
		PVA-PLLA	0.03–0.70	
		PVA-PLLA/Cur	0.05–0.75	
PVA–PVP/CHM	Wound dressing	PVA	~ 0.10	[189]
		PVA-PVP	~ 0.08 to 0.10	
PVA–PU		~ 0.55		[191]
PVA–PGS/lignin	Nerve TE	PVA	0.94 ± 0.26	[193]
		PVA-PGS	0.53 ± 0.16	
		PVA-PGS-Lignin	0.37 ± 0.54	

1:1 weight ratios and electrospun by applying 20 kV, 0.3 mL h^{-1} and 15 cm to an electrospinning device. The extant PGS could increase the tensile strength up to 7 times and the elongation at break by fourfold, but with no significant alteration in elastic modulus. Cross-linking the fibers, Vogt et al. [198] showed that the blends could sustain the morphology when they are submerged within the aqueous media (Fig. 10), which may be commensurate to soft tissue regeneration [198]. To fabricate a nonwoven structure, PGS–

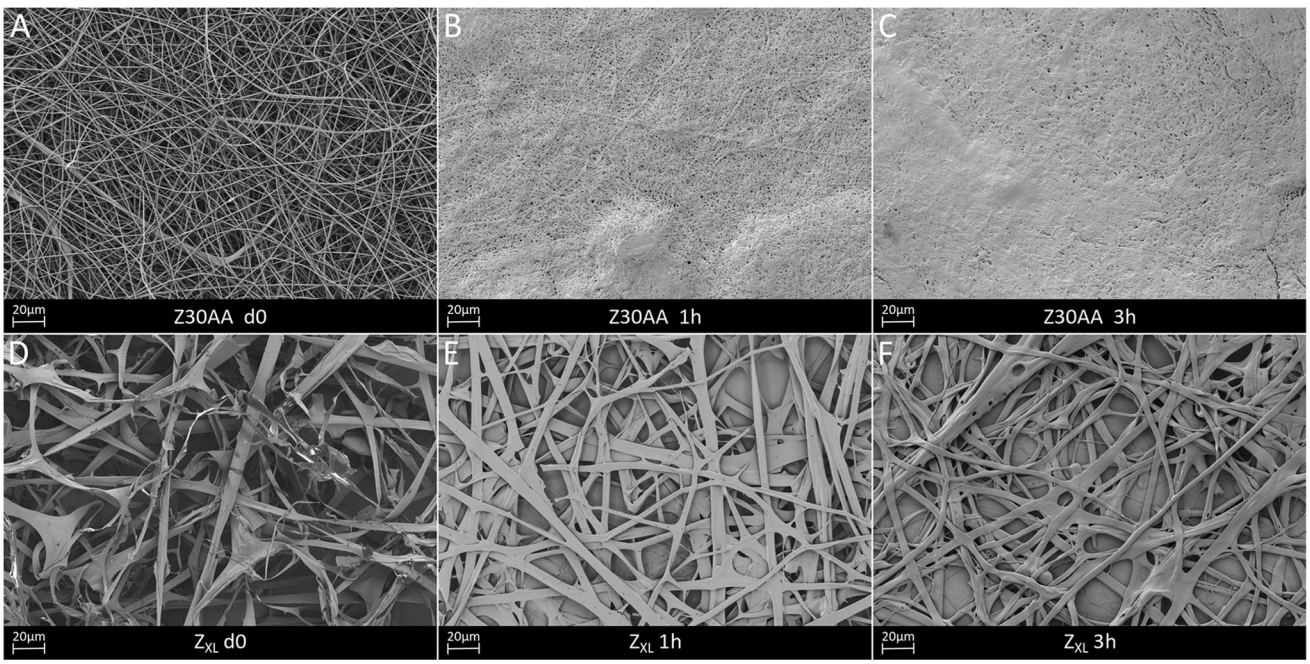


Figure 10 SEM micrographs of uncross-linked Z26E fiber mats (**a**–**c**) and EDC/NHS cross-linked ZXL fiber mats (**d**–**f**) before and after 1 and 3 h of PBS incubation. Adapted with permission from reference [198]. Copyright 2018, MDPI, Nanomaterials.

PLA blend was electrospun in different compositions of 75:25, 50:50, 25:75, 0:100 at 11 kV, 1.2 mL h^{-1} and 14 cm. Cross-linked PGS can provide excellent elasticity in nonwoven fibers [199].

The capability of electrospun nanofibers being affected by different solvents was evaluated on the PGS–PCL blend. The electrospinning parameters were also verified at the range of 10–18 kV, 15 or 25 cm and 0.2–1 mL h^{-1}. Among formic acid, formic acid/acetone, formic acid/acetic acid and chloroform/*N*,*N*-dimethylformamide (DMF), the latter was introduced as the best and the most biocompatible, beadless and non-toxic solvent [194]. Aiming to study the effect of in vitro degradation and ECM production on PGS–PCL (2:1) blend mechanical properties, Sant et al. [200] employed electrospinning apparatus (12.5 kV, 2 mL h^{-1}, 18 cm). As a result, hydrolytic degradation of PGS–PCL hybrid scaffolds became twice faster in number than neat PCL and a gradual decline in mechanical features was observed. From the biological point of view, culturing valvular interstitial cells (VICs) on the blend provided quite more ECM protein secretion than pure PCL. In fact, producing ECM proteins in the blend nanocomposite could preserve mechanical properties, compensated for accelerated degradation rate [200].

In a different study, Liverani et al. [201] blended poly(butylene succinate-*co*-dilinoleic succinate) (PBS-*co*-DLS), a novel copolymer, in PGS matrix and fabricated PGS/PBS-DLS at 2:1 ratio via electrospinning at 20 kV, 1.8 mL h^{-1} and 15 cm. The resultant fiber mats produced mechanical and degradation features fitted to soft tissue engineering [201].

In summary, the integration of strong mechanical features together with other polymers' biological properties would provide an improved platform for the objective tissue to be a better place for cells to develop. The information provided in Table 12 explains the target application of individual PGS-based blends in tissue engineering.

Table 12 A concise outline of PGS-based electrospun polymeric blends

Scaffold	Application	References
PGS–natural polymer blend electrospun scaffold		
PGS–gelatin	Cardiac TE	[193]
PGS–gelatin/loaded by CIP	Wound healing	[196]
PGS–*co*-PMMA/gelatin	Nerve TE	[197]
PGS–synthetic polymer blend electrospun scaffold		
PGS–PLA	TE	[199]
PGS–PCL		[194]
PGS–PCL	Cardiac TE	[200]
PGS/(PBS-*co*-DLS)	Soft TE	[201]
PGS–Zein		[198]

PET-based electrospun scaffolds

Serving biological stability and biocompatibility, PET can be considered as vascular substitutes or other blood-exposed alternatives. However, PET may not bear long-lasting pressure in blood vessels and is likely to undergo loading-based deformation. To address its limitation, electrospun PET has attracted major attention due to its adjustable mechanical properties and biological stability [202]. Having said that, however, PET fibers cannot meet all the requirements for the subjected tissue; therefore, there is an exact need to be blended with other polymers, from both natural and synthetic groups to reach tissue engineering purposes.

Blend of PET with natural and synthetic polymers

Generally speaking, PET possesses an intrinsic degradation resistance and extremely good tensile strength, while it fails in vivo degradation [197, 198] and lacks the function of an appropriate scaffold for cells to form tissue. Thus, blending with natural polymers to enhance the biological performance and with synthetic ones to boost mechanical features should be taken into consideration.

Nanofibrous scaffolds of PET–chitosan were fabricated via electrospinning device, set at 26 kV, 0.08 mL min^{-1} and 12 cm, to evaluate fibroblast cell behavior. The findings illustrated larger L929 adhesion, proliferation and extension on fibers with smaller pore sizes, while cell infiltration was greater on those with bigger pore sizes [204]. In previous research, Lopes-da-silva et al. [205] developed PET–chitosan mats, fabricated by electrospinning at 12–20 kV, 0.3–0.7 mL h^{-1} and 10–15 cm. They revealed that the blends had higher surface hydrophilicity and bactericidal effect than pure PET. This in turn provided bigger inhibition zones against *S. aureus* and *Klebsiella pneumonia* (*K. pneumonia*) than single PET. Furthermore, biocompatibility and attachment of fibroblasts were more likely promoted on blend polymeric membranes. Another antecede

discussion on this electrospun blend provided information regarding the effect of different molecular weights of chitosan on the final nanocomposite mechanical and physical properties. The results showed that larger molecular weight will hamper the mobility of molecules, which would lead to uniform fibers structure. Having said that, however, a lower molecular weight was more favorable for the formation of the core–shell construct [205]. Another approach was based on the electrospinning of PET with collagen in a wide range of compositions. The parameters introduced to the electrospinning apparatus were 25 kV, 3 mL h^{-1} and 30 cm. Culturing fibroblasts 3T3-L1 and HUVECs, Burrows et al. [206] indicated more efficient attachment and proliferation compared to neat PET, desirable as a vascular alternative [206].

Electrospinning of PET–PVA was investigated in different compositions of 1:0, 20:1, 10:1, 6:1, 4:1 and 1:1, to obtain favorable nanocomposite in terms of good physical and mechanical properties. The voltage of 25 kV, feed rate of 2 mL h^{-1} and needle–collector distance of 15 cm were all applied to an electrospinning apparatus. The accompany of PVA could interestingly increase hydrophilicity, so that 20:1 ratio showed almost zero degree for water contact angle, though it had the least amount of PVA. Plus, the study demonstrated that cross-linked nanocomposites were associated with stronger mechanical properties than those without cross-linking [207]. Shahrabi et al. [208] conducted an investigation into blood filter production, using PET–PVP blend to eliminate leukocytes from the entire blood. According to the study, PET–PVP was electrospun with diverse weight ratios under 22 kV, 3 mL h^{-1} and 15 cm condition. Incorporation of only 5 wt% PVP in the membrane resulted in fiber uniformity along with 90% platelet permeation. Further, the influence of multilayer membranes on the remove/retention ratio of white blood cells (WBCs)/RBCs and platelets confirmed that the more the layer was constructed, the greater the number of WBCs were able to transfer across the membrane, with no RBC being involved [208]. In a different research, PEG was employed in PET-based scaffolds as reinforcement substance, and blends with different weight ratios of 1:1, 2:1, 4:1, 6:1, 8:1 and 10:1 were prepared. Then, they were electrospun at 25 kV, 0.6 mL h^{-1} and 21 cm. The results showed higher values for hydrophilicity for 10:1 composition. In terms of the 6:1 ratio, the nanocomposite fibers presented an increment in mechanical strength by twofold and porosity improvement, all caused by PEG incorporation [209]. To study vascular grafts substitutes, PET–PU blend scaffolds were fabricated at 30:70, 50:50, 70:30 and 80:20 weight ratios through applying 14–16 kV, 10 mL h^{-1} and 18–25 cm to an electrospinning machine. Excellent integration and viability of vascular endothelial cells and SMCs on the blends were reported at 70:30 ratio [210]. In a different approach, PET and PCL were mixed at weight ratios of 1:3, 1:1 and 3:1 and electrospun under 20 kV, 0.3 mL h^{-1} and 15 cm circumstances. The PET–PCL blend was suggested to be used as synthetic vascular. The results showed the best properties for the 1:3 ratio, with an enhanced tensile strength of 6.38 and 9.47 MPa, in longitudinal and transverse directions, respectively [211]. Another research was conducted based on the development of a three-component hybrid composed of PET–PU–PCL at different ratios of 50:25:25, 25:50:25, 25:25:50 and 33:33:33, via electrospinning. The results subsumed the changes from 388 ± 88 nm to 547 ± 89 nm in fiber diameters and from $56.60 \pm 2.06\%$ to $75.00 \pm 1.94\%$ in porosity percentage. Also, scaffolds with 33:33:33 composition had the greatest tensile strength of 5.27 ± 0.83 MPa. In addition, an increase in fibroblasts viability including proliferation and growth rate on 50:25:25 hybrid was reported to great content [203].

All in all, because PET has some shortcomings, the aforementioned studies have illustrated that blending with either natural or synthetic polymers can be one of the approaches to tackle its deficiencies. Table 13 provides data concerning a variety of tissue applications of PET-based blends.

Conductive polymers-based electrospun scaffolds

Conductive polymers (CPs) including PAni and polypyrrole (PPy) are likely to be introduced as a point of attraction in biomaterials for many researchers for tissue engineering applications, thanks to their ability of electrical signal delivery to cells, which may be associated with tissue regeneration. Having said that, however, due to the high charge density, they are not easily electrospinnable. Therefore, it is suggested that blending them with natural and synthetic polymers could address their difficulty. So far, they were mixed with many

Table 13 A brief outline on PET-based electrospun scaffolds blended with synthetic and natural polymers

Scaffold	Application	Fiber diameter (FD) and/or pore size(PS)			References
		Composition	FD (μm)	PS (μm)	
PET–natural polymer blend electrospun scaffold					
PET–chitosan	TE	PET	0.71 ± 0.28	PA: 9.4	[204]
		PET-CS	2.24 ± 0.85- 3.01 ± 0.72	PA: 15.9	
PET–chitosan		PET	~ 0.3 to 0.5	NA	[212]
		PET-CS	~ 0.5 to 0.8		
PET–chitosan		PET	~ 0.25	NA	[205]
		PET-CS6%	~ 0.59		
PET–collagen	Vascular TE	NA			[206]
PET–synthetic polymer blend electrospun scaffold					
PET–PVA	TE	PET	~ 0.27	NA	[207]
		PET-PVA	~ 0.68		
PET–PVP	Blood cell separation	PET	2.24 ± 1.48	9.57 ± 2.08	[208]
		PET-PVP5%	1.29 ± 0.32	14.66 ± 3.33	
PET–PEG	Filtration	PET	~ 1.7	NA	[209]
		PET-PEG	~ 1.2		
PET–PU	Vascular TE	PET	~ 4.6	~ 2.24	[210]
		PET-PU	~ 2.1 to 2.8	~ 2.79 to 5.5	
PET–PCL		PET	0.36 ± 0.09	1.4 ± 0.1	[211]
		PET-PCL	0.49 ± 0.13	3.1 ± 0.3	
PET–PU–PCL		PET	0.41 ± 0.07	NA	[203]
		Triad blend	0.38 ± 0.08		

PA pore area, *NA* not available

polymers including gelatin, chitosan, PEO, PCL, PLGA, PLLA, etc., which will be elaborated as follows [213].

Blend of CPs with natural and synthetic polymers

Aiming to study the star-shaped polymers, PAni and polyanisidine (PANIS) were electrospun with gelatin, applying 20 kV, 0.5 mL h^{-1} and 15 cm. The findings declared quite higher electrical conductivity and electroactivity in star-shaped polymers than homopolymers. The incorporation of gelatin, also, elicited more uniform fibers with greater biocompatibility [214]. Focusing on antibacterial activity, Moutsatsou et al. [215] prepared PAni–chitosan blends at 1:3, 3:5 and 1:1 weight ratios and then electrospun. Mats with higher PAni quantity led to an increment in antibacterial feature against *B. subtilis* and *E. coli*, which are the most common bacteria associated with wound infections [215]. This group also reported another study with the same blend and composition to investigate in vitro cell behavior. Moutsatsou et al. [216] indicated that the higher the PAni extent, the stronger the electrical conductivity and the more hydrophobicity the scaffold could present. In vitro assay revealed no toxicity in osteoblasts and fibroblasts, but well-performed attachment and proliferation support (Fig. 11). Membrane with 1:3 composition could provide significantly desirable performance and hydrophilicity, caused by chitosan extant, as well as great conductivity owing to PAni incorporation [216].

Electrospinning of PAni copolymer, poly(aniline-*co*-3-aminobenzoic acid) (3ABAPANI), with PLA at different ratios of 5:95, 15:85, 30:70 and 45:55 was studied. Electrospun nanofibrous scaffolds were fabricated at 10–15 kV, 2 mL h^{-1} and 6–8 cm. The resultant mats with larger copolymer extent promoted cell growth and proliferation, accompanied by enhanced antibacterial capability against *S. aureus* as well as showing great electrical conductivity. The final mat may be presented as a novel wound dressing without the limitations that are generally associated with their commercial counterparts [217]. Highlighting the efficacy of conducting polymers in nerve cell stimulation, PAni–PLLA blends (15:85)

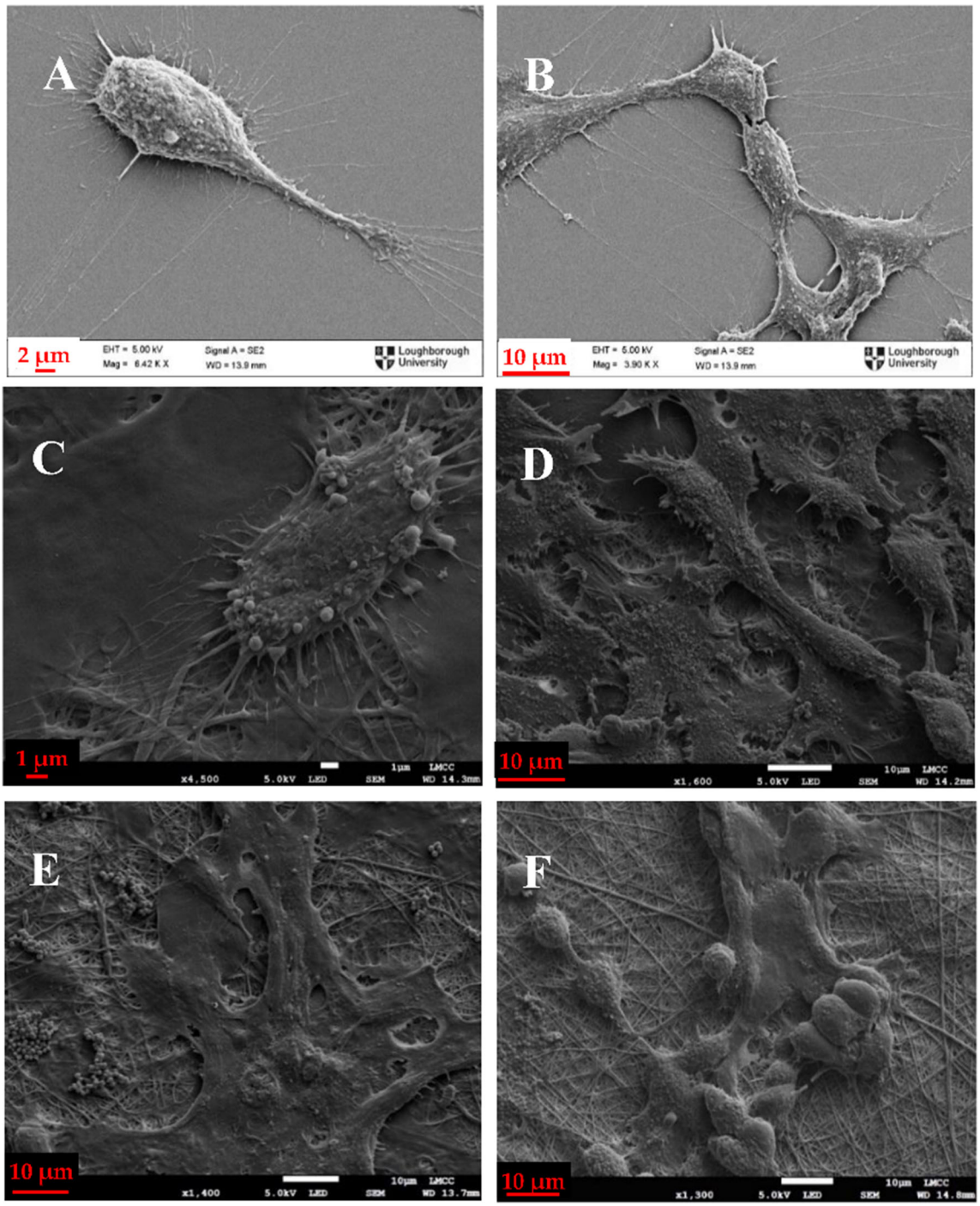


Figure 11 Scanning electron microscope images of: **a**, **b** osteoblasts on glass slide; **c** 1:3 PANI/CS membrane; **d**, **e** 3:5 PANI/CS membrane; and **f** 1:1 PANI/CS membrane. Adapted with permission from reference [216]. Copyright 2017, MDPI, Polymers.

were fabricated by electrospinning. Culturing nerve stem cells and applying electrical stimulation, Prabhakaran et al. [218] showed a well-defined and extended cell outgrowth on PAni–PLLA compared to cells without scaffold [218]. A different study was conducted on the functionality of random and aligned electrospun scaffolds made of PAni–PCL with 0–3 wt% PAni, in musculoskeletal regeneration, focusing on its conductivity. According to the results, PAni extant could give rise to conductivity, with the highest values for composite containing 3 wt% PAni. Furthermore, aligned nanofibers particularly

promoted the myoblasts' orientation, along with myotube formation by 40%, more than that of random. The nanocomposite electrical conductivity also ameliorated the myotube maturation in comparison with random [219]. In another research, PAni was blended with PEO or PMMA to study the electrical conductivity. The PAni was used to the extent of 11–67 wt% and 3.8–25 wt% in PAni–PEO and PAni–PMMA blends, respectively. Electrospinning was performed applying the voltage of 25–40 kV, feeding rate of 0.015–0.05 mL min^{-1} and distance of 30 cm. Electrical conductivity of the blend scaffolds dramatically rose by the addition of PAni [220].

Zamani et al. [221] produced conductive scaffolds composed of PCL–PAni blend as the core and PLGA–PAni and PLGA as two different shells by core–shell electrospinning, set at 10–11 kV voltage, 0.8–1 mL h^{-1} flow rate and 8–18 cm operating distance. Both PCL–PAni/PLGA and PCL–PAni/PLGA–PAni presented perfect performance regarding in vivo spinal cord regeneration, while PCL–PAni/PLGA introduced more efficiency in vitro study [221]. In another study, an electrospun conductive blend was developed using PAni at 10 and 15 wt% with PCL–gelatin 70:30 mixture, directed under 14 kV, 1 mL h^{-1} and 12 cm circumstance. The results introduced the scaffold containing 15wt% of PAni, as the most desirable electrical stimulator for nerve stem cells. The cellular assay also showed an enhancement in cell proliferation and neurite outgrowth in electrically stimulated scaffolds compared to those with no stimulation [222].

PPy at 5, 10, 15, 20, 25 wt% ratios was used as a matrix for chitosan and collagen polymers to acquire PPy–chitosan–collagen blends. The nanocomposite fibers were produced by applying 12–20 kV, 0.4 mL h^{-1} and 12 cm at an electrospinning device. Resultant nanofibers showed a decline in fiber diameter accompanied by the addition of PPy in the composite. PPy incorporation also could raise conductivity and also cellular proliferation and adhesion. Having a wide range of mechanical properties, the nanocomposites presented features commensurate to many tissues including muscle, heart, skin and nerve [223]. An approach of the combination of PPy with PCL and gelatin was studied in different compositions (0–30 wt%) for cardiac regeneration. The blend was electrospun adjusted at 12 kV, 1 mL h^{-1} and 10 cm. The assay findings showed a decrease in fiber diameter, along with an increment in tensile modulus, as long as the PPy concentration rose from 0 to 30 wt%. Nevertheless, the conductive blend with only 15 wt% PPy could present favorable features including conductivity, mechanical properties and biodegradability in line with cardiac tissue. In vitro assessment, on the other hand, provided data on higher proliferation, adhesion and cardiac-specific protein expression, for 15 wt% PPy than 30 wt% [224]. A novel blend was evaluated consisted of poly(ethylene glycol)-modified polypyrrole [PEG-b-(PPy)4] and PCL for tissue engineering applications. The electrospun nanofibers presented biocompatibility, uniformity and conductivity, which are likely suited for tissues with electroactivity requirements to be regenerated [225].

In short, with conductive biocompatible attributes, CPs have been extensively used as conduits for nerve tissue engineering and other applications. Nevertheless, weak mechanical properties caused some restrictions, which can be dealt with by using other polymers in blend with subsequent electrospinning. Reviewing related papers, it has been indicated that both biological and mechanical characteristics improved via employing electrospun blends of CPs with other polymers. A brief statement is represented in Table 14 of the application of CPs-based electrospun blends in tissue regeneration.

Table 14 A summary outline of CPs polymeric blends used in different tissue applications

Scaffold	Application	References
CPs–natural polymer blend electrospun scaffold		
PAni–gelatin, PANIS–gelatin	Nerve TE	[214]
PAni–chitosan	Wound healing	[215, 216]
CPs–synthetic polymer blend electrospun scaffold Ref		
3ABAPANI–PLA	Wound healing	[217]
PAni–PLLA	Nerve TE	[218]
PAni–PCL–gelatin		[222]
PAni–PLGA–PCL	Spinal cord TE	[222]
PAni–PCL	Musculoskeletal TE	[219]
PAni–PEO–PMMA	TE	[220]
PPy-*co*-PEG/PCL		[225]
PPy–PCL–gelatin	Cardiac TE	[224]

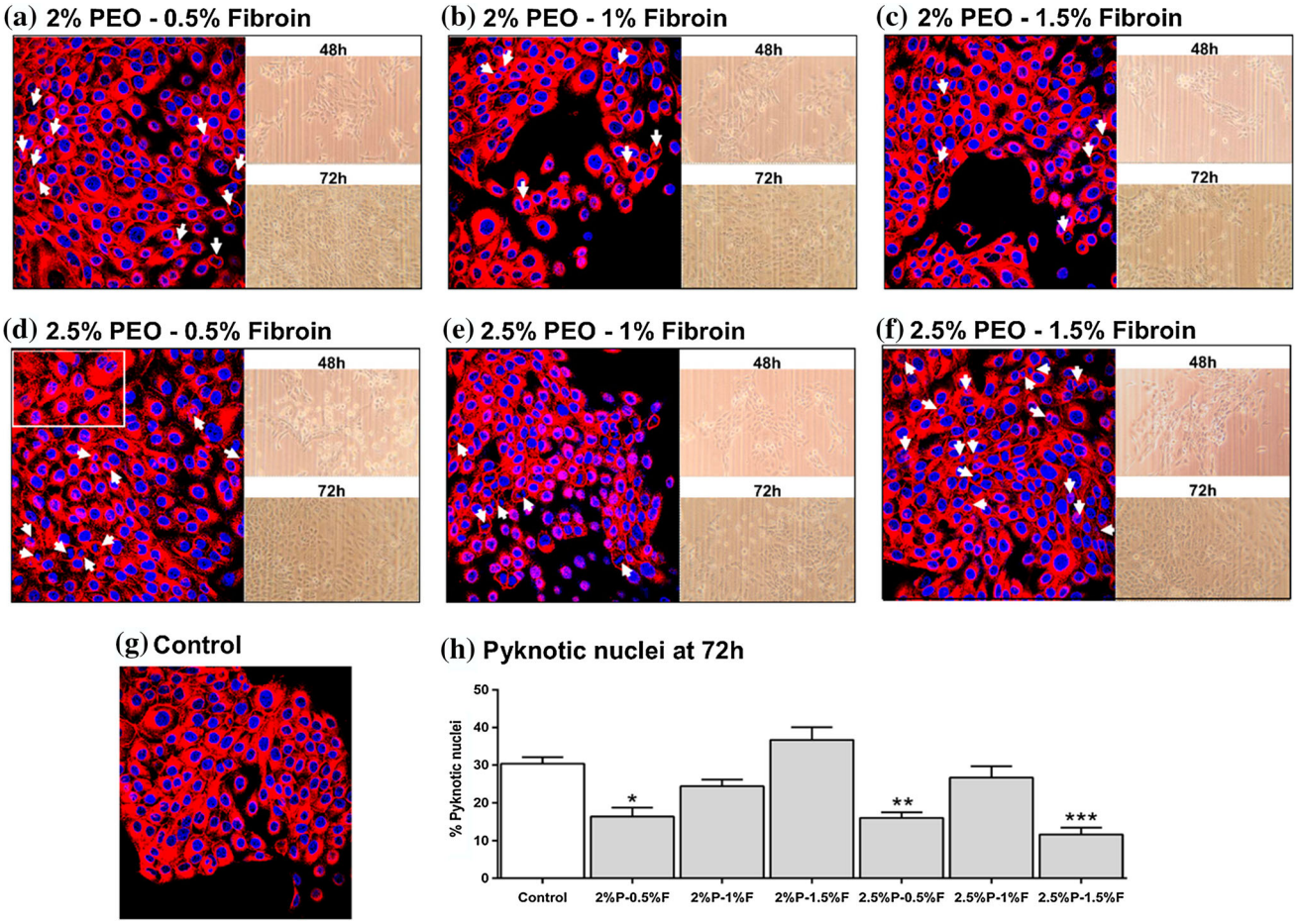


Figure 12 HaCaT cells seeded on PEO–fibroin electrospun mats after 72 h. **a**–**f** Fluorescence staining of nucleus (blue), f-actin of cytoskeleton (red), and phase contrast photographs; (h) % pyknotic nuclei quantification at 72 h. Results are expressed as the mean ± standard deviation of triplicates. p value less than 0.05 ($*p < 0.05$, $**p < 0.01$, and $***p < 0.001$) indicates statistically significant difference by one-way ANOVA and Tukey's test. Adapted with permission from reference [231]. Copyright 2019, MDPI, Polymers.

Other synthetic polymers-based electrospun blend scaffolds

Other synthetic polymers have also been involved in electrospun blends, but their application and diversity are limited.

PEI, a functional group provider for biological macromolecules, is a hydrophilic polymer with a plethora of amine groups, which has extensive usage in drug delivery and tissue engineering application [226]. Involving other polymers, in a blend with PEI, may create more desirable features. Lakra et al. [227] developed PEI-based electrospun scaffolds incorporating different gelatin ratios (1:3, 1:6 and 1:9), with 16 kV, 0.5 mL h^{-1} and 16 cm adjusted parameters. PEI–gelatin blends increased Young's modulus and thermal stability at the 1:9 ratio more than others. Additionally, in vitro studies showed greater viability and attachment at 1:9, and the hemolytic index introduced the nanocomposite as a non-hemolytic material as well [227].

Another synthetic polymer that has been rarely used in electrospun blends is PMMA, with thermal stability, transparency and antibacterial activity [228]. In terms of promoting antibacterial and mechanical performances of PMMA-based scaffolds, Karatepe et al. [229] combined a cationic polymer, PEI, with SF to fabricate tri-component electrospun scaffolds. The device parameters were set at the voltage of 20 kV, feeding rate of 1.4 mL h^{-1} and 20 cm distance. According to the research findings, the blend could improve tensile strength and Young's modulus of PMMA along with its bacterial resistance against *P. aeruginosa* [229]. In an approach, three-component

PMMA–PCL–gelatin blends were characterized in three different compositions of 50:25:25, 25:50:25 and 25:25:50 at 20 kV, 10 mL h^{-1} and 20 cm that was applied to electrospinning device. A promotion in mechanical properties and degradation rate was observed. Furthermore, Rhodamine B release profile was affected due to a correlation with porosity, degradation rate and other factors [230].

Showing a wide versatility, PEO can be also used in electrospun blends to facilitate electrospinning. Developing the coatings for breast prosthesis composed of PEO–SF, Carrasco-Torres et al. [231] prepared the blends by mixing 2 and 2.5 wt% of PEO with 0.5, 1 and 1.5 wt% SF, with subsequent electrospinning under 10 kV, 1 mL h^{-1} and 10 cm circumstances. They reported an improvement in biological compatibility including HaCaT proliferation, outgrowth and adhesion, which was likely to stem from SF incorporation. That is, to further investigate the effect of PEO–SF on cytoskeleton organization, as it is shown in Fig. 12, the immunofluorescence staining was performed and the frequency of pyknotic nuclei was reported. As a result, 2.5% PEO–1.5% SF turned out the best matrix with the lowest percentage of pyknotic nuclei. Also, the PEO presence could accompany boosted mechanical stability [231]. In another research, the electrospun web of SPI and PEO was investigated, under 15 kV, 1 mL h^{-1} and 15 cm conditions. Thirugnanaselvam et al. [232] indicated that this blend may have the potential to provide enough moisture for the wound bed. Moreover, they confirmed a positive antibacterial influence mediated by these blends. PEO–SPI nanofibers also resulted in well-performed wound healing due to the epithelium neo-formation, with no severe interaction [232]. An antecede study was based on PEO–sodium alginate (SA) at diverse ratios of 1:1, 1:2, 1:3, 2:1, 2:2 and 2:3 with the incorporation of 0.3 wt% lecithin, a substance for fibers integration. The group performed the electrospinning at 0–40 kV, 0.2–1 mL h^{-1} and 15 cm. PEO–SA represented high water absorption and structural morphology along with biocompatibility. This blend provided information regarding its potential for wound healing with exudate [233]. To investigate the effect of different electrospinning parameters on the fiber diameter and pore size, PEO–ALG was studied with 0.5 and 1 wt% ALG content. The presence of PEO in ALG scaffolds increased the viscosity and made it electrospinnable. The survey results showed an increment in fiber diameter from the range of 0.14 ± 0.02–0.17 ± 0.03 μm to 0.15 ± 0.03–0.17 ± 0.02 μm by a rise in the needle–screen distance. Rinsing the blend and removing the PEO, the fiber diameter diminished to a range of 0.10 ± 0.03–0.30 ± 0.08 μm. The pore size measuring also revealed a similar pattern, which surged by applying larger working distances, produced 0.70 ± 0.31–1.29 ± 0.66 μm pore size in the blend [34]. Saquing et al. [234] conducted a study to evaluate the possibility of PEO being a carrier when ALG is used, within the electrospun fibers. The PEO–ALG was electrospun applying 12 kV, 0.5 mL h^{-1} and 15 cm. The findings supported that accruing interaction between PEO molecules could provide a status during electrospinning procedure to carry the ALG particles within the fibers. Also, PEO could alleviate surface tension and electrical conductivity of ALG and made it electrospinnable [234].

An investigation was developed, focused on the physical properties of polyetherimide (PEII), an amorphous polymer with unique mechanical, physical and thermal properties [235]; and its blends with polyacrylonitrile (PAN) were produced at different ratios of 100:0, 75:25, 50:50, 25:75 and 0:100. Applying a range of voltage (13–24 kV), feeding rate (0.3–1.5 mL h^{-1}) and working distance (10–30 cm), Aijaz et al. [235] fabricated the PEII–PAN nanofibers to obtain the most suitable integrity, uniformity and smoothness of the surface. Nanofibers with the highest fit and uniformity were fabricated under 19 kV, 0.6 mL h^{-1} and 15 cm electrospinning conditions. The resultant blend was inherently hydrophilic with a reported water contact angle of around 28°. It would be worth mentioning that fiber orientation may be a key factor for water diffusion onto the mats [235].

A study on poly(ethylene oxide terephthalate)–poly(butylene terephthalate) (PEOT/PBT)/ALG was carried out to evaluate the effect of ALG on the physical properties of synthetic blend polymer. Electrospun scaffolds were produced adding 14 wt% of PEOT/PBT in 0, 0.5 and 1 wt% of alginic acid solution. PEOT/PBT fibers showed a lower diameter, a reduction from 15.62 ± 4.14–18.61 ± 5.86 μm to 2.67 ± 1.10–0.87 ± 0.69 μm, in the presence of ALG. The pore size also diminished from 63.90 ± 22.45 μm to 10.16 ± 4.10 μm, by the addition of 0.5% ALG. Although they experienced a decrease in their water contact angle, they were still in the hydrophobic zone [34].

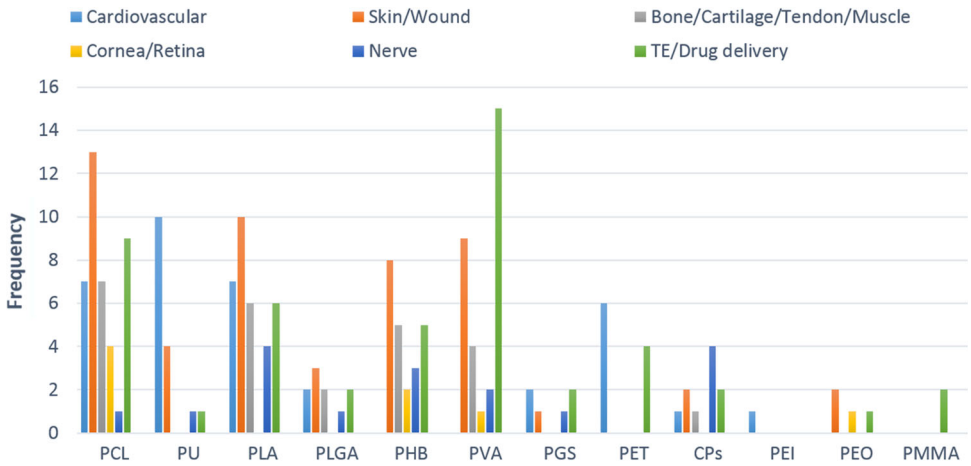


Figure 13 A brief overview of the application of synthetic polymers over the last 10 years based on their frequencies.

To highlight the effect of electrospinning parameters on morphology and fiber diameter, poly(*N*-vinyl carbazole) (PVCz)/polystyrene (PS) blends were prepared at different ratios of 9:1, 7:3, 5:5 3:7 and 1:9. To do so, the voltage and working distance were adjusted at a wide range of 15–35 kV and 10–40 cm, respectively. The findings revealed that either PS incorporation or voltage alteration could decrease the fiber diameter. Although needle–screen distance did not have any impact on morphology, it gave a decrease in fiber diameter [236].

Cellulose acetate butyrate (CAB), an ester of cellulose, presents a hydrophobic feature, which limited its application in tissue engineering. The combination of CAB/PEG was studied at 2:1 weight ratio, fabricated by electrospinning under 11 kV, 1.5 mL h^{-1} and 12 cm condition. The resultant tensile strength showed a twofold improvement compared to pure CAB. With the addition of PEG, the blend displayed more hydrophilicity, associated with a higher degradation rate. The nanocomposite also caused an improvement in cell adhesion and viability to a large extent [237]. In another approach, Shrestha et al. [238] developed the biomimetic nanocomposite composed of polyamide-6,6 (PA-6,6) and chitosan (10, 15 and 20 wt%), using an electrospinning device, at 20 kV, 0.5 mL h^{-1} and 17 cm. The fabricated mats provided an appropriate osteophilic medium for biomineralization and cell growth. The hydrophilicity and mechanical properties were strongly reinforced mainly in mats with 20 wt% of chitosan. Furthermore, osteoblasts could more perfectly attach, proliferate and maturate on this composition than other ratios [238].

From the above novel blends, it is obvious that the blending procedure would emerge with better properties for the final product, especially as in this review, when electrospinning is used as a fabrication method.

Conclusion and future perspectives

Being introduced as a procedure for repair and regeneration of a variety of tissues, advancements in tissue engineering have been promoted toward fabricating scaffolds with preferable features including biocompatibility, biodegradability, cellular attachment and hemocompatibility along with mechanical strength, etc. Versatility, being low-priced and tunable fiber diameter and morphology led scientists to undertake electrospinning process, using blend polymeric solutions. Electrospinning undoubtedly is one of the most advantageous and promising techniques, since it provides the opportunity for the user to manipulate the fiber morphology and physical properties through differing applied parameters. This in turn could produce nanofibers that gain attributes with an enormous similarity to human body biological constructs.

Over the recent decade, more than 200 studies have reported the use of electrospinning to fabricate polymeric blend scaffolds based on synthetic polymers. Blending with both natural and synthetic polymers, researchers have shown that synthetic polymers will emerge with higher favorable properties commensurate to target tissues. According to these studies, an alteration in parameters such as voltage, flow rate and working distance would

change the fibers morphology in a way that supports the cellular growth, proliferation, infiltration and dispersion, providing a suitable matrix. In vivo assays on animal models have brought about promising consequences on tissue integration and triggered repair and regeneration. However, the engagement of different polymers in different tissues is diverse, largely because of showing off a variety of intrinsic properties of every single synthetic biopolymer. To the most extent, the polymeric-based scaffolds have been prepared using PCL and its copolymers, PU, PLA and its copolymers, PHB and its derivatives, PVA, PGS and CPs. Also, synthetic polymers such as PVA, PVP, PEO and PEG act mostly as helper components that could improve the capability of being electrospun accompanied by ameliorating mechanical and physical properties. That is to say, PEG and PEO, in particular, are known as sacrificial agents, which can be eliminated via rinsing, and thus remaining pores. These scaffolds have been studied for various purposes, either including heart, nerve, bone, cartilage, etc., tissue engineering, or drug and growth factor delivery. Figure 13 presents a compendium explanation of the frequency of synthetic polymers' application in tissue engineering over the last decade.

Among these polymers (Fig. 13), it seems that researchers may place a premium on PCL-based scaffolds rather than others, which have been engaged in a wide category of tissues. Many applications have been bestowed on either skin tissue engineering and wound healing or cardiac and nerve regeneration, while some are associated with drug delivery and antibacterial activity. Taken the second place, PVA and PHB, somewhat PLA and also their copolymers, allocate the skin substitutes and wound dressings to themselves, mostly by incorporating chitosan, SS and gelatin as natural polymers and PU, PVA and PVP as synthetic ones. Furthermore, the trace of given polymer blends can be found in hard tissue and musculoskeletal engineering.

In terms of cardiac tissue engineering, along with vascular alternatives and blood-contact applications, PU and PCL have outperformed as two pioneers, blending with collagen, gelatin, fibrinogen or synthetic polymers including PCL, PLLA, PEGMA, etc., to create a stroma with higher support for RBCs and less hemolysis. PET also has been used in the former area, for the most part in blood cell filtration or separation, with promising results.

Being conductive, on the other hand, is a definite need for substances employed in nerve substitutes and conduits, to facilitate the electrical current conduction. This issue has been studied through employing CPs, PLA, PVA and PHB more often, blended with synthetic polymers, rarely with chitosan or gelatin. A tiny footprint of PLGA, PGS, PU and PCL also can be observed in nerve regeneration. Also, PLA and PLGA seem to be involved in all the previously noted fields. Studying soft tissue and eye tissue is confined to only a small proportion of polymers including PCL, PU, PHB, PVA, PGS and PEO.

On a concluding note, this review aimed to elaborate on the recent advances in nanostructured synthetic polymer-based electrospun blends concerning tissue engineering. We have put together the last decade's works of literature and reports to assess the merits of synthetic polymers in blends. Although electrospun polymeric scaffolds have already represented their capability for being used in tissue engineering in vitro and in a few cases in vivo, there are still more demands for fabricating ECM-resembled nanofibrous mats to meet a broad range of requirements and reach the best fit for the target tissue in the clinical scale. In the future, the considerations should be taken for clinical applicability, with further emphasis on the research clinical trials of the electrospun blends. Novel biopolymers synthesis, further investigations about their key features and their effects on each other likely play a pivotal role in physical, chemical and biological behavior to come to a prosperous regeneration process. Filling the gap between laboratory findings and clinical implications, there is a decisive need for in vivo evaluations to appraise the clinical response of these compositions beforehand.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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