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REVIEW PAPER

Nano-Fibrous and Tubular Poly (lactic acid) Scaffolds for Vascular Tissue Engineering

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ABSTRACT

In recent years, the adaptation of tissue engineering techniques is necessary to progress the field of cardio-vascular bio-logy and advancing patient care. Through the high event of cardio-vascular disease and increasing amount of patients needing vascular admission, there is a considerable require for small-diameter (<6mm inner diameter) vascular graft that can supply long-period patency. Vascular tissue engineering is a novel field that has undergone massive growth more than the final decade and has suggested suitable keys for blood-vessels darn. The objective of vascular tissue engineering is to manufacture neo-vessels and neo-organ tissue from autologous cells by means of a bio-degradable polymer like Poly (lactic acid) (PLA) as a scaffold. PLA Nano-fibrous scaffolds have high surface area–to-volume ratios and porosity that simulate the structure of protein fibers in native extra cellular matrix (ECM). The versatilities of polymer components, fiber structures, and functionalization have made the fabrication of PLA Nano-fibrous scaffolds with suitable mechanical strength, transparency and biological properties for vascular tissue engineering feasible. The most significant benefit of tissue engineered implants is that these tissues can grow, remodel, rebuild, and respond to damage. This review explains the fabrication, properties and advantages of different types of PLA scaffolds with emphasis on Nano-fibrous ones for vascular tissue engineering.

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INTRODUCTION

Vascular sicknesses have taken the principal choice in death causing diseases generally[1]. Conventional diagrams in managing of vascular illnesses include angioplasty, bypass graft, and auto-graft[2, 3]. Autologous vessels and vascular grafts, to be selected with a small diameter in bypass surgery, are proposed alike as golden option. Vascular tissue engineering has become a hopeful advance in small diameter vessels[4, 5]. Blood-vessels are structurally multifaceted and basically active tissue, with smallest regeneration potential that have composite extracellular matrix (ECM) and arrangement [6, 7]. Natural blood-vessels are categorized into three kinds, which are arteries, veins, and capillaries [8, 9]. Arteries transfer the blood away from the heart and veins provide the blood back to the heart. Arteriole is the name of small diameter artery[10-12]. The left anterior descending coronary artery offers a main blood supply to the myocardium [13, 14]. Capillaries link arteries and arterioles with vein, and they as well move gases and nutrients to tissues and vice versa[15, 16]. The vessel walls consist of three covers: intima (internal layer), media (central layer), and adventitia (external layer), as exemplified in Fig. 1. Intima layer is a monolayer of endothelial cells[17, 18]. Media layer contains smooth muscle cells (SMCs)[19, 20]. Adventitia layer includes collagenous extracellular matrix (ECM) that holds fibroblast and perivascular nerve cells [4, 21, 22]. Intima, media, and adventitia layers are disconnected from each other by lamina layer having elastin [23-25]. Collagenous

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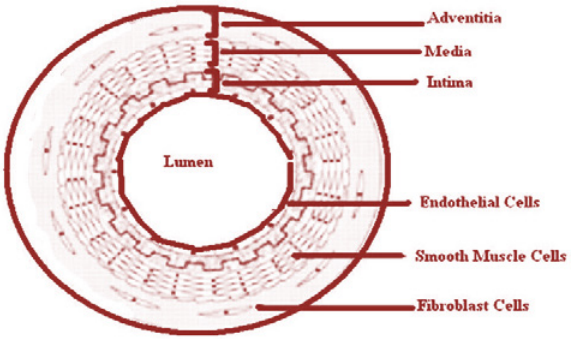

Fig. 1. Scheme of an artery. The arterial wall includes three major layers: (1) adventitia, (2) media and (3) intima. A sheet of *endothelial cells* coats the inner surface of the lumen whilst *smooth muscle cells* and *fibroblast cells* live in external layers[2].

Table 1. ECM components of blood-vessels[37].

Vessel type (diameter)	Elastic artery (30 mm to 5 mm)	Muscular artery (6 mm)	Vein (1–5 mm)	Arteriole (0.50 µm)	Veinule (20–100 µm)	Capillary (0,20 µm)
ECM components	Elastin, fibronectin, fibrillin, fibulin, collagen type I, II, III, IV, V, VI, proteoglycans	Elastin, fibronectin, fibulin, collagen type I, III, IV, V,VI, proteoglycans	Elastin, fibronectin, collagen type I, II, III, IV, VI, XII, XIV proteoglycans	Elastin, collagen I, III, fibrillin	Laminin, collagen IV, fibronectin	Collagen IV, laminin fibronectin, HSPG

ECM, extracellular matrix; HSPG, heparin sulfate proteoglycan.

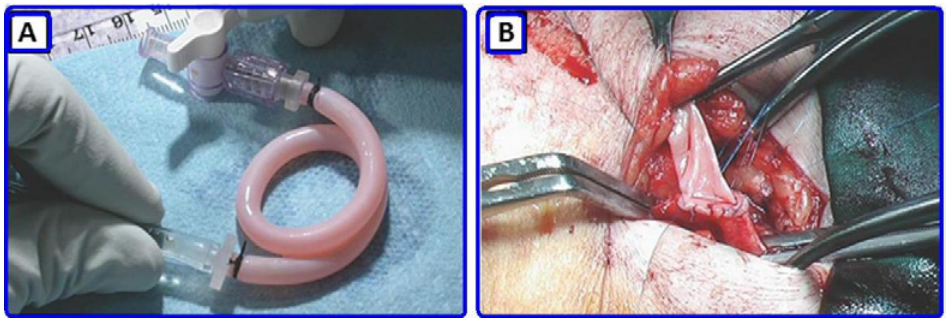

Fig. 2. Tissue engineered blood-vessels: (A) Tissue-engineered graft was implanted among the axillary vein and the humeral artery as an arterio-venous shunt, (B) The vessel exhibited normal suturing and surgical handling properties[13].

adventitia inserts inflexibility to the blood-vessel walls, whereas lamina supplies them with elasticity [4, 26-28]. Endothelial cell (EC) layer is placed at the internal wall of blood-vessel, forbidding the accretion of blood and regulating the quantity of smooth muscle cells (SMCs) in the media layer[29, 30]. Blood-vessels widen and bond in response to a signal from ECs or cytokines [4, 31, 32].

The Extracellular matrix of a blood-vessel varies in its composition (Table 1), thickness, and generally architecture selection from arteries, capillaries to veins [4, 20, 33, 34]. The interaction between ECM pieces and tissue detailed cells tenders blood-vessels their alert useful character [32, 35, 36].

A perfect scaffold should reproduce the bio-mechanical properties of blood-vessels, as serving like a stage for cell attachment and proliferation [38, 39]. It should be non-thrombogenic, non-immunogenic, bio-compatible and hemo-compatible, bio-degradable with appropriate pore size and elasticity [40-42]. Consequently the scaffold should help the in-vivo regeneration of a tissue engineered vascular mat when implanted at an appropriate location. Vascular tissue engineering tries to development of vascular replacements that

can regenerate in-vivo and act like a native vessel [9, 43, 44]. Widespread study has been carried out on Tissue Engineered Vascular Grafts (TEVGs) over the past few decades[45-47], and as an important development has been made in phrases of attaining the remodeling of the tissue in the TEHV mats similar to the native blood-vessels[48, 49], as depicted in Fig. 2[13].

Manufacturing the polymeric vascular scaffolds rigorously examined. Different polymers have been employed contain synthetic polymer, natural polymer, and polymer blends [38, 50]. Synthetic polymers display better mechanical properties than natural polymers [51-53]. Blending two synthetic polymers or two natural polymers could consequence in improved mechanical properties. Mechanical properties of artificial blood-vessels play a key function whilst the vessels are attached to the native vessels in the body [9, 50, 51, 54]. If there is a competition in the mechanical properties, the sheer stress, as well as intimal hyperplasia can be evaded [9, 38, 55]. Also, the artificial blood-vessels should be durable sufficient to resist the frequent blood circulation and the related pressure [4, 9, 56, 57]. Fig. 3 displayed some PCL Implanted Scaffolds[2].

POLY (LACTIC ACID)

A variety of efforts have been done to manufacture vascular grafts scaffolds and artificial blood-vessels in tissue engineering by means of Poly(lactic acid) (PLA) and its co-polymers like Poly(lactide-co-ε-caprolactone) (PLCL) and Poly(l-lactide-co-glycolide) (PLGA) [55, 58-62]. The ring open polymerization of lactide, results in PLA which is a chiral molecule that exist in two forms D-PLA and L-PLA[63]. It is bio-degradable thermo-plastic Poly-ester [64-66]. Poly (l-lactide) (PLLA) is a semi-crystalline polymer (~37%) and Poly (dl-lactide) is an amorphous polymer [67, 68], owing to the random distribution of l-lactide and d-lactide units [69-71]. The hydrolytic product of PLLA is lactic acid which is more catabolized in the lactic acid phase into water and carbon Di-oxide[72, 73].

This bio-polymer has certain benefits in bio-medical fields like wound dressings, tissue engineering scaffolds, anti-bacterial mats, surgical sutures, drug-delivery systems and gene delivery materials [67, 74-78], that are:

- ✓ PLA can undergo scission in the human body [63, 72, 79, 80].
- ✓ PLA degrades to monomeric units of lactic acid as a natural intermediary in carbohydrate-metabolism[81, 82].
- ✓ PLA has good bio-logical interactions with the host cells when it is implanted [72, 81, 83, 84].
- ✓ The degradation time of PLA have been stated to be around 6 to 12 months [62, 85, 86].

Lactic acid can be polymerized to create PLA polymers by means of direct poly condensation under controlled temperatures and pressures

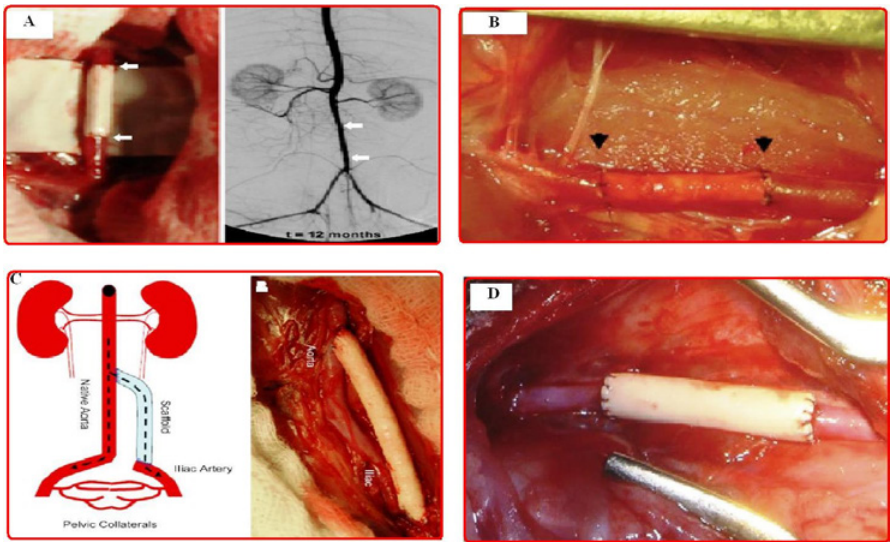

Fig. 3. A) PCL nano-fibrous scaffold implanted in Rat-aorta, B) PCL-CAG peptide nano-fibrous scaffold implanted in Rat-carotid, C) PCL-Collagen nano-fibrous scaffold implanted in Rabbit-aortic-bypass, D) PCL-Elastin nano-fibrous scaffold implanted in Rabbit-carotid[2].

without catalyst, solvent or initiators[87, 88]. The effects of the reaction temperature and pressure on the resulting molecular weights have been studied. The results showed that at 200 °C after about 90 h under vacuum, high molecular weights of 90 kDa can be attained[89, 90]. In addition, other technique using the organic solvents were developed to formulate poly-DL-lactic acid (PDLLA) via directs solution poly- condensation. In this process the lactic acid, catalysts, and solvents were diversified in a reactor so as to produce high molecular weights polymer of 300 kDa. On the other hand, the greatest usually method to create higher molecular weight PLA was ring-opening polymerization (ROP), occurred by ring opening of the lactide (cyclic dimmer of lactic acid) in the presence of a catalyst. This method resulted in production of PLA with a controlled molecular weight [91-93].

This review focuses on the constructing different types of PLA scaffolds like Nano-fibrous scaffolds, Porous scaffolds, Cylinder-shaped scaffolds, Tubular scaffolds and double-porosity scaffolds for vascular regeneration; Cell culturing into the scaffold, non-cytotoxicity of scaffolds and cell adhesion inside them will be reported and the recent advances will be discussed.

APPLICATION OF PLA NANO-FIBERS IN VASCULAR TISSUE REGENERATION

In a novel work in 2018, PLCL were electro-spun for manufacturing nano-fibrous vascular scaffolds, Thrombo-genicity valuation of scaffolds exposed high Thrombo-genic possessions of samples that was comparable to great amount of naturally collagen Thrombo-genicity. The level of platelet activation was dependent on chemical composition and surface-morphology of experienced samples[94].

A different kind of hybrid PLA-Fibrinogen (PLA-FBG) nano-fibrous scaffolds developed in 2017[14], which have improved stiffness, combining the good mechanical assets of PLA with the excellent cell recognition properties of FBG. HUVECs cells (human umbilical endothelial cells) expanded a stellate-like morphology within multiple shells. The fine-expanded focal adhesion compounds proposed a successful cellular interaction. Nevertheless time-lapse investigation explains notably lowered cell movements, resultant in the cells traversing a quite small space in multiple ways. In opposition, an elongated cell form and considerably increased cell mobility were viewed in aligned nano-fibers. Time-lapse investigation explained considerably more rapidly wound coverage (within 12 h) of HUVECs on aligned mats vs. approximately absent directional migration on random ones. Though, nitric oxide (NO) release confirms that endothelial cells hold lowered functionality on aligned nano-fibers compared to random samples, wherever considerably higher NO creation was established. Randomly structured nano-fibers could hold the endothelization of implants whereas aligned nano-fibers would slightly direct cell locomotion for guided neovascularization[14].

Tara et al.,[95] definite the in-vivo viability of PLA scaffolds coated with PLCL in high pressure, small diameter mouse arterial situations. Large-pore PLA-PLCL grafts prompted a well-organized neointima after 12 months, and Alizarin Red S staining displayed neointimal calcification only in the thin neointima of small-pore PLA nano-fibrous grafts. The vascular smooth muscle cells (VSMCs) of PLLA-PLCL graft expressed transcription factors of both osteoblasts and osteoclasts.

Wang et al. [35] constructed PLLA-Chitosan core-shell nano-composite fibers through a novel method, from heterologous solution through coaxial electro-spinning system was designed for vascular gasket. Chitosan surface was cross-linked by Genipin and modified with heparin. Core–shell structures shaped with a PLA-CS ratio at 1:3. Higher biocompatibility and mechanical properties were achieved by optimizing the core–shell structure morphology and surface cross-linking of CS. UE7T-13 cells grew fine on the core–shell nano-fibers since showing with MTT assays and SEM images. Corresponding to the PLA mats and profitable vascular patch, PLA-CS core–shell nano-fibers had better mechanical strength (Fig. 4). The elastic modulus was 117.18 MPa, although the yield stress of the fibers was lesser than that of the commercial vascular patch. Attachment of red blood cells on the nano-fibers was assessed by blood anticoagulation tests and in vitro blood flow experimentations. SEM images specified there were scarcely any red blood cells attached to the fibers with chitosan coating and heparin modification[35].

In another work, researchers study whether the nano-Hydroxyapatite-PLLA (nHAC-PLLA) scaffold is appropriate to be compounded with VEGF to improve the axial vascularization in vivo. Thirty rabbits were splinted into 2 sets of 15 animals each. In control collection, a PLLA-nHAC scaffold

slice was vascularized axially with an included ligated femoral arterio-venous (AV) bundle in the animal. In experimental set, a piece compounded with VEGF gel was applied. The animals were surrendered at 2 weeks, 6 weeks, and 10 weeks after surgical procedure; the samples of scaffold slices undergo histo-morphometric assessment; examination of the micro-vessel density (MVD) of both groups was done. The blend with VEGF (Group B) did not improve the vascularization in early stage (2 and 6 weeks, $P > 0.05$) but worked in later time (10 weeks, $P < 0.05$) [26].

Deng et al. [62] prepared a cylinder-shaped PLA scaffolds and cultured HUVECs on them. The researchers used Poly Glycolic Acid-PLA (PGA-PLA) mesh for fabrication of scaffolds. Novel air-spun PLA nano-fibers modified with hydrophilic surfaces for vascular tissue engineering is reported by Ko et al.[18] . Surface-initiated atom transfer radical polymerization permits for grafting pendant Oligo (Ethylene Oxide)-holding poly (methacrylate) (POEOMA) from PLA nano-fibers labeled with disulfide linkages(Fig. 5). The resulting PLA-ss-POEOMA fibers exhibit enhanced thermal

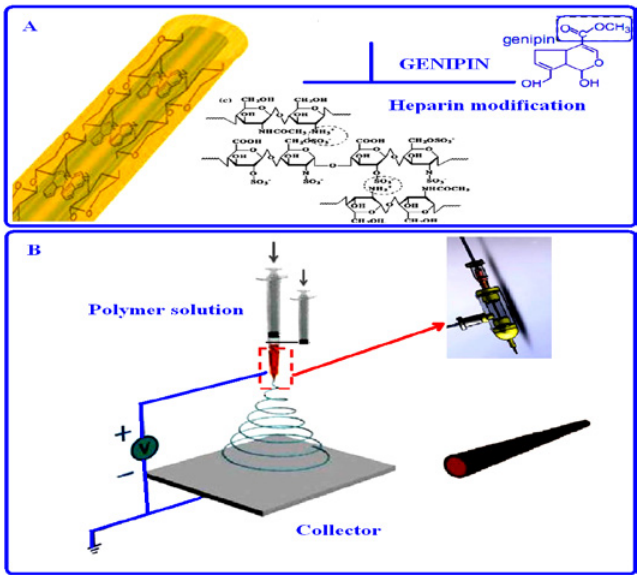

Fig. 4. (A) Illustration of electro-spinning of nano-scaffolds, (B) Illustration of polymer electro-spun[35].

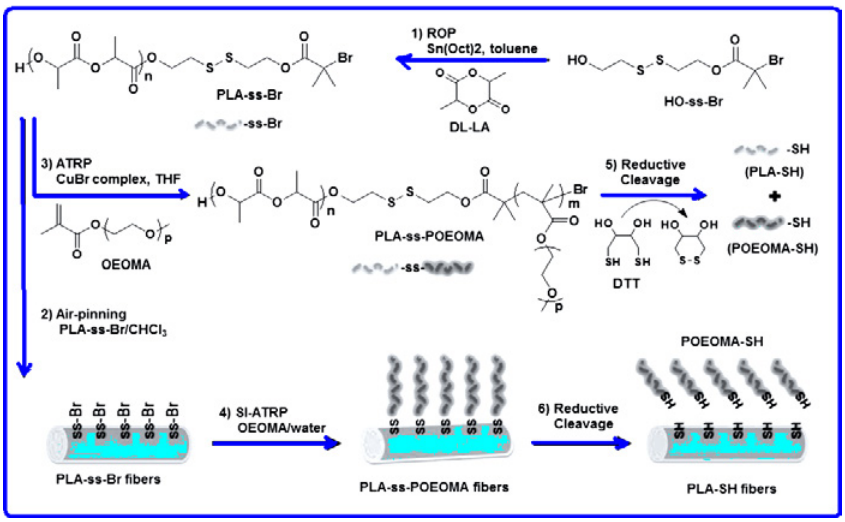

Fig. 5. Illustration of the method to synthesize PLA-ss- POEOMA nano-fibers by surface-initiated atom transfer radical polymerization of OEOMA in the presence of PLA-ss-Br fibrous macro-initiators and their degradation in response to reductive reactions[18].

stability and improved surface properties, as well as Thiol-responsive shedding of hydrophilic POEOMA by the cleavage of its disulfide linkages in response to reductive reactions, thus tuning the surface properties.

In another work, PLLA-Collagen were electro-spun to gain a nano-fibrous scaffold with the best mechanical feature, owing to the presence of PLLA, and capable to signify an optimal substratum for cell adhesion. Bone marrow derived Mesenchymal Stem Cells (MSCs) were seeded on the nano-fibers to explore the ability of these cells for differentiating into vascular endothelial cells while cultivating through differentiating medium. The assays revealed that cells grown on PLLA-Coll nano-fibrous scaffolds differentiated in endothelial cells illustrating cobblestone phenotype with expression of vascular specific proteins, for instance the platelet endothelial cell adhesion molecule-1[6].

A Different scaffold for vascular tissue engineering was made-up by co electro-spinning PLA-Collagen-Chitosan at room temperature and normal pressure (Fig. 6). By analyzing the effects of composition and collecting distance on the morphology of electro-spun meshes, Zhu et al. [30] stated that the proper collecting distance and the concentration of the solution are the keys to the success of the co-electro-spinning procedure. The outcomes specified that scaffolds fabricated through co electro-spinning: (a) had a more biomimetic structure than PLA, as the fiber diameters advanced the size of the extracellular matrix; (b) displayed better blood-compatibility. This work proves the feasibility of by means of two different solutions to build a scaffold for blood-vessel tissue engineering via co electro-spinning [30].

Shalumon et al.[96] manufactured aligned and random PLLA-Gel nano-fibers via electro-spinning method. Morphological and chemical characterization of the nano-fibrous scaffolds was carried out and the size of fibers ranged in 100 - 500 nm. The SEM, fluorescent staining and viability examines exposed an increasing in viability and proliferation of Human Umbilical Vein Endothelial Cells (HUVECs) and Smooth Muscle Cells (SMCs) proportional to Gel content. The aligned fiber-morphology comforts cells to orient and elongate along their long axis. Pavia et. al. [64] produced PLLA-PLA tubular scaffolds for vascular tissue engineering with different ratios (100-0, 90-10, 75-25 wt-wt) . ECV304 continuous human endothelial cells were cultured on the scaffolds. The outcomes have demonstrated that the scaffold do not make cell toxicity; cells are able to grow into the tubular form scaffold coating its inner surface [64].

Samantha L. Wilson et al. [5] electro-spun multiple orthogonal aligned poly (L, D lactic acid) (PLDLA) scaffolds inoculating human corneal

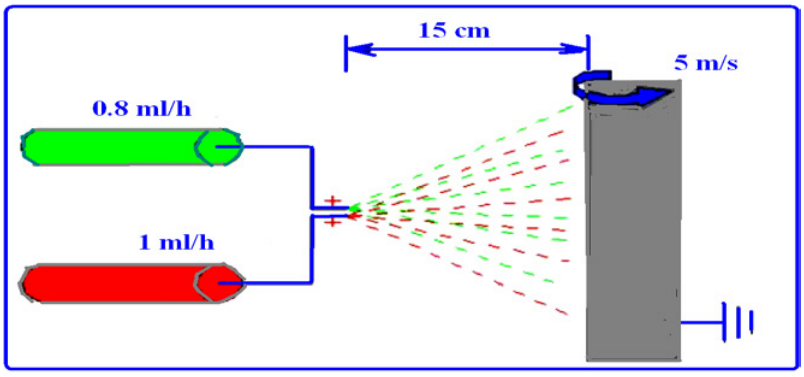

Fig. 6. Scheme of the coelectro-spinning [30].

Table 2. Name and type of PLA scaffolds.

Type of Scaffold	Type of Treatment	Ref.
PLLA	—	[65]
PLLA + COll	Soaked with type—I collagen gel.	[65]
PLLA PdE: N	plasma deposited ethylene : nitrogen coating, PdE:N	
PLLA PdE: N+ COll	Plasma deposited ethylene: nitrogen coating, PdE:N , followed by collagen soaking.	[65]
PLLA PdE:NH2	Plasma deposited ethylene: nitrogen coating, followed by a H2 post treatment.	[65]
PLLA PdE:NH2 + COll	Plasma deposited ethylene: nitrogen coating, followed by a H2 post treatment, followed by collagen soaking.	[65]

stromal cells on the surfaces of them. The matrix elasticity (elastic modulus) and the dimensional changes were analytical of alters in cell phenotype from contractile fibroblasts to quiet keratocytes. Researchers deliberate the persuading of topographical and chemical signals on the phenotypical performances of adult human-derived corneal stromal (AHDCS) cells in 3D (PLDLA) nano-fibrous mats. The results designated that the synergistic effect of nano-fibers and serum-free media plus insulin supplementation offered the most suitable topographical and chemical location for relapsing corneal fibroblasts to a keratocyte phenotype in a 3D construct.

3D PLLA Scaffolds prepared with thermally induced phase separation by Rigogliuso et. al.[65] then treated with plasma processes to modify the surface of them for enhancing cell adhesion on the scaffolds as in Table 2.

Assays proved better interaction of plasma treated scaffolds with HUVEC (Human Umbilical Vein Endothelial Cells) cells compared to untreated ones. Moreover, different chemistry, obtained throughout the two different plasma procedures, permitted different cell behavior. Actually, HUVEC cells seeded on PdE:N scaffolds demonstrated a characteristic Mesenchymal Phenotype of Endothelial Cells, in active proliferation-migration status. In a different way, in scaffolds treated with PdE:N-H2 plasma method, HUVEC cells illustrated the classical phenotype of cells shaping a differentiated endothelium[65].

PLA-PCL bi-layered tubular nano-fibrous scaffolds fabricated by means of layer-by-layer using electro-spinning method from PCL at the inner layer and PLA at the outer layer. PCL scaffolds consists of microfibers and nano-fibers with diameters of 1.5 µm to 6 µm and 400-600 nm, correspondingly, and interrelated pores with 15 µm average pore size. PLA scaffolds consist of nano-fibers with diameters variety from 800 nm to 3000 nm and interconnected pores with 10 µm average pore-size. The total porosity of PLA-PCL scaffolds is approximately 79 %. The PCL layer imitates the intima sheet of natural blood-vessel, whilst the PLA layer mimics the adventitia cover of natural blood-vessel. The PLA-PCL nano-fibrous scaffolds demonstrate suitable mechanical properties, with Young's modulus of 30.9 MPa nearly three times higher than that of PCL scaffold (10.7 MPa). Fibroblast cells adhered fine to the surface of PLA-PCL scaffolds after four weeks of culturing. Human Venous Myo-fibroblasts (HVS) cells were focused in the outer layer of PCL more willingly than in the inner layer of PLA, which was perhaps owing to the small pore size. On the other hand, the cell content was almost 64% comparable to the native porcine pulmonary valve tissue, signifying the

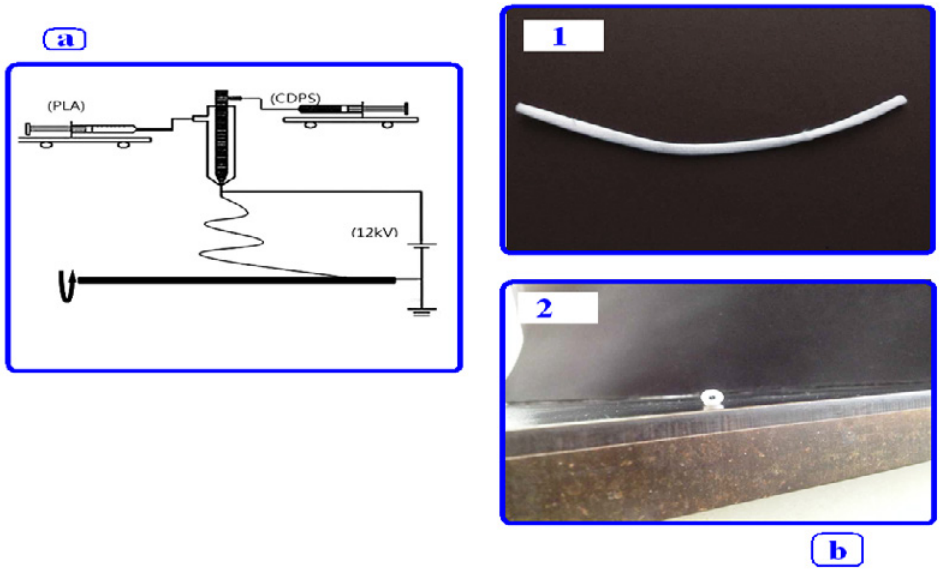

Fig. 7. (a) Co-axial electro-spinning apparatus. The voltage was regulated to constant 12 kV and the distance of coaxial facility to round bar was 10 cm. The flow rate of PLA organic solution and CDPS aqueous solution was 4, 1 (mL/h). A whole scaffold was fabricated with 2 h; (b) 1- Platform of scaffold. The scaffold was 8.7 cm in length and presented white; 2- The cross section of scaffold. The scaffold was hollow and the diameter of cross section was 0.42 cm; (c) 1- Cross-section of the microfiber. The microfiber was produced to form core-sheath structure by means of co-axial electro-spinning technology (500×); 2- SEM graph of transplanted scaffold (15 days) [98].

advancement of tissue growth[40].

In another work, Melt electro-spinning technique was employed for the manufacturing of PLA Tubular vascular grafts. It was found that the mass flow rate (MFR) had more important influence on the structure of electro-spun scaffolds when compared to the other fabrication parameters, such as voltage and distance between the spinneret and the collector. Tubular vascular grafts were produced by means of PLA and Poly-Propylene (PP) at the suitable MFR (25 g/10 min and 2.16 kg at 230 ºC) [33].

Mixture of cell matrix with electro-spinning technique resulted in constructing PLCL nano-fibrous based vascular grafts seeded with SMCs(Smooth muscle cells). SMCs were cultured for up to 7 weeks[97].

PLA-Silk Fibroin-Gelatin (PLA-SF-Gel) hybrid scaffolds were prepared for vascular tissue engineering and 3T3 mouse fibroblast cells cultured on scaffolds for 21 days that proved good proliferation. In Vivo assays showed that Subcutaneous-implantation investigation in Sprague rat after 3 months caused in bio-compatibility of the graft [24].

Weijie et al.[98] utilized co-axial electro-spinning method for combining Cistanche-Poly (saccharide) [CDPS] with PLA. CDPS and PLA were placed at the internal and outside layer correspondingly so as a core-sheath tubular scaffold was shaped (Fig. 7). Compared to natural tissues, CDPS-PLA co-axial scaffolds presented outstanding bio-mechanic possessions and blood-compatibility, so CDPS-PLA scaffolds retained respectable potential in vascular tissue engineering[98].

Poly (l-lactic acid-co-ε-caprolactone) [P(LLA-CL)] has good mechanical properties but poor biocompatibility. Blending Silk Fibroin (SF) with P(LLA-CL) can preserve the benefits of both these materials and conquer their disadvantages. P(LLA-CL)-SF nano-fibrous membranes may be appropriate for regeneration of the Corneal-Endothelium. Five nano-fibrous scaffolds having different P(LLA-CL)-SF blended ratios (100:0, 75:25, 50:50, 25:75, 0:100) were created. A human corneal endothelial (B4G12) cell line was cultured on the samples. Expression of some useful genes was as well noticed by real-time polymerase chain reaction. The 25:75 blended ratio membranes had the best transmittance among these scaffolds. All electro-spun nano-fibrous membranes demonstrated improved speed of cell adherence when compared with the control collection, particularly when the P(LLA-CL) ratio increased. The 25:75 blended ratio mats also had the highest cell proliferation. B4G12 cells could appearance a monolayer on all scaffolds, and most functional genes were also steadily expressed on all scaffolds. Just two genes proved changes in expression. All scaffolds confirmed good biocompatibility for cell adherence and monolayer formation. Amongst them, the 25:75 blended ratio P(LLA-CL)-SF nano-fibrous scaffold had the best transmittance and the highest cell proliferation[19].

In a different exploration, Wu et al.[99] fabricated PLCL-Collagen-Chitosan vascular graft in a canine femoral artery by means of electro-spinning process.

Blending of PLLA and Gelatin for enhancing cell adhesion sites were employed in fabricating PLLA-GEL tubular scaffolds for vascular tissue engineering. Aligned and random PLLA-GEL nano-fibers were fabricated via electro-spinning method. The size of fibers ranged from 100 to 500 nm. The SEM, fluorescent staining and viability analyzes tolled an increase in viability and proliferation of Human Umbilical Vein Endothelial Cells (HUVECs) and Smooth Muscle Cells (SMCs) proportional to gelatin substance. The aligned fiber morphology aids cells to orient and elongate along their long axis. Therefore the assays show that topographically aligned nano-fibrous scaffolds manage cellular organization and probably supply a good hold for attaining the vital association and physical properties of blood-vessel [23].

Wang et al.[32] mixed vascular endothelial growth factor (VEGF) with Heparin and overloaded in the core of a Poly(l-lactide-co-caprolactone) nano-fibrous mat using emulsion electro-spinning for helping rapid endothelialization.

In a different research, PLLA-GEL nano-fibrous scaffolds were electro-spun by Zhang et al.[15] and the blended material also exhibited high transparency. Poly (d,l-lactide-co-glycolide)-Collagen (PLGA-Col) blend was used in manufacturing scaffolds (4.75 mm internal diameter, 477 to 765 nm average fiber diameter, and 0.5 mm wall width). The nano-fibrous scaffolds displayed tensile strength of 0.37 MPa and young's modulus of 0.85 MPa, correspondingly[2].

Montini et al.[100] worked on the electro-spinning procedure as an adaptable method for obtaining nano-fibrous tubular constructions for vascular tissue engineering. A bi-layered scaffold composed of Poly(l-lactic acid) and Segmented

Poly(urethane) (PLLA-SPEU) blends for small diameter (5mm) vascular-bypass-grafts was attained with multi-layering electro-spinning[100].

A 50:50 PLCL co-polymer was productively melt-spun and electro-spun to individual and combined porous tubular scaffolds having dimensions of 5 mm in diameter and porosity of over 75% (Fig. 8). By means of two alternative solvent systems–acetone and HFIP(1,1,1,3,3,3-hexafluoro-2-propanol) for electro-spinning supplied different results in

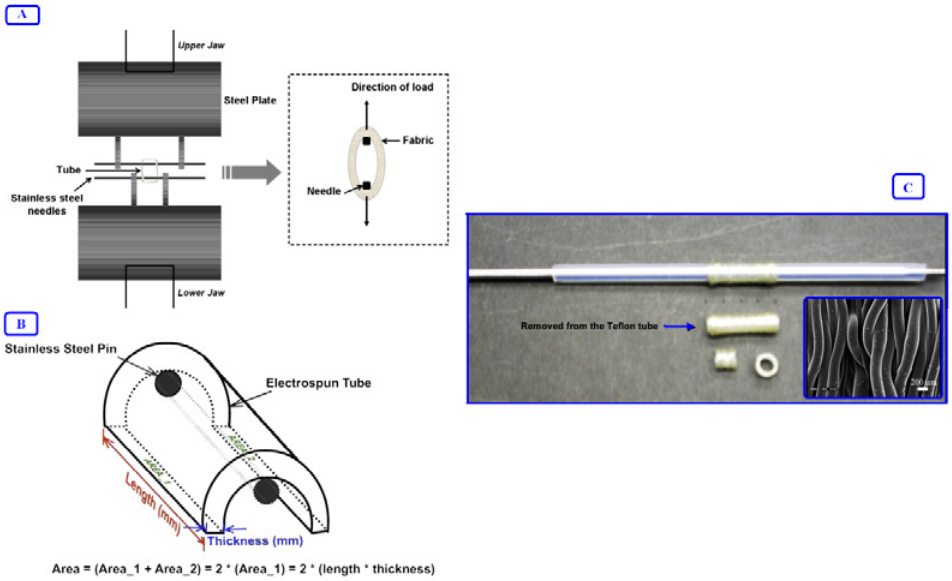

Fig. 8. (A) Commissioned holding border , (B) diagram presentation area-calculation , (C) Macroscopic appearance and SEM photo-micrograph of the melt-spun PLCL tubes[52].

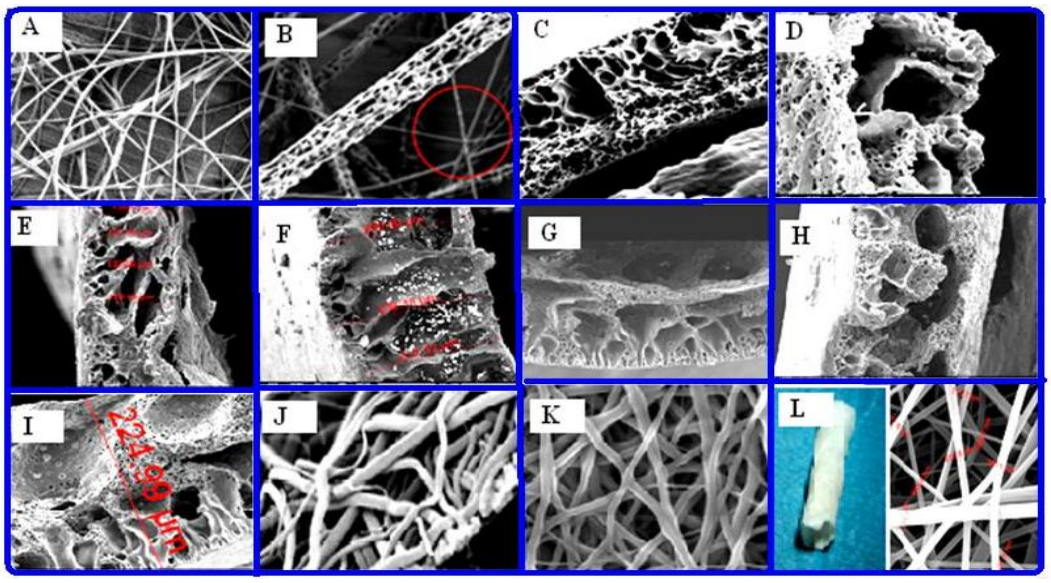

Fig. 9. SEM images of different PLA scaffolds for vascular tissue engineering; A) PLLA-CS (1:3) scaffolds; B) PLLA-CS (1:1) scaffolds; C) PLLA-PLA 90-10 tubular scaffolds prepared from a 8% wt polymer-dioxane solution at extraction rate of 20 cm/min, D) PLLA-PLA 90-10 tubular scaffolds prepared from a 8% wt polymer-dioxane solution at extraction rate of 30 cm/min ; E) PLLA-PLA 90-10 tubular scaffolds prepared from a 10% wt polymer-dioxane solution at extraction rate of 15 cm/min ; F) PLLA-PLA 90-10 tubular scaffolds prepared from a 10% wt polymer-dioxane solution at extraction rate of 20 cm/min ; G) PLLA-PLA 75-25 tubular scaffolds prepared from a 10% wt polymer-dioxane solution at extraction rate of 30 cm/min ; H) PLLA-PLA 75-25 tubular scaffolds; I) PLLA-PLA 75-25 tubular scaffolds prepared from a 10% wt polymer-dioxane solution at extraction rate of 40 cm/min ; J) Bilyered PLA-PCL scaffolds , K) SF-P(LLA-CL) 0:100 scaffplds; L) Tubular PHEA-PLA-PCL scaffold [8, 19, 35, 52, 64].

fiber dimensions, mechanical properties and cytotoxicity, but the HFIP solvent was ideal because it gave a more stable thread line. The mechanical properties of both types of tubes revealed greater strength and compliance than natural arteries of equivalent caliber. Results showed that these two systems can be combined to fabricate double-layered tubular scaffolds holding both melt-spun macro-fibers (<200 μm in diameter) and electro-spun submicron-fibers (>400 nm in diameter) [52].

Pitarresi et. al.[8] electro-spun a mixture of PCL and α,-poly(N-2-hydroxyethyl) (2-aminoethyl-carbamate)-D,L-aspartamide-graft-Poly(lactic acid) (PHEA-EDA-g-PLA) as scaffold for blood-vessel regeneration. PHEA-EDA-g-PLA functional groups were utilized to covalently bond a considerable quantity of heparin (36 μg per mg of scaffold) which has been occupied to organize the release of fibroblast growth factor. Results reveal that the existence of both heparin and growth factor controls the capability of endothelial cells cultured in vitro upon the scaffold to create an integral endothelial layer[8].

P(LLA-CL)-Collagen-Chitosan 3-D nano-fibrous tubular scaffolds electro-spun for vascular grafts. in vitro examinations performed with culturing ECs cells days on scaffolds. Results illustrated that ECs cells have good adhesion and proliferation on P(LLA-CL)-Collagen-Chitosan scaffolds compared to pure P(LLA-CL)[2]. A dual-porosity PLLA scaffold was developed for blood-vessel invasion. The nano-sized platelets were combined with PLLA solution, which was successively electro-spun and mechanically entangled by a cold compression molding procedure for a 3D scaffold[101].

Small diameter blood-vessel manufactured from Poly(l-lactic acid)-co-poly (ε-caprolactone) P(LLACL 70:30) (3 mm inner diameter) had mechanical assets nearer to that of native abdominal aorta. For instance, P(LLACL) nano-fibrous scaffold exhibited tensile strength of 3.9 ± 0.3 MPa in the circumferential direction, whilst the native abdominal aorta illustrated tensile strength of 5.29 MPa in the similar way. Also the scaffold approximately kept its integrity equipped 3 month in PBS solution at 37 °C. Collagen coated P(LLACL) nano-fibrous scaffold via air plasma treatment aided adhesion, spread, and proliferation of Human coronary artery endothelial cells (HCAECs) after 10 days of culturing[2].

SEM Observation

Fig. 9 demonstrates SEM images of different PLA scaffolds for vascular tissue engineering that

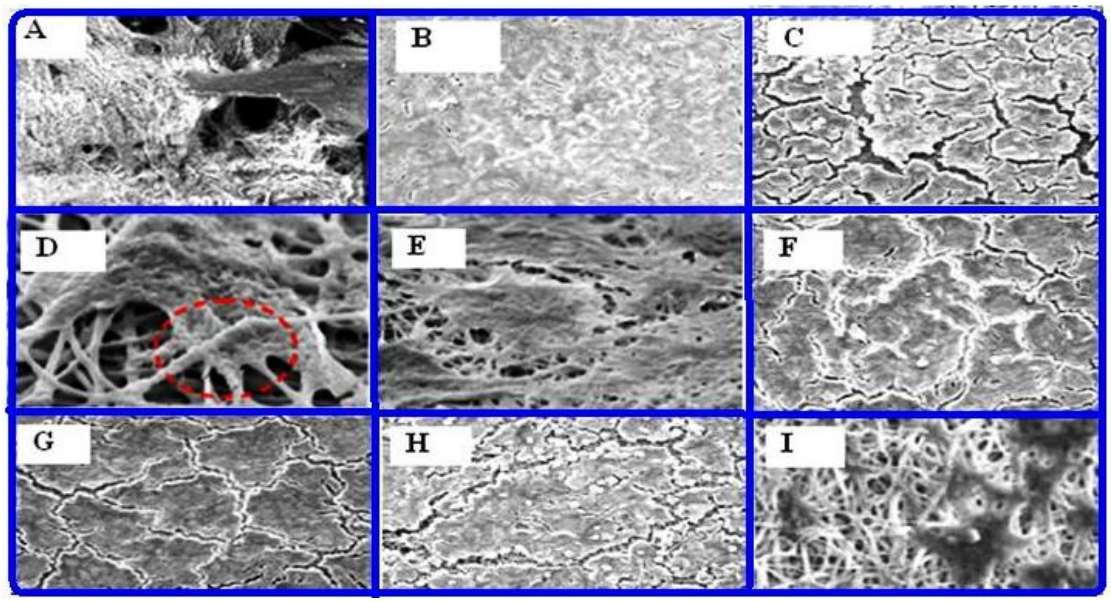

Fig.10. SEM images of different cells cultured on the PLA scaffolds: A) 3T3 mouse fibroblasts cells cultured on PCL-PLA nano-fibrous scaffold after 4 weeks. B) HCEC-B4G12 cells cultured on SF-P(LLA-CL) 100:0 nano-fibrous membrane after 1 week. C) Cells cultured on PLLA-CS after 1 day. D) Cells cultured on PLLA-CS after 7 days. E) Cells cultured on the PLLA-PLA scaffold after 14 days. F) HCEC-B4G12 cells cultured on SF-P(LLA-CL) 50:50 nano-fibrous scaffolds after 1 week. G) HCEC-B4G12 cells cultured on SF-P(LLA-CL) 25:75 nano-fibrous scaffolds after 1 week. H) HCEC-B4G12 cells cultured on SF-P(LLA-CL) 0:100 nano-fibrous scaffolds after 1 week. I) NIH 3T3 fibroblast cells (ATCC) cell attachment on PLCL scaffolds after 7 days of culture [14, 19, 35, 52, 64].

Table 3. Cytotoxicity and Cell Viability on PLA Vascular Scaffolds.

Type of Scaffold	Type of Cells	Unit of Cell Viability	Cell Viability (According to number of the days)								Cytotoxicity (%)	Ref.
			2 Hours	1 Day	2 Days	3 Days	4 Days	7 Days	14 Days	49 Days		
PLLA	UE7T—13	% (MTT assay)	—	0.6	—	—	0.62	0.7	—	—	—	[35]
PLLA—CS	UE7T—13	% (MTT assay)	—	0.61	—	—	0.7	1	—	—	—	[35]
PLLA	HUVECS	Cell number	—	—	120	—	—	—	—	—	—	[65]
PLLA + COll	HUVECS	Cell number	—	—	160	—	—	—	—	—	—	[65]
PLLA PdE: N	HUVECS	Cell number	—	—	180	—	—	—	—	—	—	[65]
PLLA PdE: N+ COll	HUVECS	Cell number	—	—	80	—	—	—	—	—	—	[65]
PLLA PdE:NH2	HUVECS	Cell number	—	—	70	—	—	—	—	—	—	[65]
PLLA PdE:NH2 + COll	HUVECS	Cell number	—	—	65	—	—	—	—	—	—	[65]
P(LLA—CA)—SF (8% w/v) 0:100	HCEC	OD 490 nm	—	0.35	—	—	—	—	—	—	—	[19]
P(LLA—CA)—SF (8% w/v) 25:75	HCEC	OD 490 nm	—	0.32	—	—	—	—	—	—	—	[19]
P(LLA—CA)—SF (8% w/v) 50:50	HCEC	OD 490 nm	—	0.5	—	—	—	—	—	—	—	[19]
P(LLA—CA)—SF (8% w/v) 75:25	HCEC	OD 490 nm	—	0.65	—	—	—	—	—	—	—	[19]
P(LLA—CA)—SF (8% w/v) 100: 0	HCEC	OD 490 nm	—	0.62	—	—	—	—	—	—	—	[19]
Electro—spun PLCL (Solvent : Acetone)	NIH 3T3 fibroblast	Absorbance, 550 nm (WST Assay)	—	0.77		0.07	—	0.1	0.63	—	—	[52]
Electro—spun PLCL (Solvent : HFIP)	NIH 3T3 fibroblast	Absorbance, 550 nm (WST Assay)	—	0.4		0.2	—	0.1	0.21	—	—	[52]
PLA— Fibrinogen (Random nano—fibers)	HUVECS	OD 490 nm	—	—	—	—	—	0.9	—	—	—	[14]
PLA— Fibrinogen (Aligned nano—fibers)	HUVECS	OD 490 nm	—	—	—	—	—	0.85	—	—	—	[14]
PLCL	SMCs	Cell number	—	—	—	—	—	—	—	11×10^5	—	[97]
PLA	BHK—21	—	—	—	—	—	—	—	—	—	154.3±11.7	[98]
PLA + 1% wt CDPS	BHK—21	—	—	—	—	—	—	—	—	—	173.7±13.5	[98]
PLA + 3% wt CDPS	BHK—21	—	—	—	—	—	—	—	—	—	193.8±14.2	[98]
PLA + 5% wt CDPS	BHK—21	—	—	—	—	—	—	—	—	—	209.6±15.7	[98]
PLA + 7% wt CDPS	BHK—21	—	—	—	—	—	—	—	—	—	214.6±13.4	[98]
PLA + 9% wt CDPS	BHK—21	—	—	—	—	—	—	—	—	—	100.0±3.8	[98]
PLA—Collagen	J774 Macrophages	Cell number	—	120	—	—	—	—	—	—	—	[102]
PLA—graft—Maleic Anhydride/Collagen	J774 Macrophages	Cell number	—	520	—	—	—	—	—	—	—	[102]
PLCL	Red Blood Cells	Absorbance, 570 nm (MTT Assay)	0.043 ± 0.002	—	—	—	—	—	—	—	—	[94]
PCL80	Red Blood Cells	Absorbance, 570 nm (MTT Assay)	0.078±0.01	—	—	—	—	—	—	—	—	[94]
PCL45 22%	Red Blood Cells	Absorbance, 570 nm (MTT Assay)	0.065±0.02	—	—	—	—	—	—	—	—	[94]
PCL45 16%	Red Blood Cells	Absorbance, 570 nm (MTT Assay)	0.081 ± 0.010	—	—	—	—	—	—	—	—	[94]

HUVECs : Human umbilical vein endothelial cells; HCEC : human corneal endothelial cells; SMCs : Smooth muscle cells; OD : Optical Density; WST : Water Soluble Tetra—Zolium Salt;

reviewed above and Fig. 10 illustrates the SEM images of different cells cultured on PLA scaffolds for vascular regeneration.

CONCLUSIONS

Vascular defects and damages are the utmost significant medical trouble and PLA scaffolds can be thought as a proficient key for this difficulty and support vascular regeneration. PLA bio-polymer has captured the most interest amongst the bio-degradable polymers as a tissue engineering material as PLA is easily process-able and degrades

Table 4. Comparison the Mechanical Properties of PLA Scaffolds with Some Natural Native Human Blood-vessels.

Type	Transverse Tensile Breaking Properties						Ref.
	Ultimate Stress (MPa)	Strain at Failure (%)	Elastic Modulus (MPa)	Burst Strength (mmHg)	Estimated Compliance (ml mm Hg^{-1})	Stiffness (N/m)	
Saphenous vein (circ.)	3	180	43	1680–3900	NA	NA	[2]
Saphenous vein (long.)	13	83	130	NA	NA	NA	[2]
Left internal mammary artery (circ.)	4.1	134	8	2000	NA	NA	[2]
Left internal mammary artery (long.)	4.3	59	16.8	NA	NA	NA	[2]
Femoral artery (circ.)	1–2	63–76	9–12	NA	NA	NA	[2]
Native Rabbit Aorta	2.61±0.4	86.7	—	1647±201	—	—	[2]
Melt—spun PLCL tubes	—	—	23.5 ± 0.9	—	0.0159	—	[52]
Electro—spun PLCL using acetone	—	—	24.6 ± 1.9	—	0.052	—	[52]
Electro—spun PLCL using HFIP	—	—	9.34 ±0.59	—	0.053	—	[52]
P(LLA—CA)—SF (8% w/v) 0:100	1.90±0.75	—	—	—	—	—	[19]
P(LLA—CA)—SF (8% w/v) 25:75	2.39±0.22	—	—	—	—	—	[19]
P(LLA—CA)—SF (8% w/v) 50:50	5.29±0.66	—	—	—	—	—	][19
P(LLA—CA)—SF (8% w/v) 75:25	9.39±0.69	—	—	—	—	—	][19
P(LLA—CA)—SF (8% w/v) 100: 0	7.47±0.38	—	—	—	—	—	][19
PLCL	1.91±0.56	135	—	604±4	—	—	[97]
PLLA	1.5	—	65	—	—	—	[35]
PLLA—CS	3	—	115	—	—	—	[35]
PLA—PCL	4.3 ± 0.2	47.0 ±6.3	30.9 ± 6.6	—	—	—	[2]
PLLACL coated with collagen	3.9 ± 0.3	—	16.6 ± 4.4	—	—	—	[2]
PLA	—	—	—	—	—	8000	[14]
PLA—Fibrinogen	—	—	—	—	—	500	[14]
Fibrinogen	—	—	—	—	—	50	[14]
PLA	0.55	34	—	—	—	—	[98]
PLA + 1% wt CDPS	0.575	35	—	—	—	—	][98
PLA + 3% wt CDPS	0.56	33	—	—	—	—	][98
PLA + 5% wt CDPS	0.58	35	—	—	—	—	][98
PLA + 7% wt CDPS	0.59	39	—	—	—	—	][98
PLA + 9% wt CDPS	0.62	37.5	—	—	—	—	][98
PLA	3.5	180	75	—	—	—	[102]
Collagen	0.75	20	25	—	—	—	[102]
PLA—Collagen	2.2	70	30	—	—	—	[102]
PLA—graft—Maleic Anhydride/Collagen	3.1	120	73	—	—	—	[102]
PLA—PGA	—	—	3	—	—	—	[62]
PLA—SF—Gel	2.21 ± 0.18	60.58 ± 1.23	—	1596±20	—	—	[24]

*Circ: circumferential; long: longitudinal; NA: not available; Ref: Reference number.

and disintegrates into natural metabolites while matching its degradation rate with the healing time of damaged human tissues. Therefore, this paper reviewed the potential of PLA scaffolds to favor vascular tissue engineering owing to its biological care and tunable degradation structures. At last, the authors suggest different approach "UV/Ozone Irradiation" for surface functionalization of PLA scaffolds so as to development the vascular cell adhesion, differentiation and proliferation. This approach is predictable to increase the success of vascular regeneration.

Table 5. Basic features of the PLA vascular scaffolds.

Type of PLA scaffold		Nano—fiber diameter (nm)	Specimen Thickness	Contact Angle (Degrees)	Tg (°C)	Tm (°C)	*Ref.**
P(LLA—CA)—SF (8% w/v) 0:100	Nano—fibrous	147±24	30±9.53 µm	38.36±0.41 (at 20 seconds)	—	—	[19]
P(LLA—CA)—SF (8% w/v) 25:75	Nano—fibrous	226±31	56±5.12 µm	49.03±0.67 (at 20 seconds)	—	—	][19
P(LLA—CA)—SF (8% w/v) 50:50	Nano—fibrous	255±37	62.5±7.93 µm	62.93±0.50 (at 20 seconds)	—	—	][19
P(LLA—CA)—SF (8% w/v) 75:25	Nano—fibrous	226±24	56±4.20 µm	71.58±0.15 (at 20 seconds)	—	—	][19
P(LLA—CA)—SF (8% w/v) 100: 0	Nano—fibrous	542±107	128±6.65 µm	125.78±0.02 (at 20 seconds)	—	—	][19
PLA— Fibrinogen (Random)	Nano—fibrous	400	—	—	—	—	][14
PLA— Fibrinogen (Aligned)	Nano—fibrous	250	—	—	—	—	][14
PLA—CS—HLC	Nano—fibrous	148	—	—	—	—	[30]
PLLA—PLA 90:10	Tubular	—	180 µm	—	—	—	[64]
PLLA—PLA 75:25	Tubular	—	165 µm	—	—	—	[64]
Air—Spun PLA Nano—fibers	Nano—fibrous	—	—	110 (at 20 seconds)	—	—	[18]
Air—Spun PLA Nano—fibers	Nano—fibrous	—	—	80 (at 40 seconds)	—	—	][18
Air—Spun PLA Nano—fibers	Nano—fibrous	—	—	45 (at 60 seconds)	—	—	][18
Air—Spun PLA Nano—fibers	Nano—fibrous	—	—	10 (at 80 seconds)	—	—	][18
Electro—spun PLCL Tubes (Solvent : Acetone)	Tubular	—	0.033 mm	—	—	—	[52]
Electro—spun PLCL Tubes (Solvent : HFIP)	Tubular	—	0.118 mm	—	—	—	][52
PLA—graft—Maleic Anhydride	Nano—fibrous	—	—	—	52.11	148.71	][102
PLA—graft—Maleic Anhydride : Collagen 30:1	Nano—fibrous	450	—	—	61.82	152.3	][102
PLA—graft—Maleic Anhydride : Collagen 15:1	Nano—fibrous	650	—	—	61.73	152.51	][102
PLA—Col	Nano—fibrous	500	—	—	60.44	151.75	][102
PLA	Nano—fibrous	100	—	—	60.36	151.75	][102
PLCL	Nano—fibrous	1100	—	—	—	—	][94
PCL80	Nano—fibrous	860	—	—	—	—	][94
PCL45 22%	Nano—fibrous	470	—	—	—	—	][94
PCL45 16%	Nano—fibrous	300	—	—	—	—	][94

HFIP : 1,1,1,3,3,3—Hexafluoro—2—Propanol

CONFLICT OF INTEREST

The author declares no conflict of interest.

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