

BIODEGRADABLE POLY-EPSILON-CAPROLACTONE (PCL) FOR TISSUE ENGINEERING APPLICATIONS: A REVIEW

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Abstract. Biodegradable polymers have been used in biomedical applications generally, and in tissue engineering especially, due to good physical and biological properties. Poly-epsilon-caprolactone (PCL) is a one of biodegradable polymers, which has a long time of degradation. But the mechanical properties, biodegradability and biocompatibility of the pure PCL cannot meet up with the requirement for some of the biomedical applications such as bone tissue engineering, for that many researches have established to focus on the modification of the PCL. In this review, different results on the fabrication of PCL for specific field of tissue engineering, tissue engineering incorporated in different PCL, surface modifications, blending with other polymers and their micro-porous structure are represented in brief outcomes. In addition dissolution of PCL in different organic solvents and the effect on their properties was attainable. Moreover, the physical and biological properties of PCL for different type of tissue engineering applications (hard and soft tissue) are obtainable.

1. INTRODUCTION

PCL is biodegradable polyesters, and these include polymers such as polyglycolic acid (PGA), poly-L-lactide (PLLA) and their copolymers. It is a semi-crystalline polymer due to its regular structure, and its melting temperature is above body temperature (59-64 °C), but its T_g is -60 °C, so in the body the semi crystalline structure of PCL results in high toughness, because the amorphous domains are in the rubbery state [1-3]. PCL was used as a biodegradable packaging material as it could be degraded by microorganisms [4]. However, afterwards, it was confirmed that PCL could also be degraded by a hydrolytic mechanism under physiological conditions [5]. Most the biodegradable polyesters show slower degradation rates than natural biopolymers. The erosion rate of Nano-fiber matrices made from these materials follows the order $PGA > PLGA > PLLA > PCL$ [6]. Among the polyesters, PCL degrades

more slowly due to the presence of five hydrophobic $-CH_2$ moieties in its repeating units, thus limiting its application to delivery devices or commercial sutures [7,8]. PCL is subjected to hydrolytic degradation due to the susceptibility of its aliphatic ester linkage to hydrolysis [9]. PCL is useful for biomedical materials due to its physical properties [10-14] and biological properties [15-18].

Tissue engineering (TE) is a multi-disciplinary field focused on the development and application of knowledge in chemistry, physics, engineering, life and clinical sciences to the solution of critical medical problems, as tissue loss and organ failure [19]. It involves the fundamental understanding of structure function relationships in normal and pathological tissues and the development of biological substitutes that restore, maintain or improve tissue function [20]. Scaffolds with designed microstructures provide structural support and adequate mass transport to guide the tissue

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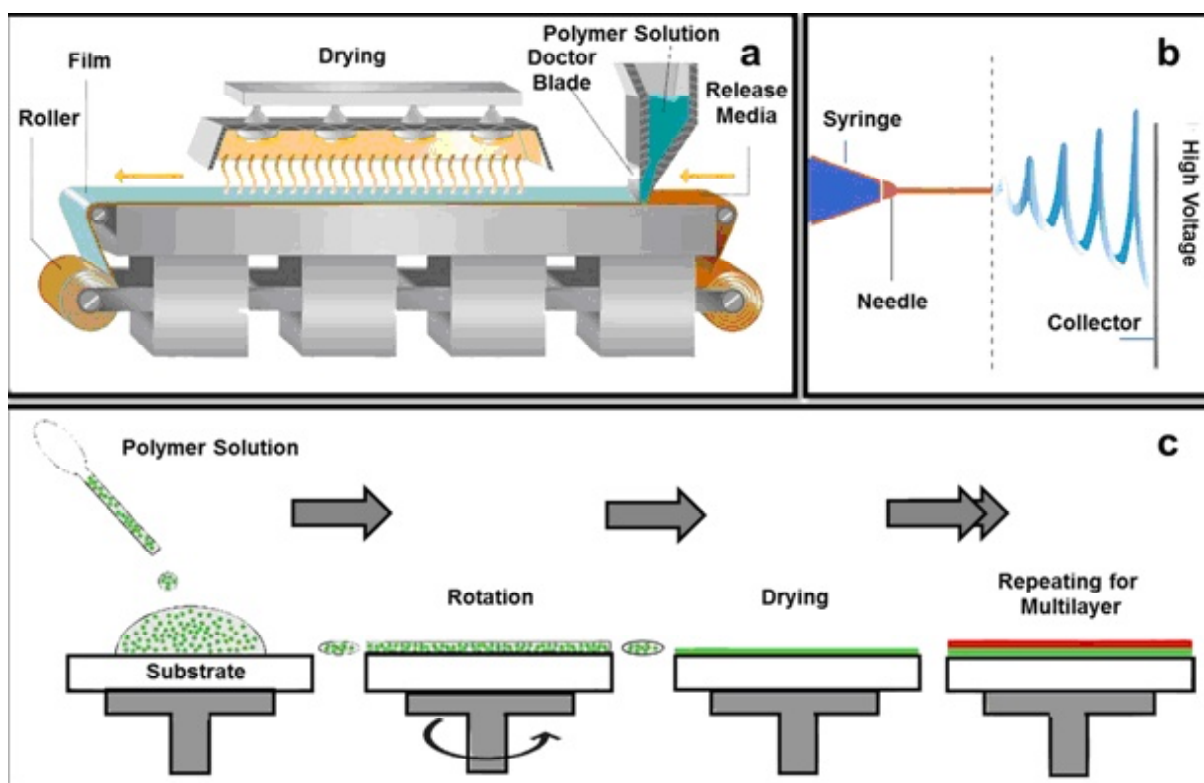


Fig. 1. Schematic representation of common fabrication technology methods that have been used to fabricate PCL. (a) Solvent casting, (b) Electrospinning, and (c) Spin coating.

regeneration [21]. In TE the scaffold also serves as a 3D template for cell adhesion, proliferation, differentiation, extracellular matrix (ECM) formation and provides an appropriate environment for the newly formed tissue. Generally, the ideal scaffold for tissue regeneration should possess good biocompatibility, biodegradability with controllable degradation kinetics, easy fabrication and sufficient mechanical properties. The modified PCL nanofibers can be used as a suitable broad spectrum scaffold for skin, cartilage, bone, cardiac constructs for efficient tissue engineering applications [22].

The mechanical properties, biodegradability, and biocompatibility of the pure PCL aren't enough with the requirements for some of the application engineering, such as bone tissue engineering. For that reason PCL can also be used as one of the blend component of biomaterials or as a copolymer. The mechanical properties of available polymeric porous scaffolds revealed insufficient stiffness and compressive strength compared to human tissues, so the possibility to use inorganic/organic nanostructures to include in biodegradable polymers could be an important possibility to increase and modulate mechanical, electrical and degradation properties. The interface adhesion between nanoparticles and polymer matrix is the major factor affecting the nano-composite properties. In order to

increase the interfacial strength between the two phases, various methods have been tried in the past [23-27].

The aim of this paper is to put in evidence the evolution and potential of developing PCL approaches in tissue engineering applications. So, this paper reviews current research trends in relevant PCL materials for tissue engineering: blending, dissolution, microstructure, mechanical properties, degradation, including strategies for the fabrication of PCL scaffolds with inter-connected pores.

2. FABRICATION OF PCL SCAFFOLD

Tissues in the body are organized into three dimensional (3D) structures as functional organs and organ systems. To engineer functional tissues and organs successfully, the scaffolds have to be designed in order to facilitate cell distribution and guide tissue regeneration in three dimensions [28-30].

One critical issue is the realization of artificial supports, with detailed physical, mechanical and biological properties [19,31]. Several preparation methods have been reported for porous scaffolds, including porogen leaching [32-34], saturation and release of CO₂ [35,36], 3D printing [37] and phase separation techniques [34,38-41], while the

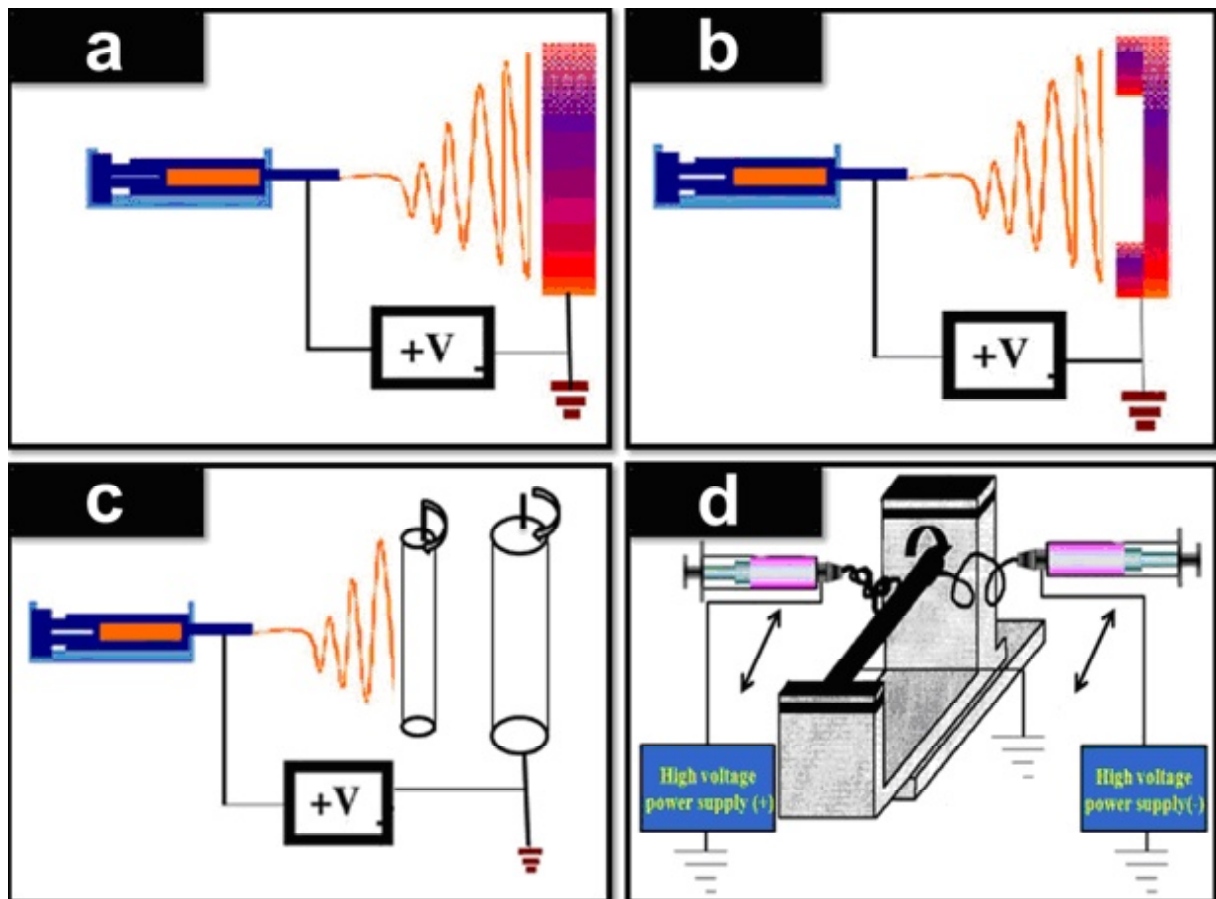


Fig. 2. Schematic representation for development in the electrospinning technology. (a) conventional electrospinning, see [57]; (b) novel electrospinning collector to fabricate 3D scaffold, see [57]; (c) novel electrospinning collector to fabricate nano-fibrous tubes, see [66], and (d) double-ejection electrospinning system to fabricate multilayered scaffold, see [29].

electrospinning technology have been used to fabricate fibrous scaffold. In this part of the review different techniques that are widely used to fabricate PCL for the tissue engineering applications will be shown. Fig. 1 shows the common fabrication methods that are used to fabricate PCL.

2.1. Solvent casting technology/ particulate leaching

The solvent casting/particulate leaching method is the most commonly mentioned method, and it used relatively for thick films, but it can also use for thin PCL membrane, when the process of casting onto a glass substrate, Fig. 1a shows schematic representation for the solvent casting technology. The surface properties of this kind of films depend on the nature of the solvent that was used [42]. Polymer films produced by casting a solution of the polymer on a cold or heated polished surface, and removal of the solvent from the polymer. The resultant film undergoes thermal treatment to

remove internal stresses, and also, when necessary, uniaxial or biaxial orientation [43,44].

Solvent casting has been used to fabricate PCL films [5,42], blending PCL with PLA [45] nano-composite scaffold (combination of PCL and forsterite nano-powder, Magnesium Phosphate (MP), nanohydroxyapatite (nHA) or hydroxyl apatite (HA)) for bone tissue engineering applications [46-49].

2.2. Electrospinning technology (ES)

The electrospinning process is a technique used to produce ultra-fine polymer fibers, Figs. 1b and 2a show the schematic representation of the electrospinning technology. There are many research groups that have produced ES nano-fibers using various types of polymers for different applications [50-52]. The biomedical applications are one of the main applications for the ES technology. PCL can be fabricated by the electrospinning technology into nonwoven membranes [10,53-56] and 3D scaffold which was obtained by modifying

the collector of the conventional electrospinning by novel collector as seen in Figs. 2a and 2b [57].

ES has been used to fabricate nano-composite materials, composed of PCL and other ceramic materials such as Aluminum Oxide (Al_2O_3) to nano-fibrous scaffold [58]. In addition, ES has been used to fabricate PCL blending with other polymers such as (recombinant spider silk protein and gelatin) (pNSR32&Gt) [59], polylactic acid (PLA) [60], PLGA [61], silk fibroin (SF) [62-64] and polyurethane (PU) [65].

In order to fabricate different structures for the biomedical applications, ES has been devolved. Huang *et al.* (2011) developed a novel collector (as shown in Fig. 2c)) to electrospin different polymers into seamless tubular scaffold with highly aligned nano-fibers along their axial directions [66]. While Nguyen and Lee (2012) used a double-ejection electrospinning system to fabricate multilayered scaffold composed of PCL–gelatin/PLGA–gelatin/PLGA–chitosan artificial blood vessels (Fig. 2d), they showed that the cross-linked PCL–gelatin/PLGA–gelatin/PLGA–chitosan artificial blood vessel scaffold displayed excellent flexibility, and was able to withstand high pressures and promoted cell growth. Thus, this novel material holds great promise for eventual use in artificial blood vessels [29].

2.3. Separation phase technique

The phase separation mechanism could be liquid–liquid demixing, which generates polymer-poor and polymer-rich liquid phases. In addition, when the temperature is low enough to allow the freeze of the solution, the phase separation mechanism would be solid–liquid demixing, which forms frozen solvent and concentrated polymer phases. After the removal of the frozen solvent, the remained space would become pores. By adjusting the polymer concentration, using different solvent, or varying the cooling rate, phase separation could occur via different mechanisms, resulting in scaffolds with various morphologies [38,40,41].

Ho *et al.* (2004) studied compared with the freeze-drying method; the presented methods are time and energy-saving, with less residual solvent, and easier to be scaled up. Besides, the problem of formation of surface skin can be resolved and the limitation of using solvent with low boiling points can be lifted by the presented methods. They showed that with the freeze extraction and freeze gelation methods, porous PLLA, PLGA, chitosan and alginate scaffolds were successfully fabricated. In addition they

showed that the preliminary data of cell culture on the new fabricated scaffolds were well [67].

PCL/PLA porous scaffold has been fabricated by separation phase technique (freeze extraction) [68,69]. While GRANDI *et al.* (2010) proved that the separation phase technique is a useful method to process PCL into a desired shape and size, prepared with Ca_2+ alginate, which has been shown threads resemble the porosity and the homogeneous pore size distribution of native bone [70].

2.4. Spin coating (casting) technology

Spin coating is a procedure used to apply uniform thin films (below 10 nm) to flat substrates, an extra amount of a solution is placed on the substrate, which is then rotated at high speed in order to spread the fluid by centrifugal force, spin coating is called a spin coater, or simply spinner, as shown in Fig. 1c. The film thickness can be adjusted by varying the rotation speed, the rotation time, and the concentration of the used solution. The disadvantage of this method is that it is limited by the solvent and that no lateral resolution is possible. Spin coating has been used to fabricate polystyrene (PS)/PCL blends into thin films, which have great potential application in the field of biomaterials [71].

Tiaw *et al.* (2006) studied comparison between the Spin casting, 2-Roll Milling, and Solution Casting as fabrication methods to fabricate ultrathin PCL films, and they showed that the fabrication of sub-micrometer ultrathin PCL films were successfully carried out through biaxial drawing of the spin cast films. All films were biaxial drawn to their limit, and it was found that films made from 2-roll mill have the highest drawing ratio while that of spin cast film have the lowest drawing ratio [72].

2.5. Other methods

Other preparation methods have been reported for porous scaffolds including:

Gas Foaming and Spontaneous Emulsion Droplets Adherence (GF-SEDA) technique: GF-SEDA technique can be used to fabricate PCL scaffold, Bao *et al.* (2004) used GF-SEDA to prepare PCL/BCP-HCM 3D scaffolds [73].

Hot Pressing technique: Hot pressing is the simultaneous application of elevated temperature and compressive stress to consolidate fine green pressed powders into partially or fully sintered components. Hot pressing can be used to fabricate soft tissue engineering, it has been used to fabricate PCL membrane scaffold for vascular graft application [74,75].

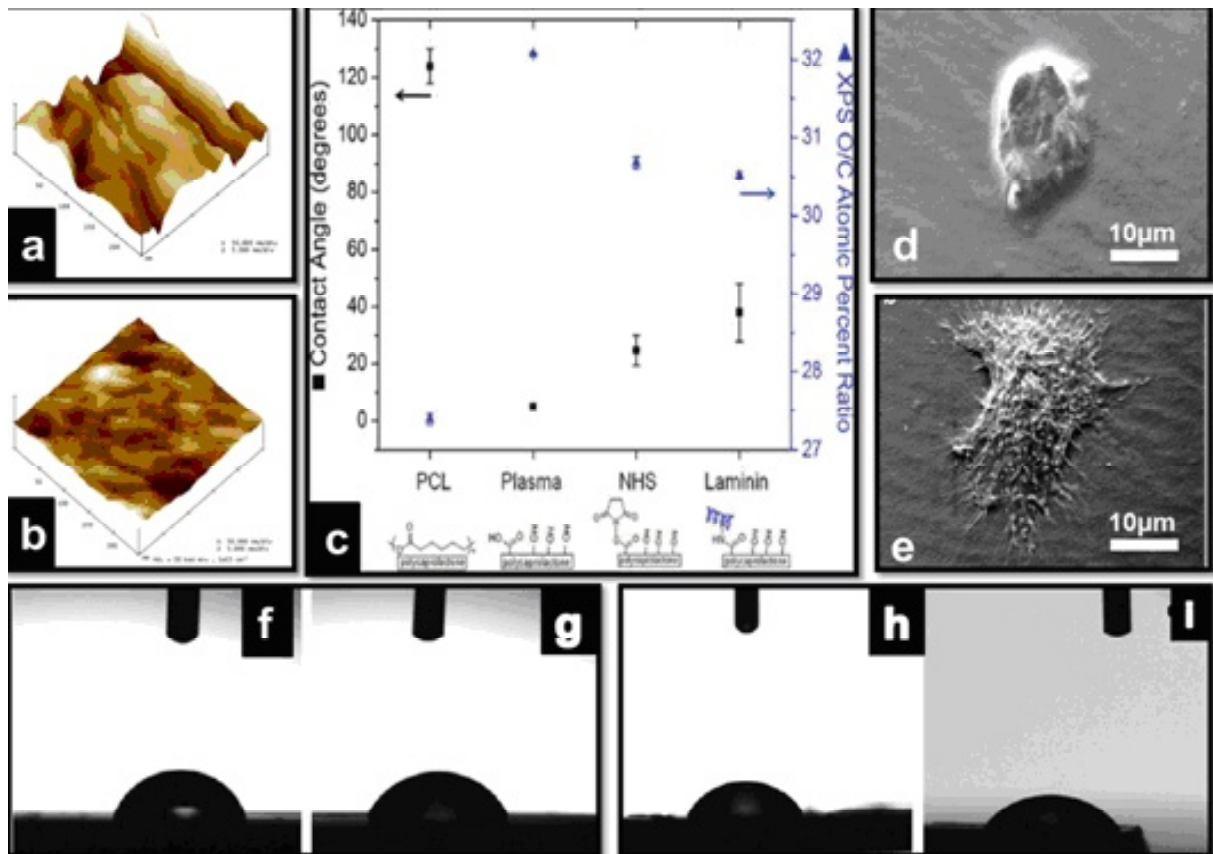


Fig. 3. The surface modifications of PCL (a) and (b) AFM images (a) PCL untreated (b) PCL irradiated, see [80], (c) Relationship between (Left vertical axis) Sessile-drop water contact angle, (Right vertical axis) Atomic O/C ratios of native and modified polycaprolactone nanofibers as determined by X-ray photoelectron spectroscopy and electrospun PCL fiber mats with the following surface chemistries: (left to right) unmodified control (PCL), plasmatedreated PCL (Plasma), plasma-treated PCL with covalently attached N-hydroxysuccinimide (NHS), plasma-treated PCL + NHS with covalently attached laminin (Laminin), see [55], (d) and (e) SEM micrographs of cells attached to (d) Untreated PCL and (e) ASPN treated PCL, see [81], and (f), (g), (h) and (i) Assessment of mean static contact angles of (f) ungrafted (pure) PCL, 78°, (g) AA grafted PCL, 69°, (h) HMD coupled PCL, 65°, and (i) VEGF-protein coupled PCL, 54°, see [86].

Fused Deposition Modeling (FDM): FDM is another rapid prototyping technique. With FDM, the layers are laid out one by one using a heated nozzle. A coiled wire of material is fed through the nozzle and extruded out onto the prototyping platform. By turning the flow of the material on and off and moving the nozzle relative to the platform, complex structures can be built. The resolution of this technique depends on how small the extruded strand of material can get. (Bio Cell Printing instrument has been invented by Bartolo *et al.* (2011) to fabricate PCL scaffolds [76].

3D Plotting System: 3D plotting has been used to fabricate scaffold for biomedical applications [77], and it has been used for fabricating PCL scaffold to enhance bone regeneration [78].

Melt stretching and multilayer deposition (MSMD): MSMD has been introduced as a novel to

fabricate PCL /chitosan (CS) scaffolds obtained optimum results in terms of physical properties and cellular response [79].

3. SURFACE MODIFICATION OF PCL

The surface modification of synthetic tissue engineering scaffolds is essential to improving their hydrophilicity and cellular compatibility, in this part of the review different modification methods that are widely used on the surface of PCL will be shown.

Arginine-glycine-aspartic acid (RGD) is used commonly to modify the surface of PCL, RGD-containing molecule has been coated on PCL small-diameter tubular grafts scaffolds to improve the functional surface (thrombus formation) [54]. On the other hand Marletta *et al.* (2005) used human bone-derived osteoblasts to test the effects of surface modification by low energy ion beams of a PCL

substrate and subsequent RGD adsorption. They suggested that new strategies involving irradiation-based treatments can be adopted to promote the initial steps of bone deposition onto synthetic surfaces, exploiting the surface-induced reorganization of the ECM matrix. Figs 3a and 3b show AFM images of PCL surfaces before and after irradiation. One can see clearly that the irradiated PCL surfaces were smoother than the untreated ones and exhibited also characteristic fiber-like features of nanometric dimension [80].

Plasma treatment is an effective way to increase the hydrophilicity of a surface, but the incorporation of biomolecules is also important to control cellular adhesion and differentiation, among many other outcomes. The active screen plasma nitriding (ASPN) technique has been used to improve cell attachment, as shown in Figs. 3d and 3e. The ASPN treated PCL has shown good cell attachment compared with untreated PCL. However after the treatment the enzymatic degradation rate is slower compared with untreated PCL film [81]. In addition, the hemocompatibility and endothelialization of PCL intended as a scaffold material for bioartificial vessel prostheses have been improved by terminal amino groups via ammonia (NH_3) plasma, oxygen (O_2) plasma/aminopropyltriethoxysilane (APTES), and 4,4'-methylenebis (phenyl isocyanate) (MDI) /water. The two modification methods have shown promising methods to optimize PCL as scaffold material for bioartificial vessel prostheses [82]. While stable hydrophilic surfaces has been achieved modifying electrospun PCL grafts with a class II hydrophobin (HFBI) coating, which may have potential for development of vascular grafts for introducing cell-specific binding molecules into PCL scaffolds, that can endothelialize rapidly in vivo [83].

Other methods of plasma treatment can use to modify surface of PCL, Zander *et al.* (2012) oriented PCL ES fibers were modified by air plasma treatment, followed by the covalent attachment of laminin. They controlled the amount of protein incorporated onto the fiber surface by varying the reaction time and the protein solution concentration. In addition they showed that the effect of protein concentration on the neurite outgrowth of neuron-like PC12 cells was evaluated, and outgrowth rates were found to be positively correlated to increasing protein concentration. Figure 3(b) displays the water contact angle and XPS oxygen-to-carbon ratio (O/C) for electrospun PCL fiber mats with the following surface chemistries: unmodified control (PCL), plasmatreated PCL (Plasma), plasma-treated PCL with covalently attached N-hydroxysuccinimide (NHS), plasma-treated PCL + NHS with covalently

attached laminin (Laminin), and it showed clearer that Electrospun PCL nano-fibers were fabricated and functionalized with covalently attached laminin to test for improvements in bioactivity [55].

Marletta *et al.* (2007) evaluated the attachment, proliferation and differentiation to the osteoblastic phenotype of human marrow stromal cells (MSC) when seeded on PCL thin films before and after irradiation with 10 keV He⁺. They showed that the change of PCL surface properties induced by ion beam irradiation is confirmed to enhance the adhesion of MSC and support their differentiation [84].

Composite of fibrin, fibronectin, gelatin, growth factors, and proteoglycans has been coated on the PCL scaffold which was prepared using PEG as a porogen. The endothelial cell growth has been improved, and the scaffold can be a suitable candidate for cardiovascular tissue engineering [85]. While, wettability of PLLA and PCL has been improved by a functionalization process to immobilize vascular endothelial growth factor (VEGF) proteins onto the surfaces, modification is exemplified by PCL samples in Figs 3f, 3g, 3h, and 3i. Optimal water contact angle values for maximal cell adhesion have been reported to be in the range of 45–70° or in the region of 30–60°. Such moderate surface polarities were achieved for both VEGF-modified polymers. At very low contact angles polymeric materials increase their water uptake which leads to a reduction of protein adsorption, which is necessary for cell recognition and attachment. Even if cell receptors are present, they cannot provide the mechanical strength to promote cell spreading. Very high contact angles, where the surface energy is low, are associated with a very low cell-conductive behavior and exhibit a protein denaturing response [86].

Double Protein has been coated on PCL surfaces, and XPS and ToF–SIMS have been used as high-vacuum surface analysis techniques. It shows clearly that the complementarities of XPS and ToF–SIMS in biomedical surface modification research [87]. While, the biological performance of the double protein-coated PCL (involving gelatin type B and fibronectin, from 2D PCL films to 3D PCL scaffolds produced by rapid prototyping) substrates reflected, by the initial cell adhesion, proliferation, and colonization was superior compared to the other surface modification steps [88].

4. BLENDING OF PCL

The foundation of tissue engineering for diagnostic applications is based on the ability to exploit living

cells in a variety of ways. Tissue engineering research includes the following areas: biomaterials, cells, biomolecules, engineering design aspects, biomechanical aspects of design, informatics to support tissue engineering, stem cell research, etc. [61]. The PCL scaffolds currently used for biomedical application, however, are still far from optimal in terms of mechanical endurance and biocompatibility. Many studies in blending PCL have been established for the purpose of improving mechanical endurance and biocompatibility, which we will be shown in this part. Table 1 shows the blending of PCL with natural polymer, synthetic polymer and ceramic.

4.1. Blending with natural polymer

In order to improve the mechanical endurance and biocompatibility, PCL has been blended with natural polymer such as chitosan (CS), silk fibroin (SF), spider silk, collagen, elastin and gelatin (Gt).

PCL and chitosan have been shown well mixed and physically co-existed in the composite structures, as long as the mechanical properties of three dimensional (3D) CS/PCL composite hydrogels scaffolds have been improved compared with pure PCL [89]. The physical properties of the composite scaffolds have been tailored by altering the proportion of PCL and CS, as the PCL/20%CS scaffolds obtained optimum results in terms of physical properties and cellular response, the increasing in the CS proportions tended to reduce the micro-groove pattern, surface roughness, tensile strength and elasticity of the filaments, whilst compressive strength of the PCL/CS scaffolds was not affected [79].

PCL and silk fibroin have been fabricated to hybrid scaffolds in a porous structure; however the hydroid scaffolds have been shown good cell adhesion, growth and proliferation, and have

Table 1. Blending of PCL with other polymers.

No	Type of polymers	Blending with	Fabrication Technique	Application	Ref.			
1	Natural	Chitosan	Lyophilisation	T E	[89]			
			MSMD	Bone .TE	[79]			
		Silk	Lyophilisation	Scaffold. TE	[74]			
			Electrospinning	TE	[63,64]			
			Electrospinning	Scaffold. TE	[62]			
			Electrospinning	Vascular. TE	[59]			
		2	Synthetic	Spider silk and Gelatin	Separation Phase	Bone. TE	[70]	
					Electrospinning	TE	[90]	
				Alginate	PLL and MWCNTs	Solvent-Casting	TE	[45]
					Polyurethane (PU)	Electrospinning	Vascular TE	[65]
PLGA	Electrospinning				TE	[61]		
PLLA	Freeze Extraction				Membranes TE	[68,69]		
3	Ceramic	Polystyrene (PS)	Spin-coating	Biomaterials	[71]			
			PGA	Separation Phase	Bone. TE	[70]		
		Forsterite (Mg_2SiO_4)	Solvent-Casting and Particle Leaching	Bone. TE	[48]			
			Separation Phase	Bone. TE	[70]			
		Calcium Alginate	Aluminum oxide	Electrospinning	TE and dental	[58]		
			Magnesium Phosphate	Particulate Leaching	Bone. TE	[46]		
			Biphasic Calcium Phosphate	GF-SEDA	Bone. TE, DDS, and Other	[73]		
			Nanohydroxyapatite (nHA)	MM-M/LT	Cartilage. TE	[47]		
	Bioactive glass microspheres	Solvent-Casting	Bone. TE	[91]				

Note: TE is Tissue engineering, DDS is Drug Delivery Systems, MSMD is Melt Stretching and Multilayer Deposition, GF-SEDA is Gas Foaming and Spontaneous Emulsion Droplets Adherence, and MM-M/LT is Modified Melt-Molding /Leaching Technique.

excellent biodegradability and biocompatibility [62-64,92].

The addition of hyaluronan (HA) component transformed current PCL/SF components into hydrophilic fibers, which caused the suppression of non-specific protein adsorption, resulting in the reduction of fibrosis tissue thickness and macrophages adhesion in vivo [92].

SF, collagen, elastin and PCL composite have been fabricated by electrospun to create a tri-layered structure (small diameter bioresorbable arterial grafts), gradual decrease in medial layer compliance has been shown with the increasing PCL content, while changes in PCL, elastin and the silk content in the adventitial layer have shown varying effects [93]. While as spider silk protein (pNSR32), PCL and gelatin (Gt) composite polymer solution have been fabricated to using ES to nanofibrous structure (tubular scaffold), which has been shown high porosity and good cytocompatibility [59].

4.2. Blending with synthetic polymer

As it's known PCL degrades most slowly due to the five hydrophobic $-CH_2$ moieties in its repeating units, thus limiting its application to delivery devices or commercial sutures. For all this PCL has been blended with other synthetic biodegradable polymer such as PLLA, PGA, PLGA, PU and PS to control the degradation time.

Blending PLLA with PCL has been fabricated to porous membranes. The addition of PCL led to the increase in the degradation time of PLLA and unfortunately a limited loss of the mechanical properties. However, compression stress-strain experiments show the characteristic behavior of porous materials with a yield stress that rapidly drop [68,69]. Whereas MWCNTs have been added to the blending of PLLA and PCL as nano-composite for scaffold, the degradation kinetics of nano-composite for scaffolds can be engineered by varying the contents of MWCNTs [45].

PCL has been blended with PGA, and then has been fabricated by separation phase technique for bone tissue engineering applications [70].

PCL has been blended with PLGA, and the composite scaffolds have been shown increasing in the biocompatibility at increasing percentages of PLGA, and also good cell adhesion and proliferation of fibroblast cells on electro-spun mats [61].

Gravity spun PCL fibers with elastic electrospun PU fibers have been fabricated to a compatible PCL/PU composite scaffold; the luminal PCL surface of the scaffold supports the formation of stable functional endothelial cells (EC) monolayer, these

attributes, combined with controlled release of bioactive molecules, show the potential of this material as a favorable scaffold for vascular tissue engineering [65].

In addition unique phase separation and crystal morphologies thin films have been fabricated from polystyrene (PS)/PCL blends, which have great potential application in the field of biomaterials [71].

4.3. Blending with ceramic

Blending PCL with ceramic has been applied for bone applications, to improve the mechanical properties. Calcium alginate as porogen agents have been used to prepare PCL scaffolds, which has shown threads resemble the porosity and the homogeneous pore size distribution of native bone [70]. While as, the mechanical properties of ES PCL scaffolds have been improved, when blended with aluminum oxide (Al_2O_3) [58]. Magnesium Phosphate (MP) has been blended with PCL to fabricate MP/PCL composite porous scaffolds, which lead to accelerate the degradation time of composite compared with pure PCL [46].

Hydroxyapatite (HA) has been widely used as a biocompatible ceramic material in many areas of medicine, but mainly for contact with bone tissue, due to its resemblance to mineral bone [28]. HA ($Ca_{10}(PO_4)_6(OH)_2$) is the major mineral component (69% wt.) of human hard tissues, it could be natural or synthetic, and it possesses excellent biocompatibility with bones, teeth, skin and muscles, both in-vitro and in-vivo. HA promotes bone in growth, biocompatible and harden in situ and it has Ca/P ratio within the range known to promote bone regeneration (1.50-1.67). HA is biocompatible and osteoinductive and it is widely employed in the hard tissue repair in orthopedic surgery and dentistry [31,94]. In addition PCL/nHA composite scaffolds have shown promising potentials for cartilage tissue engineering [47].

The improvement of the mechanical properties and biological performance of PCL have been applied by reinforcing PCL with bioactive glass microspheres (BGMs) [91], and glass fibers from a binary calcium phosphate ($50P_2O_5 + 50CaO$) glass [95]. In addition Forsterite (Mg_2SiO_4) has been blended with PCL to improve the mechanical properties, bioactivity, biodegradability, and non-cytotoxicity [48].

5. DISSOLUTION OF PCL

PCL has dissolved in most of the organic solvent; Table 2 shows the solubility of the PCL in different organic solvent and the fabrication methods. Different

Table 2. The solubility of the PCL in the different organic solvents.

NO	Solvent	Concentration	Fabrication Technique	Ref.
1	Acetone (AC)	10 W/V%	Gravity Spinning	[65]
		15 w/w%	Electrospinning	[53,96]
		5 g\100 ml	Solvent Casting	[42,96]
2	Acetic Acid	5-15 w/w%	Electrospinning	[95]
3	Chloroform (CF)	4 g\100 ml	Evaporation of the solvent	[82]
		1-5 g/100 ml	Solvent Casting	[16,42,48,81]
		10 wt. %	Electrospinning	[10]
		3% w/v	Thin film onto p- doped silicon	[80,84]
4	CF and Methanol	10-20 W/V%	Electrospinning	[54,56,57,97]
5	Dichloromethane (DCM)	4.5 w/w%	Solvent Casting	[85]
		15 w/w%	Electrospinning	[53]
		10% (w/v)	Particulate Leaching	[46]
6	Dimethylformamide (DMF)	15 w/w%	Electrospinning	[53]
7	DCM/Methanol	10 wt%	Electrospinning	[58]
8	DCM/DMF	10 w/v%	Electrospinning	[83]
		-	GF-SEDA	[73]
9	Dioxane	15 w/w%	Freeze Extraction	[68,69]
10	Ethyl Acetate	5 g\100 ml	Solvent Casting	[42]
11	Formic Acid	30 w/v%	Electrospinning	[59,62]
12	Hexafluoroisopropanol (HFIP)	10 w/v%	Electrospinning	[90]
13	Methylene Chloride	3 wt. %	SC and Spin Casting.	[72]
14	Methylene Chloride/DMF	8 to 10 wt. %	Electrospinning	[98]
15	1-Methyl-2-Pyrrolidone (NMP)	15 w/w%	Electrospinning	[53]
16	Tetrahydrofuran (THF)	15 w/w%	Electrospinning	[53]
		5 g\100 ml	Solvent Casting	[42]
		17.5% w/w	Phase Separation	[70]
17	THF/DMF	2 g /14 ml	Electrospinning	[52]
		15 wt. %.	Electrospinning	[99]
18	Toluene	0.24-1 wt. %	Spin-coating	[71]

Note: GF-SEDA is Gas Foaming and Spontaneous Emulsion Droplets Adherence, SC is Solvent Casting.

solvents used to dissolve PCL, effect on the surface properties, biocompatibility of the film [42], the surface morphologies and the electrospinnability [53].

Yogeshwar *et al.* (2012) replaced HFIP with an environmentally solvent (acetic acid) to fabricate PCL/collagen by the ES, and their result showed that it can be used in tissue engineering [90].

6. THE MICRO-POROSITY AND THE ROUGHNESS OF PCL

Surface characteristics of fabricated parts are also important when fabricating scaffolds for tissue

engineering applications. The acceptable surface roughness range is between 5-50 μm , while the pore size greater than 20 μm . In the rapid prototyping or rapid manufacturing applications, the aim is to control micro-porosity and surface roughness. This parameter is considered as a good indicator of sintering efficiency, however very few surface roughness models have been published to date.

Layer thickness and part orientation have shown a strong effect on surface quality; the only investigated parameter that was not found significant in the examined range was laser power [100]. More recently, Bacchewar *et al* developed a statistical model for determining surface roughness using the

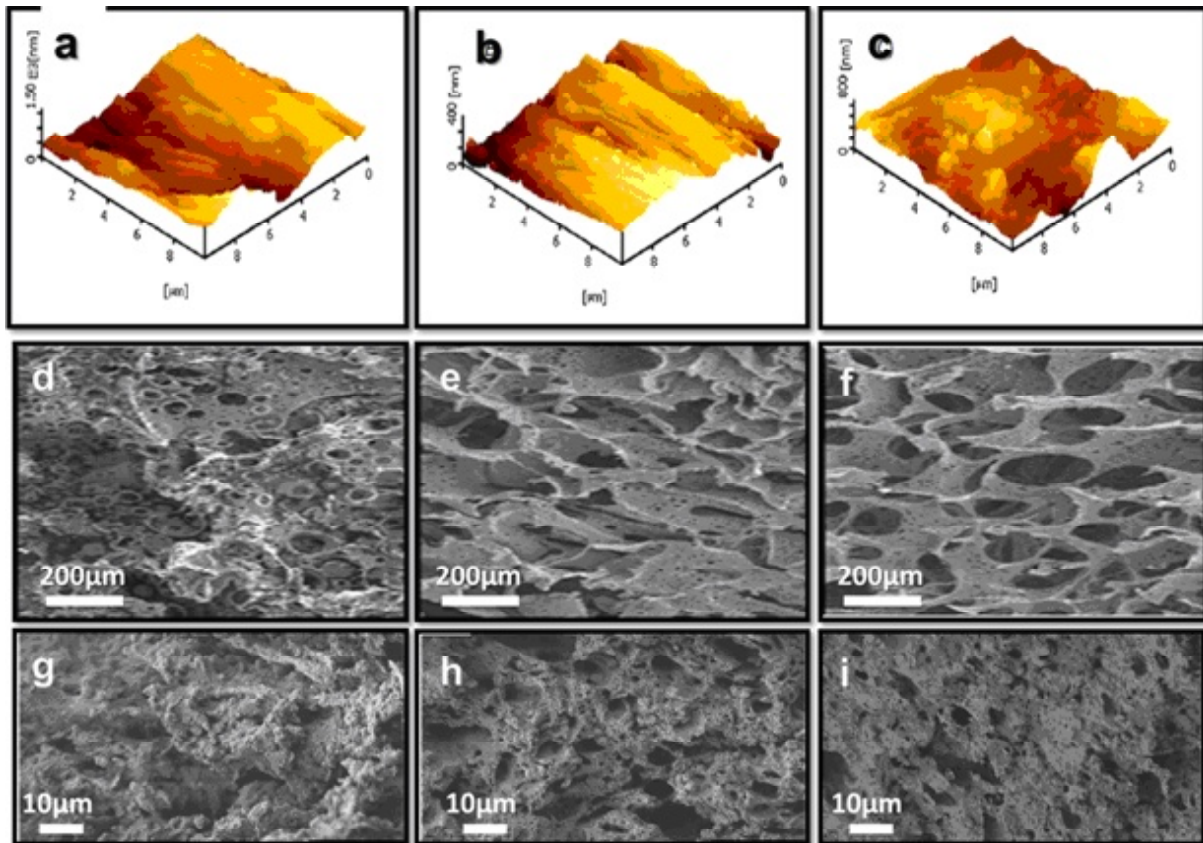


Fig. 4. The surface modification of PCL, (a), (b) and (c) 3D simulated AFM pictures demonstrate surface texture of the scaffold's filaments; pure PCL (a), PCL-10%CS (b) and PCL-20%CS (c), see [79], (d), (e) and (f) SEM images of composite hydrogels (PCL/chitosan) (d) 25 wt.% CS, (e) 50 wt.% CS and (f) 75 wt.% CS, see [89] and (g), (h), and (i) SEM micrographs of the cross-section of PCL/nHA porous scaffolds fabricated by co-porogens (NaCl and PEG): (g) 20%PCL, 10%nHA, 35%PEG and 35%NaCl, PEG 20000 (crystallizing point 58.0–63.00C) (h) 20%PCL, 10%nHA, 20%PEG and 50%NaCl, PEG 20000 (crystallizing point 58.0–63.00C) and (i) 20%PCL, 10%nHA, 20%PEG and 50%NaCl, PEG 4000 (crystallizing point 50.0–55.00C), see [47].

following input variables: laser power, laser speed, builds orientation, scan spacing and layer thickness. It was found that the surface roughness of the top surface of fabricated parts are determined by building orientation and layer thickness, while that of the bottom surface is determined by build orientation, layer thickness and laser power [101]. The surface topography and the surface roughness of the PCL scaffolds have been improved by blending with chitosan (CS), AFM has been demonstrated the surface topography and the surface roughness, Figs. 4a, 4b, and 4c show that the highest surface roughness were founded in the pure PCL group followed by PCL/10%CS and PCL/20%CS [79]. On the other hand, CS has been used also to improve the pore size of PCL scaffold as shown in Figs 4d, 4e, and 4f [89].

Sodium chloride (NaCl) particles have been used to control the level of porosity in Hydroxyapatite (HA) and PCL composite scaffolds [49]. While NaCl

particles have been used as porogen to fabricate Magnesium Phosphate (MP)\PCL composite porous scaffolds [46]. Whilst Liu *et al.* (2012) used the combination of salt particulate (NaCl) and water-soluble polymer (PEG) as co-porogens to fabricate porous PCL/nanohydroxyapatite (nHA) composite scaffolds, and they show that crystallizing point of PEG and rate of NaCl: PEG have effect of the scaffold morphology which indecat in Figs 4g, 4h, and 4i [47]. Moreover, the calcium alginate has been succeeded alginate threads resemble the porosity and the homogeneous pore size distribution of native bone [70].

7. MECHANICAL PROPERTIES OF PCL

The requirements for these materials to perform as substrate for the development of different types of cells are not only related to the correct adhesion,

Table 3. Improving the mechanical properties of PCL scaffold.

No	The mechanical properties	Blending materials	Fabrication methods	The mechanical properties (MPa)		Increasing rate	Ref.
				Pure PCL	Blending		
1	Compressive modulus	MP	Particulate leaching	4.32±0.13	2.37±0.15	1: 1.8	[46]
2	Elastic modulus Compressive stress	Mg ₂ SiO ₄	Salt leaching/ solvent casting	3.1 0.0024	6.9 0.3	1: 2.23 1: 125	[48]
3	Tensile Stress	Al ₂ O ₃	Electro-spinning	3.4	7.3	1:2.15	[58]
4	Tensile Stress	BGMs	Solvent casting	14	17.5	1: 1.25	[93]

proliferation, preservation of the phenotype. But also to mechanical aspects, since these substrates should ensure the appropriate performance of the device until the new tissue generated is capable of restoring the original functionality.

PCL porous scaffold and fibrous scaffold have low value of the tensile strength and the elastic modulus, due to pore structure compared with bulk PCL, which has tensile strength about 25–43 MPa and elastic modulus 330–360 MPa [102]. PCL was used as raw material to make small diameter blood vessel scaffold by Electrospinning but the mechanical properties cannot meet up with the requirement of vascular grafts [59, 74]. Croisier *et al.* (2012) produced PCL fibers by Electrospinning, and they measured the mechanical properties of the fibrous scaffolds and individual fibers by different methods. Their results showed that the modulus obtained by tensile-testing eight different fiber scaffolds was 3.8 ± 0.8 MPa. Assuming that PCL fibers can be described by the bending model of isotropic materials, a Young's modulus of 3.7 ± 0.7 GPa was determined for single fibers [99].

To improve the properties of PCL scaffold for bone tissue engineering, PCL has been blended with different type of ceramic materials, Table 3 show the different ceramic materials used to improve the mechanical properties of the PCL scaffold.

Tiaw *et al.* (2006) studied the effect of the fabricated methods on the mechanical properties, where they fabricated PCL to ultrathin films by spin casting, 2-roll milling and solution casting; all films exhibited a reduction in elongation, an increase in tensile strength, and an increase in modulus. However, for solvent cast films, the modulus decreased. In addition biaxial drawn 2-roll mill films

not only possessed the preferred mechanical properties, they also offered reduced thickness as compared to the solvent cast films because of higher drawing ratio. With their good mechanical properties, they can match the commercially available wound dressings such as Omiderm [72].

8. DEGRADATION OF PCL

The applications of PCL scaffold might be limited due to its hydrophobicity and slow degradation rate. The hydrophobic property of PCL is adverse to cell attachment and penetration into the porous structure. The degradation of PCL is considered through the hydrolytic cleavage of ester groups causing random chain scissions [16]. Previous research demonstrated that some PCL-based polymers took about 3–4 years to degrade completely [5, 103]. Among the polyesters, PCL degrades most slowly due to the five hydrophobic –CH₂ moieties in its repeating units, thus limiting its application to delivery devices or commercial sutures [7, 8].

Pena *et al.* (2006) studied the long term degradation behavior of PCL films, potentially useful as substrates for tissue engineering, obtained by two different methods (compression moulding or casting in chloroform) in two biologically related media: phosphate buffered solution (PBS) and Dulbecco's modified Eagle's medium (DMEM). Their results showed that the degradation after one year and a half (18 months), the layers become more fragile but maintain their consistency, although the chemical structure has been modified. In addition higher degradation rate is obtained for membranes obtained by casting with respect to those obtained by compression moulding [16].

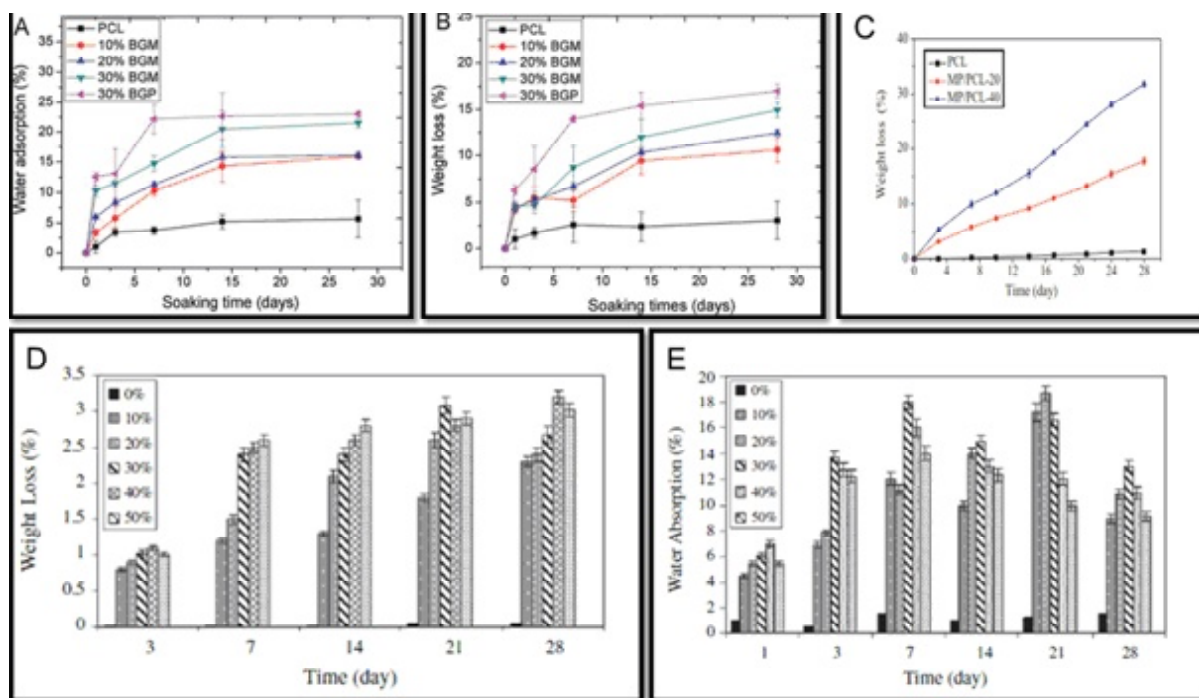


Fig. 5. Accelerate the degradation time of the PCL. (a) Water absorption and (b) weight loss of the PCL-BGMs composites with various BGMs contents (0, 10, 20, and 30 wt.%) and PCL-BGPs with a BGP content of 30 wt.%, see [93], (c) Weight losses of the PCL-MP composites with various MP contents (0, 20, and 40 wt.%), see [46], and (d) weight loss, and (e) Water absorption of PCL- Forsterite (Mg_2SiO_4) composites with various Mg_2SiO_4 contents: 0, 10, 20, 30, 40, and 50 wt.%, see [48].

For the order to accelerate the degradation time of PCL, there are many studies on modifications of PCL have been established: Wu *et al.* (2012) used magnesium phosphate (MP) to accelerate the degradation time, and they showed that the degradation rate of MP/PCL is fast than pure PCL, which indicate in Fig. 5c [46]. In addition Bioactive Glass Microspheres have been reinforced with PCL, and the composites have excellent mechanical properties, biocompatibility, bioactivity and the degradation rate was fast compared with pure PCL. Figs. 5a and 5b show that the weight loss and water absorption were increased, with increasing BGM content %. While, the higher weight loss and water absorption was showed in PCL- Bioactive Glass Particles (BGP) 30 wt.% composites [91]. Moreover, Diba *et al.* (2012) accelerated the degradation time of PCL by fabrication PCL-forsterite nanocomposites, and they showed that the weight loss and the water absorption were increased, with increasing the content of the forsterite %, as has been shown in Figs. 5e and 5d [48].

Kulkarni *et al.* (2008) studied the degradation of PCL and PCL containing multifunctional copolymers, and they showed that the PCL homopolymer samples were subjected to enzymatic and hydrolytic degradation, while that selective enzymatic degradation of PCL containing

multifunctional polymers is a beneficial tool for controlling their degradation properties [104].

Some of the biomedical applications need to slow degradation rate, while in same case of PCL blending and modification lead to slow the degradation rate. Fu *et al.* (2012) investigated that after active-screen plasma treatment, the PCL film is still degradable, but the enzymatic degradation rate is slower compared with untreated PCL film [81]. While, chitosan (CS) has been lead to increase in water uptake, but decrease in degradation rate [79]. Arginine-glycine-aspartic acid (RGD) has been used to modify PCL to decrease the time degradation [54].

Moreover, scaffold structures have an effect on the degradation behavior, as it was proved by Bosworth and Downes (2010). Where they studied the degradation of different PCL scaffold structures (2D Electrospinning mats and 3D Electrospinning bundles, and solvent cast films) spent in phosphate buffer solution at 37 °C was performed over a three month period [96].

9. CELL PROLIFERATION AND BIOCOMPATIBILITY

Synthetic scaffolds are crucial to applications in regenerative medicine; however, the foreign body

response can impede regeneration and may lead to failure of the implant.

Tang *et al.* (2004) proved that used different solvents used to fabricate PCL do not have an effect on the surface properties and biocompatibility (adhesion and proliferation) of the film [42]. Whilst the biocompatible has been improved when Aluminum oxide (Al_2O_3) [58] and Hydroxyapatite (HA) [49] added to PCL nano-composite scaffolds.

During the culture period, the growth of the cells in recombinant spider silk protein (pNSR32), PCL and gelatin (Gt) (pNSR32/PCL/Gt) composite scaffold, PCL/silk fibroin (SF) composite scaffold, PCL/biphasic calcium phosphate (BCP) hybrid composite scaffolds, and PCL/chitosan (CS) composite scaffold were significantly higher than in the pure PCL [59,64,73, 9].

Endothelial cell growth has been improved on the PCL/PEG scaffold by modifying as composite with fibrin, fibronectin, gelatin, growth factors, and proteoglycans [85]. In addition when comparing PCL/SF composite scaffold with PCL/SF composite scaffold based on HA, the HA-based scaffolds showed a significant increase in cell proliferation and filopodia protrusions, but decreased in collagen-I production [92]. The bone morphogenetic protein 4 (BMP4) -expressing bone marrow stromal cells (BMSCs) strongly favoured osteoinductivity of cellular constructs, as demonstrated by a more extensive bone/scaffold contact [9].

Pektok *et al.* (2011) evaluated *in vivo* healing and degradation characteristics of small-diameter vascular grafts made of PCL Nanofibers compared with expanded polytetrafluoroethylene (ePTFE) grafts. They showed that small-diameter PCL grafts represent a promising alternative for the future because of their better healing characteristics compared with ePTFE grafts. In addition faster endothelialization and extracellular matrix formation, accompanied by degradation of graft fibers, seem to be the major advantages. Further evaluation of degradation and graft healing characteristics may potentially lead to the clinical use of such grafts for revascularization procedures [97].

10. APPLICATIONS

PCL is a promising biodegradable polymer with a longer degradation time, and has been widely used both *in vivo* and *in vitro* [105-109]. In particular, PCL possesses superior mechanical properties as compared to other biodegradable polymers, namely very high strength and elasticity, depending on its molecular weight. PCL-based material is therefore

suitable for use in sutures, tendons, cartilage, bone, and other biomedical applications in which mechanical strength is required. The biomedical applications of PCL include:

10.1. Vascular graft

Vascular grafts are special tubes that serve as artificial replacements for damaged blood vessels. Which are already commercially available, mainly produced from polyester knitted or woven fabrics [110,111] or the expanded polytetrafluoroethylene (PTFE) [112-115]. Knitted constructions are made of interlocking yarns in horizontal rows and vertical columns of stitches. Knitting constructions account for more than 50% of the structures available, due to softer, more flexible and easily comfortable, and have better handling characteristics than woven graft designs [116]. PCL was used as raw material to fabricate small diameter blood vessel scaffold by using electrospinning [59,74,117,118].

Pektok *et al.* (2008) studied comparison between ePTFE and PCL grafts, and they proved that Small-diameter PCL grafts represent a promising alternative for the future because of their better healing characteristics than ePTFE grafts. Faster endothelialization and extracellular matrix formation, accompanied by degradation of graft fibers, seem to be the major advantages. Further evaluation of degradation and graft healing characteristics may potentially lead to the clinical use of such grafts for revascularization procedures [97].

In addition PCL has been used for cartilage tissue engineering by blending with PU [70], nanohydroxyapatite (nHA) [47], and PGLA [108].

10.2. Bone

Bone scaffolds are fabricated from a biocompatible material that does not elicit immunological or clinically detectable foreign body reaction. Currently the fabrication of bone scaffolds is driven by FDA approved bioresorbable polymers [31,119] such as collagen [120-122], polylactides [123,124], polyglycolides [125], their copolymers [126,127]

PCL has been used as raw materials for bone scaffolds [10,128-131], and also has been combined with osteoconductive ceramics such as forsterite [48], calcium alginate [70], Hydroxyapatite (HA) [49,132-134], magnesium phosphate (MP) [46], bioactive glass microspheres (BGMs) [91] and tricalcium phosphate (TCP) [95,135]. In addition PCL can be blended with natural polymer to fabricate bone scaffolds such as silk fibroin (SF) [136].

10.3. Other applications

Most related to tissue engineering, taking advantage of the longer times of degradation which can be decreased to adjust to the new tissue formation rate: cartilage [13,58, 137], liver [138-142], bladder [143-148], skin [149-154], nerve [155-161].

11. CONCLUSIONS

Adequate cellular in-growth in biomaterials is one of the fundamental requirements of scaffolds used in regenerative medicine. PCL is one of the extensively studied synthetic biodegradable polymers in various formulations for tissue engineering. All the same, these trials are limited to experimental purposes and are not implicated widely as marketed formulation. Although that the hydrophobicity of PCL is the major drawback responsible for its limited using. Still, PCL is the most promising material used for tissue engineering, because it is nonimmunogenic, a highly porous network for cellular support can be produced, can be dissolved in most of organic solvents (an environmentally solvent), there are many methods to fabrication and can be blended with other polymers to improve the hydrophobicity. However, in general, adequate cell in-growth, biodegradable, biocompatible, and cell seeding have been suboptimal. Moreover the microstructures of PCL film depend of the physical properties of the solvents and the fabrication methods. In concluding observations PCL, the polymer with intact or derived properties makes it suitable to use and prepare all kinds of novel preparations for tissue engineering. From the above explanations it may be decided that PCL is indeed a versatile biodegradable polymer having tremendous potential in tissue engineering.

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