Rev. Adv. Mater. Sci. 34 (2013) 123-140

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

Mohammed Abedalwafa, Fujun Wang, Lu Wang and Chaojing Li

Key Laboratory of Textile Science and Technology, Ministry of Education, College of Textiles, Donghua University, Shanghai, P. R. China

Received: December 18, 2012

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 semicrystalline 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

Corresponding author: Lu Wang, e-mail: wanglu@dhu.edu.cn

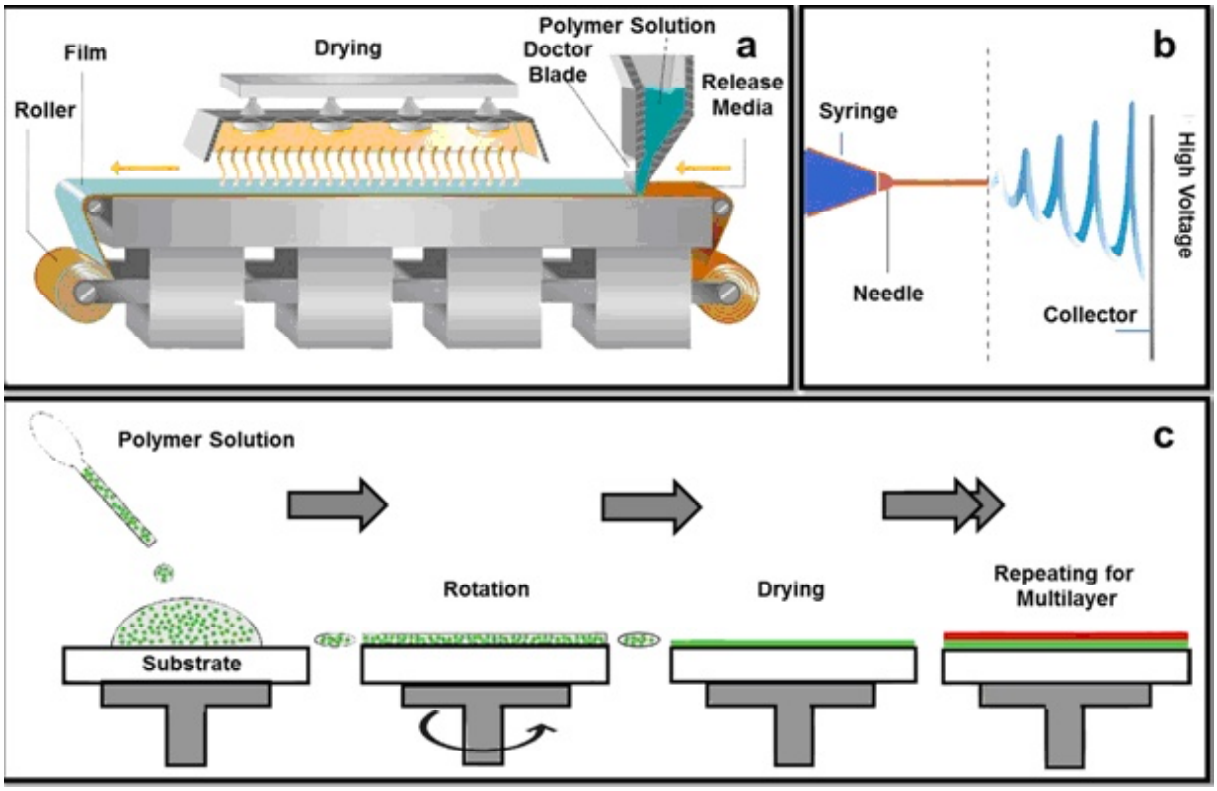


Fig. 1. Schematic representation of common fabrication technology methods that have been used to fabricate PCL. (a) Solvent casting, (b) Electrospinning, and (c) Spin coating.

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 CO_2 [35,36], 3D printing [37] and phase separation techniques [34,38-41], while the

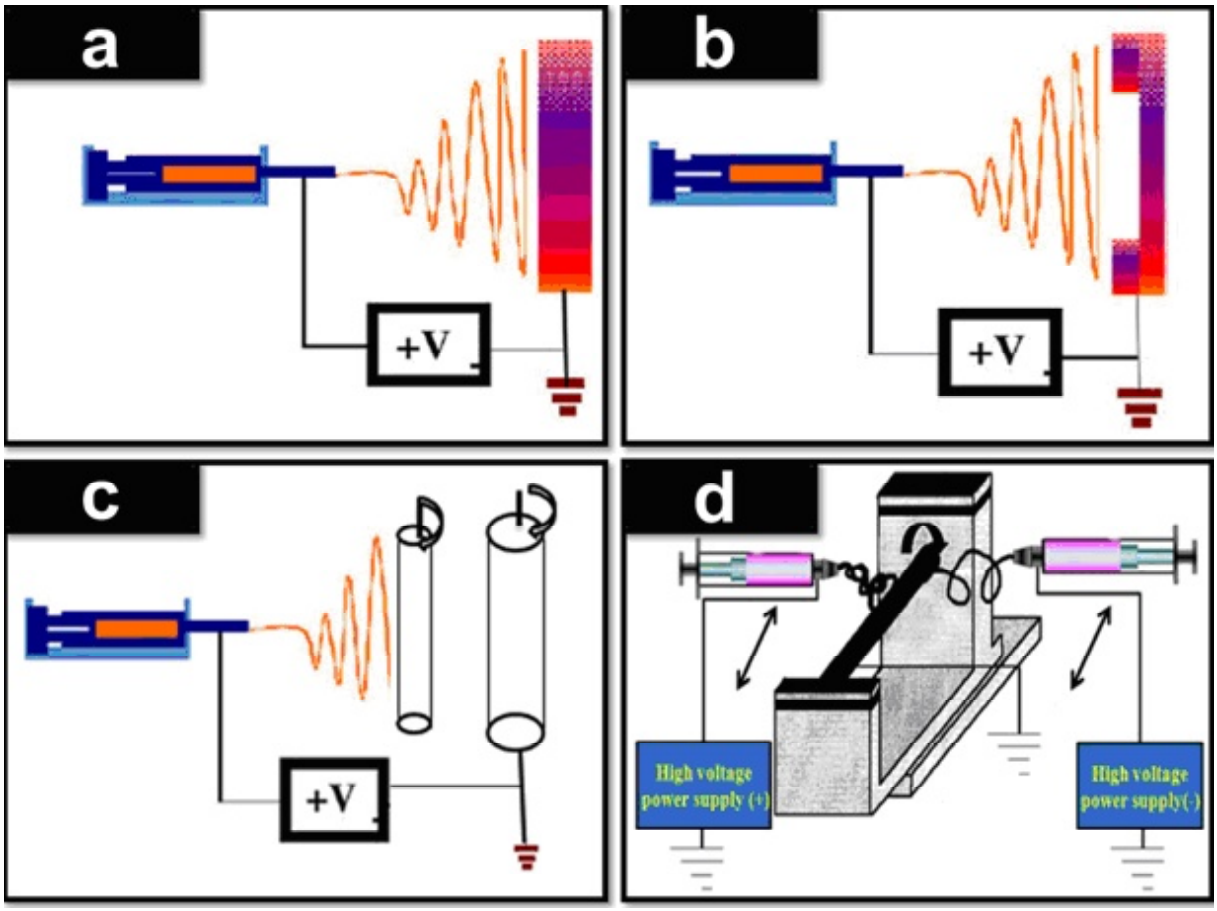


Fig. 2. Schematic representation for development in the electrospinning technology. (a) conventional electrospinning, see [57]; (b) novel electrospinning collector to fabricate 3D scaffold, see [57]; (c) novel electrospinning collector to fabricate nano-fibrous tubes, see [66], and (d) double-ejection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

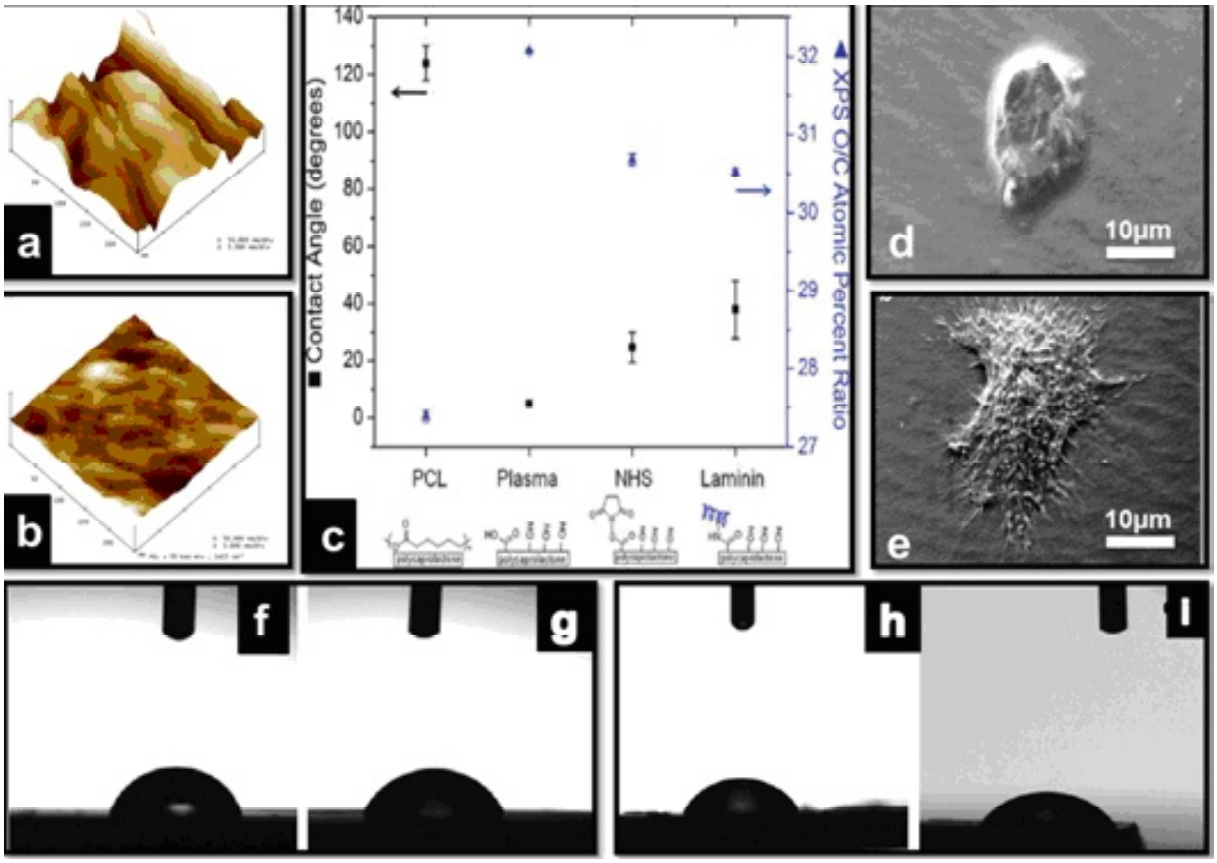


Fig. 3. The surface modifications of PCL (a) and (b) AFM images (a) PCL untreated (b) PCL irradiated, see [80], (c) Relationship between (Left vertical axis) Sessile-drop water contact angle, (Right vertical axis) Atomic O/C ratios of native and modified polycaprolactone nanofibers as determined by X-ray photoelectron spectroscopy and electrospun PCL fiber mats with the following surface chemistries: (left to right) unmodified control (PCL), plasmatreated 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 then 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 bimolecular 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 modification 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 to 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]
		Spider silk and Gelatin	Electrospinning	Vascular. TE	[59]
		Alginate	Separation Phase	Bone. TE	[70]
		Collagen	Electrospinning	TE	[90]
2	**Synthetic**	PLLA and MWCNTs	Solvent-Casting	TE	[45]
		Polyurethane (PU)	Electrospinning	Vascular TE	[65]
		PLGA	Electrospinning	TE	[61]
		PLLA	Freeze Extraction	Membranes TE	[68,69]
		Polystyrene (PS)	Spin-coating	Biomaterials	[71]
		PGA	Separation Phase	Bone. TE	[70]
3	**Ceramic**	Forsterite (Mg_2SiO_4)	Solvent-Casting and Particle Leaching	Bone. TE	[48]
		Calcium Alginate	Separation Phase	Bone. TE	[70]
		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	4.5 w/w%	Solvent Casting	[85]
	(DCM)	15 w/w%	Electrospinning	[53]
		10% (w/v)	Particulate Leaching	[46]
6	Dimethylformamide	15 w/w%	Electrospinning	[53]
	(DMF)			
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	10 w/v%	Electrospinning	[90]
	(HFIP)			
13	Methylene Chloride	3 wt.%	SC and Spin Casting.	[72]
14	Methylene Chloride/	8 to 10 wt.%	Electrospinning	[98]
	DMF			
15	1-Methyl-2-Pyrrolidone	15 w/w%	Electrospinning	[53]
	(NMP)			
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

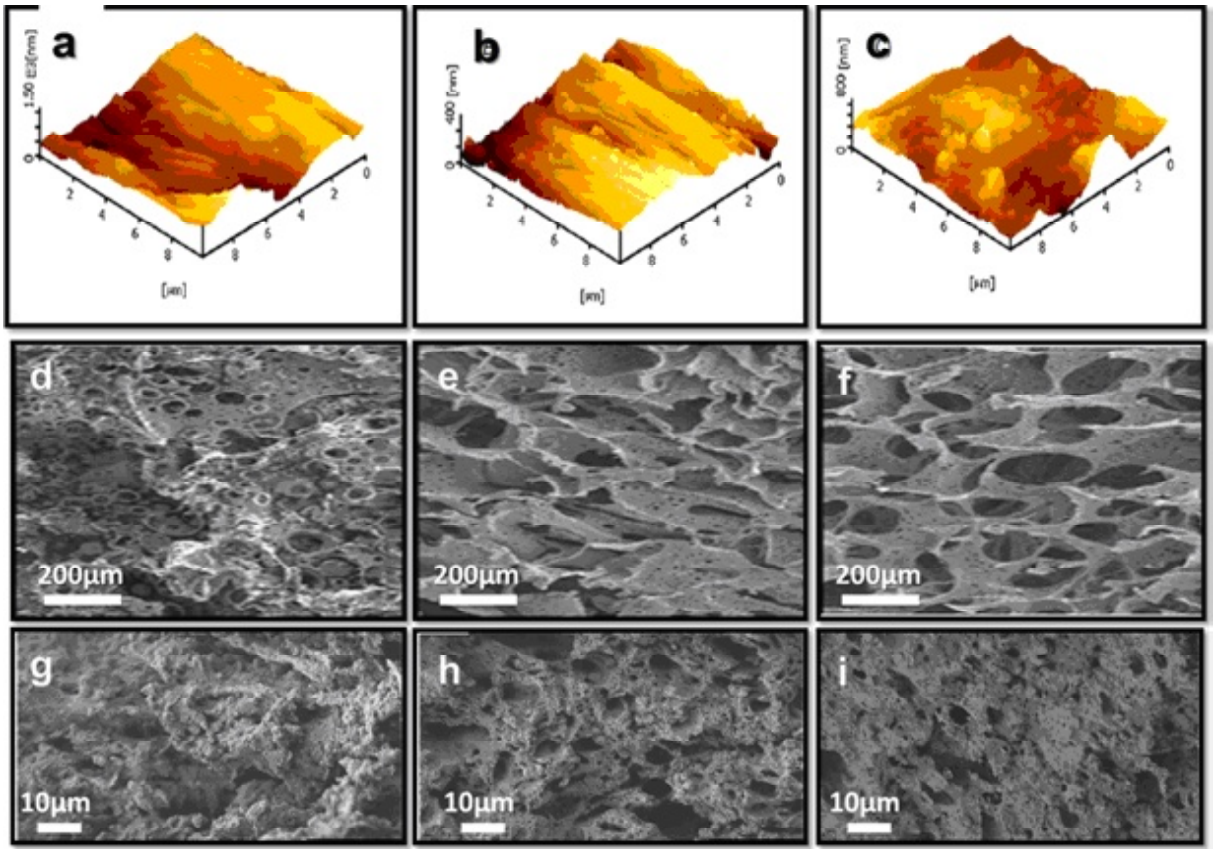


Fig. 4. The surface modification of PCL, (a), (b) and (c) 3D simulated AFM pictures demonstrate surface texture of the scaffold's filaments; pure PCL (a), PCL-10%CS (b) and PCL-20%CS (c), see [79], (d), (e) and (f) SEM images of composite hydrogels (PCL/ chitosan) (d) 25 wt.% CS, (e) 50 wt.% CS and (f) 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_2SiO_4	Salt leaching/ solvent casting	3.1 0.0024	6.9 0.3	1: 2.23 1: 125	[48]
3	Tensile Stress	Al_2O_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 –CH_2 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].

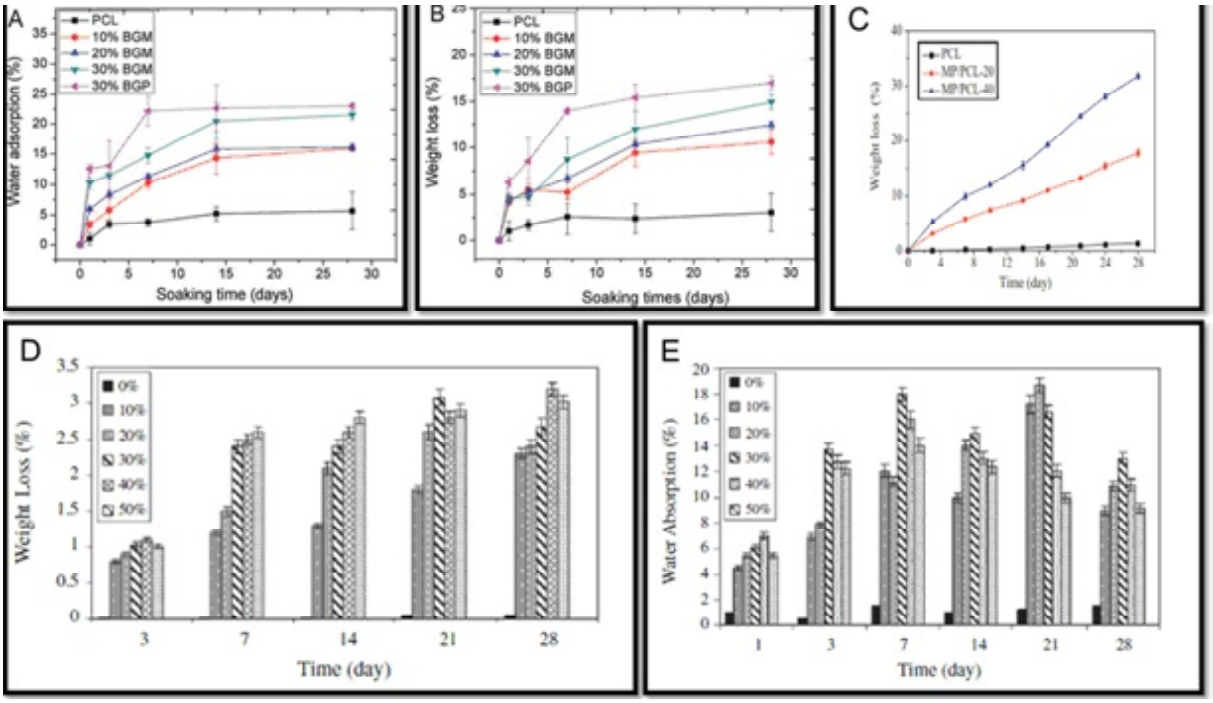


Fig. 5. Accelerate the degradation time of the PCL. (a) Water absorption and (b) weight loss of the PCL-BGMs composites with various BGMs contents (0, 10, 20, and 30 wt.%) and PCL-BGPs with a BGPs content of 30 wt.%,see [93], (c) Weight losses of the PCL-MP composites with various MP contents (0, 20, 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 nano-composites, 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 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 interloping 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.

ACKNOWLEDGEMENTS

This work was supported by FRF from the Central Universities (NS2013) and NNSF (31100682).

REFERENCES

[1] N. Mishra, A.K. Goyal, K. Khatri, B. Vaidya, R. Paliwal, S. Rai, A. Mehta, S. Tiwari, S. Vyas and S.P. Vyas // *Antiinflamm. Antiallergy. Agents. Med. Chem*. **7** (2008) 240.

[2] R.S. Bezwada, D.D. Jamiolkowski, I.Y. Lee, V. Agarwal, J. Persivale, S. Trenkabenthin, M. Erneta, J. Suryadevara, A. Yang and S. Liu // *Biomaterials* **16** (1995) 1141.

[3] J.M. Anderson and M.S. Shive // *Adv. Drug. Deliv. Rev*. **28** (1997) 5.

[4] I. Engelberg and J. Kohn // *Biomaterials* **12** (1991) 292.

[5] C.G. Pitt, F.I. Chasalow, Y.M. Hibionada, D.M. Klimas and A. Schindler // *J. Appl. Polym. Sci.* **26** (1981) 3779.

[6] Y. You, B.-M. Min, S.J. Lee, T.S. Lee and W.H. Park // *J. Appl. Polym. Sci.* **95** (2005) 193.

[7] S.R. Bhattarai, N. Bhattarai, P. Viswanathamurthi, H.K. Yi, P.H. Hwang and H.Y. Kim // *J. Biomed. Mater. Res. A*. **78A** (2006) 247.

[8] J. Hao, M. Yuan and X. Deng // *J. Appl. Polym. Sci*. **86** (2002) 676.

[9] L. Savarino, N. Baldini, M. Greco, O. Capitani, S. Pinna, S. Valentini, B. Lombardo, M.T. Esposito, L. Pastore, L. Ambrosio, S. Battista, F. Causa, S. Zeppetelli, V. Guarino and P.A. Netti // B*iomaterials* **28** (2007) 3101.

[10] H. Yoshimoto, Y.M. Shin, H. Terai and J.P. Vacanti // *Biomaterials* **24** (2003) 2077.

[11] A.-C. Albertsson and I.K. Varma // *Biomacromolecules* **4** (2003) 1466.

[12] D.W. Hutmacher, T. Schantz, I. Zein, K.W. Ng, S.H. Teoh and K.C. Tan // *J. Biomed. Mater. Res. J. Biomed. Mater. Res*. **55** (2001) 203.

[13] W.-J. Li, K.G. Danielson, P.G. Alexander and R.S. Tuan // *J. Biomed. Mater. Res. A.* **67A** (2003) 1105.

[14] N. López-Rodríguez, A. López-Arraiza, E. Meaurio and J.R. Sarasua // *Polym. Eng. Sci*. **46** (2006) 1299.

[15] W.-J. Lin, D.R. Flanagan and R.J. Linhardt // *Polymer* **40** (1999) 1731.

[16] J. Peña, T. Corrales, I. Izquierdo-Barba, A.L. Doadrio and M. Vallet-Regí // *Polym. Degrad. Stab.* **91** (2006) 1424.

[17] X. Zong, S. Ran, K.-S. Kim, D. Fang, B.S. Hsiao and B. Chu // *Biomacromolecules* **4** (2003) 416.

[18] C.H. Kim, M.S. Khil, H.Y. Kim, H.U. Lee and K.Y. Jahng // *J. Biomed. Mater. Res. Part B Appl. Biomater.* **78B** (2006) 283.

[19] R. Langer and J.P. Vacanti // *Science* **260** (1993) 920.

[20] E. Sachlos and J.T. Czernuszka // *Eur. Cell. Mater*. **5** (2003) 29.

[21] S.J. Hollister // *Nat. Mater*. **5** (2006) 590.

[22] N. Krithica, V. Natarajan, B. Madhan, P.K. Sehgal and A.B. Mandal // *Adv. Eng. Mater.* **14** (2012) B149.

[23] Z. Hong, P. Zhang, C. He, X. Qiu, A. Liu, L. Chen, X. Chen and X. Jing // *Biomaterials* **26** (2005) 6296.

[24] L. Borum-Nicholas and O.C. Wilson Jr // *Biomaterials* **24** (2003) 3671.
[25] W. Song, Z. Zheng, W. Tang and X. Wang // *Polymer* **48** (2007) 3658.
[26] J. Li, X.L.Lu and Y.F. Zheng // *Appl. Surf. Sci.* **255** (2008) 494.
[27] Z. Hong, X. Qiu, J. Sun, M. Deng, X. Chen and X. Jing // *Polymer* **45** (2004) 6699.
[28] L.E. Freed, G. Vunjak-Novakovic, R.J. Biron, D.B. Eagles, D.C. Lesnoy, S.K. Barlow and R. Langer // *Biotechnology* **12** (1994) 689.
[29] T.-H. Nguyen and B.-T. Lee // *Sci. Technol. Adv. Mat.* **13** (2012) 035002.
[30] T. Weigel, G. Schinkel and A. Lendlein // *Expert. Rev. Med. Devices* **3** (2006) 835.
[31] K. Rezwan, Q.Z. Chen, J.J. Blaker and A.R. Boccaccini // *Biomaterials* **27** (2006) 3413.
[32] G. Chen, T. Ushida and T. Tateishi // *J. Biomed. Mater. Res.* **51** (2000) 273.
[33] G. Chen, T. Ushida and T. Tateishi // *Biomaterials* **22** (2001) 2563.
[34] J. Ma, H. Wang, B. He and J. Chen // *Biomaterials* **22** (2001) 331.
[35] D.J. Mooney, D.F. Baldwin, N.P. Suh, J.P. Vacanti and R. Langer // *Biomaterials* **17** (1996) 1417.
[36] L.D. Harris, B.S. Kim and D.J. Mooney // *J. Biomed. Mater. Res.* **42** (1998) 396.
[37] Y.J. Park, K.H. Nam, S.J. Ha, C.M. Pai, C.P. Chung and S.J. Lee // *J. Control. Release* **43** (1997) 151.
[38] Y.S. Nam and T.G. Park // *J. Biomed. Mater. Res.* **47** (1999) 8.
[39] K. Whang, C.H. Thomas, K.E. Healy and G. Nuber // *Polymer* **36** (1995) 837.
[40] C. Schugens, V. Maquet, C. Grandfils, R. Jerome and P. Teyssie // *Polymer* **37** (1996) 1027.
[41] C. Schugens, V. Maquet, C. Grandfils, R. Jerome and P. Teyssie // *J. Biomed. Mater. Res.* **30** (1996) 449.
[42] Z.G. Tang, R.A. Black, J.M. Curran, J.A. Hunt, N.P. Rhodes and D.F. Williams // *Biomaterials* **25** (2004) 4741.
[43] U. Siemann and Sid // *International Display Research Conference – Eurodisplay* **25** (2005) 240.
[44] T.W.J. Steele, C.L. Huang, S. Kumar, S. Irvine, F.Y.C. Boey, J.S.C. Loo and S.S. Venkatraman // *Acta. Biomater.* **8** (2012) 2263.
[45] M. Amirian, A. Nabipour Chakoli, W. Cai and J. Sui // *Iran. Polym. J.* **21** (2012) 165.
[46] F. Wu, C.S. Liu, B. O'Neill, J. Wei and Y. Ngothai // *Appl. Surf. Sci*. **258** (2012) 7589.
[47] L. Liu, Y.Y. Wang, S.R. Guo, Z.Y. Wang and W. Wang // *J. Biomed. Mater. Res. B Appl. Biomater.* **100B** (2012) 956.
[48] M. Diba, M. Kharaziha, M.H. Fathi, M. Gholipourmalekabadi and A. Samadikuchaksaraei // *Compos. Sci. Technol.* **72** (2012) 716.
[49] H. Yu, P. Wooley and S.-Y. Yang // *J. Orthop. Surg. Res.* **4** (2009) 5.
[50] L. WJ, L. CT, C. EJ, T. RS and K. FK // *J. Biomed. Mater. Res.* **60** (2002).
[51] K.S. Rho, L. Jeong, G. Lee, B.-M. Seo, Y.J. Park, S.-D. Hong, S. Roh, J.J. Cho, W.H. Park and B.-M. Min // *Biomaterials* **27** (2006) 1452.
[52] J.M. Deitzel, J.D. Kleinmeyer, J.K. Hirvonen and N.C. Beck Tan // *Polymer* **42** (2001) 8163.
[53] X.H. Qin and D.Q. Wu // *J. Therm. Anal. Calorim*. **107** (2012) 1007.
[54] W. Zheng, Z. Wang, L. Song, Q. Zhao, J. Zhang, D. Li, S. Wang, J. Han, X.-L. Zheng, Z. Yang and D. Kong // *Biomaterials* **33** (2011) 2880.
[55] N.E. Zander, J.A. Orlicki, A.M. Rawlett and T.P. Beebe // *ACS Appl. Mater. Interfaces* **4** (2012) 2074.
[56] P.M. Mountziaris, S.N. Tzouanas and A.G. Mikos // *Biomaterials* **31** (2010) 1666.
[57] J.K. Hong and S.V. Madihally // *Acta Biomater.* **6** (2010) 4734.
[58] Z.X. Dong, Y.Q. Wu, Q. Wang, C. Xie, Y.F. Ren and R.L. Clark // *J. Biomed. Mater. Res. A* **100A** (2012) 903.
[59] P. Xiang, M. Li, C.-Y. Zhang, D.-L. Chen and Z.-H. Zhou // *Int. J. Biol. Macromol*. **49** (2011) 281.
[60] H.J. Haroosh, D.S. Chaudhary and Y. Dong // *J. Appl. Polym. Sci.* **124** (2012) 3930.
[61] N. Hiep and B.-T. Lee // *J. Mater. Sci-Mater. Med.* **21** (2010) 1969.
[62] J.S. Lim, C.S. Ki, J.W. Kim, K.G. Lee, S.W. Kang, H.Y. Kweon and Y.H. Park // *Biopolymers* **97** (2012) 265.
[63] A. Hu, B. Zuo, F. Zhang, Q. Lan and H. Zhang // *Neural. Regen. Res.* **7** (2012) 1171.
[64] G. Chen, P. Zhou, N. Mei, X. Chen, Z. Shao, L. Pan and C. Wu // *J. Mater. Sci-Mater. Med.* **15** (2004) 671.

[65] M.R. Williamson, R. Black and C. Kielty // *Biomaterials* **27** (2006) 3608.
[66] C. Huang, Q.F. Ke and X.M. Mo, In: *International Forum on Biomedical Textile Materials Location* (Donghua Univ, Shanghai, P.R. China, 2011), p. 236.
[67] M.-H. Ho, P.-Y. Kuo, H.-J. Hsieh, T.-Y. Hsien, L.-T. Hou, J.-Y. Lai and D.-M. Wang // *Biomaterials* **25** (2004) 129.
[68] L.A. Gaona, J.L.G. Ribelles, J.E. Perilla and M. Lebourg // *Polym. Degrad. Stab.* **97** (2012) 1621.
[69] M. Lebourg, J.S. Antón and J.L.G. Ribelles // *Eur. Polym. J*. **44** (2008) 2207.
[70] C. Grandi, R. Di Liddo, P. Paganin, S. Lora, D. Dalzoppo, G. Feltrin, C. Giraudo, M. Tommasini, M.T. Conconi and P.P. Parnigotto // *Int. J. Mol. Med.* **27** (2011) 455.
[71] M. Ma, Z. He, Y. Li, F. Chen, K. Wang, Q. Zhang, H. Deng and Q. Fu // *J. Colloid. Interface. Sci.* **387** (2012) 262.
[72] K.S. Tiaw, S.H. Teoh, R. Chen and M.H. Hong // *Biomacromolecules* **8** (2007) 807.
[73] T.Q. Bao, R.A. Franco and B.T. Lee // *Biochem. Eng. J.* **64** (2012) 76.
[74] M.-C. Serrano, R. Pagani, M.Vallet-Regi, J. Pena, J.-V. Comas and M.-T. Portoles // *Acta. Biomater.* **5** (2009) 2045.
[75] M.C. Serrano, R. Pagani, M. Vallet-Regi, J. Peña, A. Rámila, I. Izquierdo and M.T. Portolés // *Biomaterials* **25** (2004) 5603.
[76] P. Bartolo, M. Domingos, A. Gloria and J. Ciurana // *Cirp. Ann-Manuf. Techn.* **60** (2011) 271.
[77] P.S. Maher, R.P. Keatch, K. Donnelly, R.E. Mackay and J.Z. Paxton // *Rapid. Prototyping. J.* **15** (2009) 204.
[78] S.-W. Kang, J.-H. Bae, S.-A. Park, W.-D. Kim, M.-S. Park, Y.-J. Ko, H.-S. Jang and J.-H. Park // *Biotechnol. Lett.* **34** (2012) 1375.
[79] N. Thuaksuban, T. Nuntanaranont, W. Pattanachot, S. Suttapreyasri and L. K. Cheung // *Biomed. Mater.* **6** (2011) 015009.
[80] G. Marletta, G. Ciapetti, C. Satriano, S. Pagani and N. Baldini // *Biomaterials* **26** (2005) 4793.
[81] X. Fu, R.L. Sammons, I. Bertóti, M.J. Jenkins and H. Dong // *J. Biomed. Mater. Res. B Appl. Biomater.* **100B** (2012) 314.
[82] K. Wulf, M. Teske, M. Lobler, F. Luderer, K.P. Schmitz and K. Sternberg // *J. Biomed. Mater. Res. B Appl. Biomater.* **98B** (2011) 89.
[83] M. Zhang, Z.X. Wang, Z.F. Wang, S.R. Feng, H.J. Xu, Q. Zhao, S.F. Wang, J.X. Fang, M.Q. Qiao and D. L. Kong // *Colloid Surf. B-Biointerfaces* **85** (2011) 32.
[84] G. Marletta, G. Ciapetti, C. Satriano, F. Perut, M. Salerno and N. Baldini // *Biomaterials* **28** (2007) 1132.
[85] D. Pankajakshan, L.P. Philipose, M. Palakkal, K. Krishnan and L.K. Krishnan // *J. Biomed. Mater. Res. B Appl. Biomater.* **87B** (2008) 570.
[86] U. Edlund, T. Sauter and A.C. Albertsson // *Polym. Adv. Technol.* **22** (2011) 2368.
[87] T. Desmet, C. Poleunis, A. Delcorte and P. Dubruel // *J. Biomed. Mater. Res. A* **23** (2012) 293.
[88] E. Berneel, T. Desmet, H. Declercq, P. Dubruel and M. Cornelissen // *J. Biomed. Mater. Res. A* **100A** (2012) 1783.
[89] X. Zhong, C. Ji, A. Chan, S. Kazarian, A. Ruys and F. Dehghani // *J. Mater. Sci. Mater. Med*. **22** (2011) 279.
[90] V.Y. Chakrapani, A. Gnanamani, V.R. Giridev, M. Madhusoothanan and G. Sekaran // *J. Appl. Polym. Sci.* **125** (2012) 3221.
[91] B. Lei, K.H. Shin, D.Y. Noh, Y.H. Koh, W.Y. Choi and H.E. Kim // *J. Biomed. Mater. Res. B Appl. Biomater*. **100B** (2012) 967.
[92] L.H. Li, Y.N. Qian, C. Jiang, Y.G. Lv, W.Q. Liu, L. Zhong, K.Y. Cai, S. Li and L. Yang // *Biomaterials* **33** (2012) 3428.
[93] M.J. McClure, D.G. Simpson and G.L. Bowlin // *J. Mech. Behav. Biomed. Mater.* **10** (2012) 48.
[94] C.P. Klein, A.A. Driessen, K. Groot and A. Hooff // *J. Biomed. Mater. Res*. **17** (1983) 769.
[95] I. Ahmed, A.J. Parsons, G. Palmer, J.C. Knowles, G.S. Walker and C.D. Rudd // *Acta. Biomater.* **4** (2008) 1307.
[96] L.A. Bosworth and S. Downes // *Polym. Degrad. Stab.* **95** (2010) 2269.
[97] E. Pektok, B. Nottelet, J.-C. Tille, R. Gurny, A. Kalangos, M. Moeller and B. H.Walpoth // *Circulation* **118** (2008) 2563.
[98] M.-S. Khil, S.R. Bhattarai, H.-Y. Kim, S.-Z. Kim and K.-H. Lee // *J. Biomed. Mater. Res. B Appl. Biomater.* **72B** (2005) 117.
[99] F. Croisier, A.S. Duwez, C. Jérôme, A.F. Léonard, K.O. van der Werf, P.J. Dijkstra and M.L. Bennink // *Acta. Biomater.* **8** (2012) 218.

[100] I.Y. Turner, D.C. Thompson, K.L. Wood and R.H. Crawford // *J. Manuf. Syst.* **17** (1998) 23.
[101] P.B. Bacchewar, S.K. Singhal and P.M. Pandey // *Proceedings of the Institution of Mechanical Engineers Part B-Journal of Engineering Manufacture* **221** (2007) 35.
[102] M.C. Azevedo, R.L. Reis, B.M. Claase, D.W. Grijpma and J. Feijen // J*. Mater. Sci.-Mater. Med*. **14** (2003) 103.
[103] H. Sun, L. Mei, C. Song, X. Cui and P. Wang // *Biomaterials* **27** (2006) 1735.
[104] A. Kulkarni, J. Reiche, J. Hartmann, K. Kratz and A. Lendlein // *Eur. J. Pharm. Biopharm.* **68** (2008) 46.
[105] U. Edlund, S. Danmark and A.-C. Albertsson // *Biomacromolecules* **9** (2008) 901.
[106] Y. Wan, G. Feng, F.H. Shen, C.T. Laurencin and X. Li // *Biomaterials* **29** (2008) 643.
[107] K.W. Ng, H.N. Achuth, S. Moochhala, T.C. Lim and D.W. Hutmacher // J*. Biomater. Sci. Polym. Ed.* **18** (2007) 925.
[108] X. Mo, H.J. Weber and S. Ramakrishna // *Int. J. Artif. Organs* **29** (2006) 790.
[109] D.Y. Wong, S.J. Hollister, P.H. Krebsbach and C. Nosrat // *Tissue. Eng.* **13** (2007) 2515.
[110] R. Kowalewski, L. Zimnoch, M.Z. Wojtukiewicz, J. Glowinski and S. Glowinski // *Biomaterials* **25** (2004) 5987.
[111] S. Manju, C.V. Muraleedharan, A. Rajeev, A. Jayakrishnan and R. Joseph // *J. Biomed. Mater. Res. B Appl. Biomater.* **98** (2011) 139.
[112] P. Wong, S. Hopkins, D. Vincente, K. Williams, N. Macri and R. Berguer // *Ann. Vasc. Surg.* **16** (2002) 407.
[113] G.J. Toes, K.W. van Muiswinkel, W. van Oeveren, A.J.H. Suurmeijer, W. Timens, I. Stokroos and JJ. van den Dungen // *Biomaterials* **23** (2002) 255.
[114] K. Hirabayashi, E. Saitoh, H. Ijima, T. Takenawa, M. Kodama and M. Hori // *J. Biomed. Mater. Res.* **26** (1992) 1433.
[115] A.W. Clowes, T. R. Kirkman and M.A. Reidy // *Am. J. Philology* **123** (1986) 220.
[116] B. Pourdeyhimi and C. Text // *J. Biomater. Appl.* **2** (1987) 163.
[117] C.Y. Xu, R. Inai, M. Kotaki and S. Ramakrishna // *Biomaterials* **25** (2004) 877.
[118] S.I. Jeong, S.H. Kim, Y.H. Kim, Y. Jung, J.H. Kwon, B.S. Kim and Y.M. Lee // *J. Biomater. Sci. Polym. Ed*. **15** (2004) 645.
[119] P.A. Gunatillake and R. Adhikari // *Eur. Cell. Mater*. **5** (2003) 1.
[120] C.V.M. Rodrigues, P. Serricella, A.B.R. Linhares, R.M. Guerdes, R. Borojevic, M.A. Rossi, M.E.L. Duarte and M. Farina // *Biomaterials* **24** (2003) 4987.
[121] L.B. Rocha, G. Goissis and M.A. Rossi // *Biomaterials* **23** (2002) 449.
[122] X.M. Li, Q.L. Feng, Y.F. Jiao and F.H. Cui // *Polym. Int.* **54** (2005) 1034.
[123] S.S. Liao, F.Z. Cui, W. Zhang and Q.L. Feng // *J. Biomed. Mater. Res. B Appl. Biomater.* **69B** (2004) 158.
[124] Y. Jung, S.S. Kim, Y.H. Kim, S.H. Kim, B.S. Kim, S. Kim and C.Y. Choi // *Biomaterials* **26** (2005) 6314.
[125] L.E. Freed, G. Vunjaknovakovic, R.J. Biron, D.B. Eagles, D.C. Lesnoy, S.K. Barlow and R. Langer // *Biotechnology (NY)* **12** (1994) 689.
[126] T. Jiang, W.I. Abdel-Fattah and C.T. Laurencin // *Biomaterials* **27** (2006) 4894.
[127] W.J.E.M. Habraken, J.G.C. Wolke and J.A. Jansen // *Adv. Drug. Deliv. Rev.* **59** (2007) 234.
[128] J.W. Calvert, K.G. Marra, L. Cook, P.N. Kumta, P.A. DiMilla and L.E. Weiss // *J Biomed Mater Res.* **52** (2000) 279.
[129] H. Kweon, M.K. Yoo, I.K. Park, T.H. Kim, H.C. Lee, H.-S. Lee, J.-S. Oh, T. Akaike and C.-S. Cho // *Biomaterials* **24** (2003) 801.
[130] A.G.A. Coombes, S.C. Rizzi, M. Williamson, J.E. Barralet, S. Downes and W.A. Wallace // *Biomaterials* **25** (2004) 315.
[131] H. Chim, D.W. Hutmacher, A.M. Chou, A.L. Oliveira, R.L. Reis, T.C. Lim and J.T. Schantz // *Int. J. Oral. Maxillofac. Surg.* **35** (2006) 928.
[132] F. Causa, P.A. Netti, L. Ambrosio, G. Ciapetti, N. Baldini, S. Pagani, D. Martini and A. Giunti // *J. Biomed. Mater. Res. A* **76A** (2006) 151.
[133] K.G. Marra, J.W. Szem, P.N. Kumta, P.A. DiMilla and L.E. Weiss // *J. Biomed. Mater. Res*. **47** (1999) 324.
[134] L. Shor, S. Guceri, X. Wen, M. Gandhi and W. Sun // *Biomaterials* **28** (2007) 5291.

[135] C. Erisken, D.M. Kalyon and H. Wang // *Biomaterials* **29** (2008) 4065.
[136] S.I. Roohani-Esfahani, Z.F. Lu, J.J. Li, R. Ellis-Behnke, D.L. Kaplan and H. Zreiqat // *Acta. Biomater.* **8** (2012) 302.
[137] W.-J. Li, R. Tuli, C. Okafor, A. Derfoul, K.G. Danielson, D.J. Hall and R.S. Tuan // *Biomaterials* **26** (2005) 599.
[138] S.S. Kim, H. Utsunomiya, J.A. Koski, B.M. Wu, M.J. Cima, J. Sohn, K. Mukai, L.G. Griffith and J.P. Vacanti // *Ann. Surg*. **228** (1998) 8.
[139] Y. Qiu, Z. Mao, Y. Zhao, J. Zhang, Q. Guo, Z. Gou and C. Gao // *Macromol. Res.* **20** (2012) 283.
[140] L. Calandrelli, A. Calarco, P. Laurienzo, M. Malinconico, O. Petillo and G. Peluso // *Biomacromolecule*s **9** (2008) 1527.
[141] H. Huang, S. Oizumi, N. Kojima, T. Niino and Y. Sakai // *Biomaterials* **28** (2007) 3815.
[142] J.E. Barralet, L.L. Wallace and A.J. Strain // *Tissue. Eng*. **9** (2003) 1037.
[143] F. Oberpenning, J. Meng, J.J. Yoo and A. Atala // *Nature. Biotechnol.* **17** (1999) 149.
[144] N. Shakhssalim, M.M. Dehghan, R. Moghadasali, M.H. Soltani, I. Shabani and M. Soleimani // *Urol. J.* **9** (2012) 410.
[145] W. Zhu, Y. Li, L. Liu, Y. Chen and F. Xi // *Int. J. Pharm.* **437** (2012) 11.
[146] W. Sun, D.M. Tiemessen, M. Sloff, R.J. Lammers, E.L.W. de Mulder, J. Hilborn, B. Gupta, W.F.J. Feitz, W.F. Daamen, T.H. van Kuppevelt, P.J. Geutjes and E. Oosterwijk // *Tissue. Eng. Part C Methods* **18** (2012) 731.
[147] S.C. Baker, G. Rohman, J. Southgate and N.R. Cameron // *Biomaterials* **30** (2009) 1321.
[148] D.S. Yu, C.F. Lee, H.I. Chen and S.Y. Chang // *Int. J. Urol.* **14** (2007) 939.
[149] N.T. Dai, M.R. Williamson, N. Khammo, E.F. Adams and A.G.A. Coombes // *Biomaterials* **25** (2004) 4263.
[150] H.M. Powell and S.T. Boyce // *Tissue. Eng. Part A* **15** (2009) 2177.
[151] Y. Wang, C. Chong, C. Blaker, P. Maitz and Z. Li // *J. Tissue. Eng. Regen. Med*. **6** (2012) 96.
[152] X.L. Fu and H.J. Wang // *Tissue. Eng. Part A* **18** (2012) 631.
[153] M. Dubsky, S. Kubinova, J. Sirc, L. Voska, R. Zajicek, A. Zajicova, P. Lesny, A. Jirkovska, J. Michalek, M. Munzarova, V. Holan and E. Sykova // *J. Mater. Sci.-Mater. Med.* **23** (2012) 931.
[154] R.A. Franco, T.H. Nguyen and B.T. Lee // *J. Mater. Sci.-Mater. Med*. **22** (2011) 2207.
[155] W.F.A. den Dunnen, M.F. Meek, D.W. Grijpma, P.H. Robinson and J.M. Schakenraad // *J. Biomed. Mater. Res*. **51** (2000) 575.
[156] M.F.B. Daud, K.C. Pawar, F. Claeyssens, A.J. Ryan and J.W. Haycock // *Biomaterials* **33** (2012) 5901.
[157] I.G. Kim, S. Piao, S.H. Hong, S.W. Kim, T.K. Hwang, S.H. Oh, J.H. Lee and J.Y. Lee // *J. Biomed. Mater. Res. A* **100A** (2012) 286.
[158] N. Han, J. Johnson, J.J. Lannutti and J.O. Winter // *J. Control. Release* **158** (2012) 165.
[159] Y.C. Kuo and M.J. Huang // *Biomaterials* **33** (2012) 5672.
[160] X. Jiang, H.Q. Cao, L.Y. Shi, S.Y. Ng, L.W. Stanton and S.Y. Chew // *Acta. Biomater*. **8** (2012) 1290.
[161] Y.-C. Kuo and C.-T. Wang // *Colloids. Surf. B Biointerfaces* **100** (2012) 9.

Poly (ε-caprolactone) Fiber: An Overview

Bahareh Azimi[1], Parviz Nourpanah[1], Mohammad Rabiee[2], Shahram Arbab[3]

[1]Amirkabir University of Technology, Textile Engineering Department, Tehran, IRAN

[2]Amirkabir University of Technology, Biomedical Engineering Department, Tehran, IRAN

[3]ATMT Research Institute, Faculty of Textile Engineering, Amirkabir University of Technology, Tehran, IRAN

Correspondence to:
Parviz Nourpanah email: pnx@aut.ac.ir

ABSTRACT

Poly (ε-caprolactone), (PCL) or simply polycaprolactone as it is usually referred to, is a synthetic biodegradable aliphatic polyester which has attracted considerable attention in recent years, notably in the biomedical areas of controlled-release drug delivery systems, absorbable surgical sutures, nerve guides, and three-dimensional (3-D) scaffolds, for use in tissue engineering. Various polymeric devices like microspheres, microcapsules, nanoparticles, pellets, implants, and films have been fabricated using this polymer. It can be transformed by spinning into filaments for subsequent fabrication of desirable textile structures. Spinning may be accomplished by various approaches. The fibers may be fabricated into various forms and can be used for implants and other surgical applications such as sutures. Although numerous studies have investigated different properties and applications of PCL, there is no comprehensive study investigating different fabrication methods of PCL fibers and their biomedical applications. The present article presents a review on the production of PCL fiber via various methods, along with correlations between structure and properties of the fibers. The applications of these fibers in biomedical domains are also discussed.

Keywords: PCL, Fiber, Spinning, Medical application.

INTRODUCTION

In recent years, biodegradable polymers have attracted considerable attention as biomaterials in pharmaceutical, medical, and biomedical engineering applications, including drug delivery systems, artificial implants, and functional materials in tissue engineering. Aliphatic polyesters, due to their favorable features of biodegradability and biocompatibility, comprise one of the most important classes of synthetic biodegradable polymers. The advantage of these polyesters is their biocompatibility and higher hydrolysability in the human body [1]. Poly (ε-caprolactone) (PCL) is a family member of biodegradable aliphatic polyesters which have found important use as biomaterials in prosthetics, sutures, and drug delivery systems. As a commercial material, the main attractions of PCL are (1) its approval by the Food and Drug Administration (FDA) for use in humans, (2) its biodegradability, (3) its compatibility with a wide range of other polymers, (4) its good processibility which enables fabrication of a variety of structures and forms, (5) its ease of melt processing due to its high thermal stability and (6) its relatively low cost [2-3]. It can also be transformed by spinning into filaments for subsequent fabrication of desirable textile structures. Due to excellent characteristics, such as biodegradability, biocompatibility, mild undesirable host reactions, and three-dimensional and directional porous structures, PCL fiber, whose diameter range from nanometer to millimeter, is broadly studied. In fiber form, PCL and its copolymers have been investigated for usage in drug delivery systems [4], 'long-lasting' absorbable sutures [5-8] and, 3-D scaffolds for tissue engineering applications [9]. For example, to use in absorbable nerve guides, ε-caprolactone has been copolymerized with DL-lactide [10] and trimethylene carbonate [11]. PCL has received relatively comprehensive attention in the literature [3, 12-13], however, there are few studies investigating different fabrication methods and biomedical application of PCL fibers. The present article presents a review on the chemistry and different properties of PCL, production of PCL fiber by various methods and correlations between structure and properties of the fibers. The applications of these fibers in biological and medical domains are also discussed.

Synthesis and Physicochemical Properties of PCL

PCL is prepared by the ring opening polymerisation of the cyclic monomer ε-caprolactone (*Figure 1*) and was studied as early as the 1930s [12]. Recently a

wide range of catalysts for the ring opening polymerization of caprolactone has been reviewed [14].

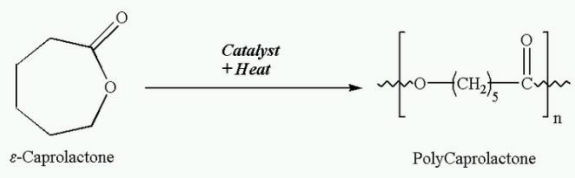


FIGURE 1. Ring opening polymerization of ε-caprolactone to polycaprolactone.

Catalysts such as stannous octoate are used to catalyze the polymerization and low molecular weight alcohols can be used to control the molecular weight of the polymer [15]. There are various mechanisms which affect the polymerization of PCL and these are anionic, cationic, co-ordination and radical. Each method affects the resulting molecular weight, molecular weight distribution, end group composition and chemical structure of the copolymers [16]. The number average molecular weight of PCL samples generally vary from 3,000 to 80,000 g/mol and can be graded according to the molecular weight [17].

It is a semi-crystalline polymer with a melting point of 59–64 ^{o}C and a glass-transition temperature of 60^{o}C [18]. PCL is soluble in chloroform, dichloromethane, carbon tetrachloride, benzene, toluene, cyclohexanone and 2-nitropropane at room temperature. It has a low solubility in acetone, 2-butanone, ethyl acetate, dimethylformamide and acetonitrile and is insoluble in alcohol, petroleum ether and diethyl ether [12]. The versatility of PCL is due to the fact that, it allows modification of its physical, chemical and mechanical properties by co-polymerization or blending with many other polymers efficiently. It has been observed that co-polymerization alters the chemical property that indirectly affects all other properties such as crystallinity, solubility, and degradation pattern resulting in a modified polymer with intended properties for drug delivery [13]. Whereas, blending that leads to altered physical property and biodegradation along with highly influenced mechanical properties is preferred for formulations of tissue engineering such as scaffolds, fibers and films. A number of polymers have been studied for their compatibility to modify the thermal, rheological as well as biophysical properties of PCL, based on its application. PCL is reported to be compatible with natural polymers like starch, hydroxy apatite (HA), chitosan and synthetic polymers namely poly ethylene glycol (PEG), poly urethane (PU), oxazolines, poly ethylene oxide (PEO), poly vinyl alcohol (PVA), polylactic acid and polylactic co-glycolic acid (PLGA) [19-26]. These PCL modifications satisfy the required biophysical properties for most of the formulation currently used in drug delivery [13].

Biodegradation

PCL is degraded by hydrolysis of its ester linkages in physiological conditions (such as in the human body) and has therefore received a great deal of attention in order to be used as an implantable biomaterial. In particular it is especially interesting for the preparation of long term implantable devices, due to its degradation which is even slower than that of polylactide. From degradation studies presented in the literature it can be concluded that PCL undergoes a two-stage degradation process: firstly the non-enzymatic hydrolytic cleavage of ester groups and secondly, when the polymer is more highly crystalline and has a low molecular weight (less than 3000) the polymer is shown to undergo intracellular degradation as this was observed during experiments of PCL fragments uptake in phagosomes of macrophages and giant cells and within fibroblasts [27]. This supports the theory that PCL may be completely resorbed and degraded via an intracellular mechanism once the molecular weight was reduced to 3000 or less. It was also noted that in the first stage the degradation rate of PCL is essentially identical to the in vitro hydrolysis at 40°C and obeyed first-order kinetics. It was concluded that the mechanism of PCL degradation could be attributed to random hydrolytic chain scission of the ester linkages, which caused a decrease in molecular weight. The homopolymer PCL has a total degradation of two to four years (depending of the starting molecular weight of the device or implant) [28-29]. The rate of hydrolysis can be altered by copolymerization with other lactones or glycolides/lactides. Surprisingly, more than 1000 papers have been published during the last decade in the biomaterials and tissue engineering literatures which use PCL-based-scaffolds. Among these studies only a small number of groups have included a study of the degradation and resorption kinetics of the PCL scaffolds [12]. *Table I* shows comprehensive data on PCL fiber degradation.

Spinning of PCL Fibers

As mentioned previously, PCL by itself is most suited biomedically to the design of long-term implantable systems. In fiber form, PCL has also been investigated for use in drug delivery systems, 'long-lasting' absorbable sutures and, most recently,

3-D scaffolds for tissue engineering applications. Extrusion of the PCL into monofilament and multifilament may be achieved by fiber formation mechanisms such as melt spinning, solution spinning, and electrospinning. There are distinct features of each of these processes that are subsequently reflected in fiber properties.

TABLE I. Comprehensive data on PCL fiber degradation.

Workers	Year	....	Brief method and outcome	Refs
N. BÖLGEN et al.	2005	*In vitro*& *in vivo*	*In vitro* and *in vivo* degradation studies of non-woven materials made of PCL nanofibers showed that electrospun PCL materials were degraded much faster *in vivo* as compared with *in vitro* due to the enzymatic degradation of PCL in addition to the hydrolytic degradation.	[30]
Lam. C.X.F. et al.	2007	*In vivo*	Over 6 months, composite PCL/ b-Tri-calcium phosphate (TCP) scaffolds degrade faster than PCL homopolymer scaffolds *in vivo*.	[31]
Pektok, E, et al.	2008	*In vivo*	In vivo healing and degradation characteristics of small-diameter vascular grafts made of PCL nanofibers compared with expanded polytetrafluoroethylene (ePTFE) grafts were evaluated.	[32]
Lam et al.	2008	*In vitro*	PCL and PCL/ TCP scaffolds degraded via a surface degradation pathway in the alkaline accelerated setting; however, this appeared to switch to a bulk degradation pathway under the long term simulated condition.	[33]
Wan et al.	2008	*In vitro*	Degradation of the PCL component with chitosan could be accelerated at various rates depending on the compositions of the scaffolds and the media, and the chitosan component could effectively buffer the acidic degradation products of the PCL component.	[34]
Mobarakeh et al.	2008	*In vitro*	By increasing gelatin content the biodegradability of PCL/ gelatin nanofibrous scaffolds increased in PBS over 2-week period.	[35]
Tillman, B.W. et al.	2009	*In vivo*	PCL/collagen electrospun scaffolds maintain a high degree of patency and structural integrity in vivo without eliciting abnormal inflammatory response over the course of 1 month.	[36]
Johnson et al.	2009	*In vitro*	The net effects of biological and non-biological environments on PCL electrospun structures following 7 and 28 days of *in vitro* exposure are established. Material degradation, as well as biological deposition, was responsible for the changes in mechanical properties.	[37]
Vieira et al.	2011	*In vitro*	Hyper elastic constitutive models were used to predict the mechanical behavior and biodegradation of a blend composed of PLA and PCL fiber.	[38]

Melt Spinning

Since PCL is thermoplastic in nature, it is possible to melt the polymer under reasonable conditions. In the melt spinning process polymer is melted, filtered, and extruded through the spinneret. The melt is drawn from the spinneret hole at a melt temperature. In the draw zone the extruded filaments are cooled to the solidification temperature and further to below the glass transition temperature. Finally, the filaments come to the take-up bobbins, and the temperature of the filaments are less than the Tg. Various research groups have studied the melt spinning of PCL fibers under various processing conditions [39-45].

Charuchinda et al. [2] studied some of the main factors affecting the small-scale melt spinning of PCL, monofilament fibers. These factors included spinning temperature, extrusion rate, take-up rate and draw ratio. The underlying influence of the polymer's own characteristic properties, were also interpreted within the context of the melt spinning process. A summary of the as-spun fiber diameters obtained under the various processing conditions is given in *Table II*. The effects of the individual processing variables are as it would be expected, namely that the fiber diameter decreases with increasing spinning temperature (initially) and take-up rate but increases with increasing extrusion rate. By manipulation of these variables, together with the appropriate choice of spinneret size, uniform PCL fibers of any required diameter could be reproducibly obtained. Krishnanand at al. [39] determined the sonic moduli and crystallinity measurements for unoriented filaments to determine the intrinsic values of the transverse modulus for the crystalline and amorphous regions of melt spun PCL filaments. These values were 3.473 GPa and 0.071 GPa, respectively. The amorphous transverse modulus has a very low value compared to other polymers and is associated with a twisted structure of the main chain. Mochizuki et al. [42] studied the effect of draw ratio on the mechanical properties of melt spun PCL filament and found that, with increasing draw ratio, stiffness and tenacity increase in a typical manner which are

associated with changes in morphological parameters. In another study, lidocaine release from PCL suture threads produced by micro-extrusion was investigated to assess the reliability of the manufacturing process. The full and rapid release of the loaded drug demonstrates that the extrusion process does not alter the drug and that the loaded amount is embedded in an open structure porosity that allows it to be available for the release [45]. An et al. [46] have reported a novel technique, named microfiber melt drawing, to fabricate a bundle of three dimensionally aligned PCL microfibers of about 10 μm fiber diameters without using any organic solvent. Orifice diameter, temperature and take-up speed have shown significant effects on the linear density of fabricated microfibers. Each microfiber bundle has a stiffness of about 1382.5 N/tex and a maximum load of 30.7 N, which can be used as a building block for larger microfiber bundles. Mechanical properties of these microfiber bundles can thus be adjusted by the number of fibers or the number of bundles. In order to prepare monofilaments to be applied as threads for surgical sutures and possessing antimicrobial properties, Scaffaro et al. [47] have used an "online" method to combine the physicochemical and biological property of PCL and chlorhexidine (CHX), respectively. A piston pressed the molten polymer from a cylindrically shaped reservoir to the capillary. At the exit of the capillary, the filaments were drawn at constant speed and free cooling at room temperature. Under these conditions, the threads had a diameter of 300±10 μm.

Wet Spinning

The solution spinning methods, dry spinning and wet spinning, are usually utilized for polymers that do not melt. In both methods polymer is dissolved into a suitable solvent and the polymer solution is filtrated, dearated, and pumped through the spinneret [48]. In dry spinning, solvents are removed by thermal evaporation while in wet spinning the coagulation of the polymer is carried out in another fluid that is compatible with the spinning solvent. However, is not itself a solvent for the polymer [49]. In practice, as the polymer solution enters into the coagulation bath, phase separation begins due to solvent out-flow and nonsolvent in-flow and the polymer precipitates as fibrils [50-51]. *Table III* shows comprehensive data on wet spun PCL fiber [52-64].

Electrospinning

Electrospinning is another interesting technique for spinning PCL (and other polymers). In the electrospinning process, a polymer solution or melt is subjected to strong electric fields, and then the liquid-phase polymer is ejected from a nozzle. The diameter of the ejected fibers is significantly reduced as they travel toward a collector. *Figure 2* shows schematically an electrospinning system. The electrospinning process of the PCL has been widely studied. *Table IV* reviews some fabrication process parameters and fiber diameter of electrospun PCL fibers.

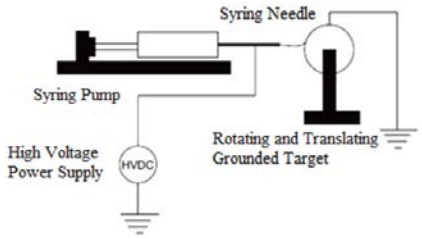


FIGURE 2. Schematic of electrospinning system [67].

Medical Application of PCL Fiber

Biodegradability, biocompatibility, pliability, good solubility, low melting point and exceptional blend-compatibility of PCL have stimulated extensive research into its potential application in the biomedical field [16, 68-69]. Following are the major applications of the PCL fibers in biomedical domain.

Suture

Sutures are the most widely used materials in wound closure and have been in use for many centuries. They are, in general made up of fibers from natural or synthetic polymers. Polymeric fibers could be absorbable or nonabsorbable. The most important advantage of synthetic absorbable sutures is their reproducible degradability inside a biological environment. Due to the development of these synthetic fibers, they have replaced some natural fibers [18]. In the past four decades, several studies related to the biocompatibility of sutures made from aliphatic polyesters have been published [70]. PCL has been regarded as tissue compatible and used as a biodegradable suture in Europe. The polymer undergoes hydrolytic degradation due to the presence of hydrolytically labile aliphatic ester linkages in physiological conditions (such as in the human body). Because the homopolymer has a degradation time on the order of two years, copolymers have been synthesized to accelerate the rate of bioabsorption. For example, copolymers of ε-CL with DLL have produced materials with more-rapid degradation rates. The introduction of monofilament sutures of ε-CL and glycolide (GL) solved many of the problems with braided sutures that were related to tissue drag and trauma as well as the possible potentiating of

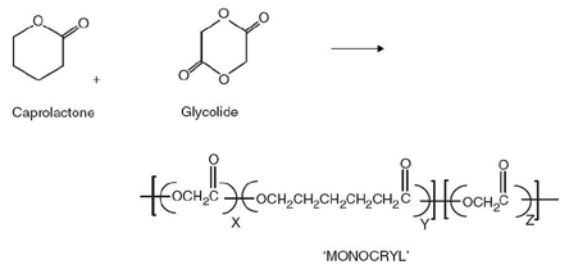
infection through the interstices of the braid structure. This block copolymer offers reduced stiffness compared to pure polyglycolide, which is being sold as a monofilament suture by Ethicon, Inc. (Somerville, NJ), under the trade name Monacryl (scheme1)[105].

TABLE II. Summary of the effects of processing variables on the as-spun monofilament fiber diameter [2].

Spinning temperature (°C)	Ram speed (mm min-1)	Extrusion rate (m min-1)	Take-up rate (m min-1)	On-line draw ratio	Fiber diameter (mm)
85	2	0.12	0.6	5	0.91
90	2	0.12	0.6	5	0.81
100	2	0.12	0.6	5	0.80
110	2	0.12	0.6	5	0.80
120	2	0.12	0.6	5	0.79
85	0.5	0.03	0.6	20	0.50
85	1	0.06	0.6	10	0.66
85	2	0.12	0.6	5	0.91
85	2	0.12	0.6	5	0.91
85	2	0.12	1	8.3	0.67
85	2	0.12	2	16.7	0.49

TABLE III. Comprehensive data on wet spun PCL fiber.

Workers	Year	Brief method and outcome	Solvents / non-solvents	Fiber diameter (μm)	Refs
Polacco et al.	2002	A 'multiple' delivery system was studied, consisting of hollow microfibers containing drug loaded nanoparticles. Copolymers of poly (lactic acid) and ε -caprolactone were used for the preparation of the fibers through both wet and dry–wet spinning procedures.	Acetone/deionized water	…	[52]
Williamson et al.	2002	PCL fibers, 150μm in diameter were produced using a wet spinning technique. Cell attachment and proliferation on these fibers was investigated.	…	150	[53]
Williamson et al.	2004	PCL fibers have been produced by wet spinning from solutions in acetone under low shear (gravity flow) conditions. Fibers were found to exhibit low tensile modulus and high extensibility, coupled with a proliferation rate of fibroblasts and myoblasts on the fibers.	Acetone/ methanol	147-190	[54]
Williamson et al.	2004	A hydrophilic macromolecule and a lipophilic drug were incorporated in PCL fibers by gravity spinning using particulate dispersions and co-solutions of PCL and steroid, respectively.	Acetone/ methanol	153	[55]
Williamson et al.	2005	PCL fibers were produced by wet spinning from solutions in acetone under low shear (gravity flow) conditions. As-spun PCL fibers were surface-modified by adsorption of gelatin from solution with the aim of improving cell adhesion.	Acetone/ methanol	140-150	[65]
Chiono et al.	2005	Poly (3-hydroxybutyrate-co-3-hydroxyvalerate)/PCL hollow fibers with various degrees of porosity have been produced by dry- jet- wet spinning. Blending PCL with PHBHV was proposed as a method for the successful continuous spinning of PCL-based hollow fibers, avoiding lumen occlusion caused by PCL dies swelling phenomena.	Chloroform/ anhydrous ethanol	…	[57]
Chang et al.	2008	The antibiotic, gentamicin sulphate (GS), was incorporated in gravity-spun PCL fibers by spinning from particulate suspensions of the drug in PCL solution to produce a controlled delivery system.	Acetone/ methanol	170–220	[56]
Tuzlakoglu et al.	2008	A new route was used to produce starch-PCL fiber mesh scaffolds. It was demonstrated that the scaffolds with 77% porosity could be obtained by a simple wet-spinning technique based on solution/precipitation of a polymeric blend.	Chloroform/ methanol	100	[58]
Shen et al.	2008	Fine and continuous ibuprofen-loaded PAN/PCL fibers were successfully prepared using wet spinning processes.	Dimethylacetamide (DMAc)/water	…	[66]
Puppi et al.	2011	A wet-spinning technique was optimized for the production of PCL fibrous scaffolds loaded with bisphosphonate and hydroxyapatite.	Acetone/ethanol	100-250	[59]
Puppi et al.	2011	The wet-spinning conditions to obtain 3D *PCL scaffolds loaded with Enrofloxacin and Levofloxacin antibiotics were optimized.	Acetone/ethanol	100–300	[61]
Wang et al.	2011	Chitosan (CHT)/PCL were fabricated into drug-enclosed fibrous membranes by loading with ketoprofen and using a wet-spinning method.	0.5% aqueous acetic acid/ 0.5 wt% NaOH solution	100-200	[62]
Neves et al.	2011	CHT/PCL blend 3D fiber-mesh scaffolds were produced by wet spinning. Three different formulations - 100:0, 75:25 and 50:50 wt % CHT/PCL were used, in order to investigate the effect of polymer composition in the physical chemical and biological properties of the fiber-meshes.	Formic acid/ methanol	…	[63]
Puppi et al.	2012	An additive manufacturing technique for the fabrication of three-dimensional polymeric scaffolds, based on wet-spinning of PCL or PCL/ hydroxyapatite (HA) solutions was developed.	Acetone/ethanol	200-250	[64]



SCHEME 1. Synthesis of copolymer of e-caprolactone and glycolide [18].

Bezwada et al. showed that Monocryl sutures displayed excellent handling properties, minimal resistance during passage through tissue, and excellent tensile properties. Absorption data on these sutures indicate that absorption is complete between the 91st and 119th days of implantation, with slight or minimal tissue reaction [106].

Pharmaceutical

The drug delivery system was developed for the purpose of bringing, uptaking, retaining, releasing, activating, localizing and targeting the drugs at the right timing, period, dose and place. The biodegradable polymer can contribute largely to this technology by adding its own characters to the drugs. The history of biodegradable polymers in drug delivery systems dates back to 1970 when PLGA was used to control the release of narcotics. PCL is suitable for controlled drug delivery due to a high permeability to many drugs, excellent biocompatibility and its ability to be fully excreted from the body once bioresorbed. Biodegradation of PCL is slow in comparison to other polymers, so it is more suitable for long-term delivery, which extends over a period of more than one year. PCL also has the ability to form compatible blends with other polymers which can affect the degradation kinetics which can be in turn tailored to fulfill desired release profiles [107-108].

Several drug delivery vehicles composed of PCL, such as microspheres, microcapsules, nanospheres and micro and nanofibers have been developed for the controlled release of drugs or protein. The biodegradability of PCL fibers has inspired several studies on controlled drug delivery systems. Williamsona et al. [55] have incorporated a hydrophilic macromolecule (ovalbumin (OVA)) and a lipophilic drug (progesterone) in PCL fibers by gravity spinning using particulate dispersions and co-solutions of PCL and steroid, respectively. PCL fibers loaded with 1% (w/w) OVA powder displayed a pronounced burst release phase (60% of the protein load) over 2 days in PBS at 37°C. The release profile then tended to plateau. In contrast, OVA nanoparticle-loaded fibers exhibited delayed protein release initially and then a major increase at day 14. The amount of progesterone release from PCL fibers in PBS increased with drug loading but the cumulative release profiles (% w/w) were little affected by the initial drug loading of the fibers or the concentration of the PCL spinning solution. Gravity spinning shows potential for producing PCL fibers-based platforms for programmed delivery of bioactive molecules of utility for tissue engineering and drug delivery. Chang et al. [56] have reported on the incorporation of gentamicin sulphate (GS) in gravity-spun PCL fibers to illustrate the potential for controlled, local delivery of antibiotics from wound closure materials, and tissue substitutes such as textile vascular grafts. The production rate of GS-loaded PCL fibers was confined to the range 1–1.5 m/min and the fiber diameter to 170–220 μm. The kinetics of drug release could be adjusted by varying the GS loading of the fibers and the suspension preparation conditions. Puppi et al. [61] optimized the wet-spinning conditions to obtain 3D *PCL scaffolds loaded with Enrofloxacin (EF) and Levofloxacin (LF) antibiotics. Most of the antimicrobial agent added to the polymer solution was found in the coagulation bath and the loading efficiency was in the range of 18%–27% depending on the type of antibiotic and its concentration. Both the EF-loaded and LF-loaded meshes, after a fast release at the early stages, provided sustained release for up to five weeks (*Figure 3*).

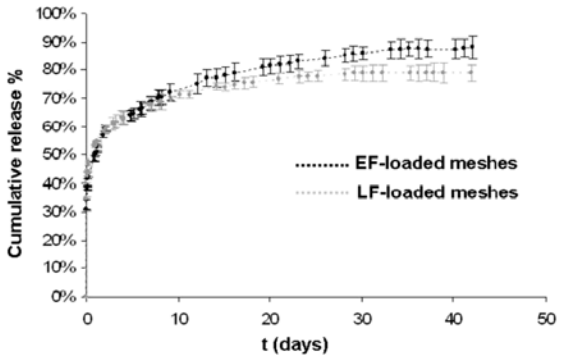


FIGURE 3. Cumulative percent release of EF and LF from *PCL meshes during in vitro drug release studies (37°C, PBS, pH 7.4). Error bars corresponding to _ standard deviation values calculated on three replicates for each time point [61].

TABLE IV. Fabrication process parameters: polymer solution properties, electrospinning process parameters.

Workers	Year	Polymer Concentration	Solvent	Voltage (KV)	Flow rate (ml/h)	Distance (cm)	Fiber diameter (nm)	Refs
Lee et al.	2002	10-15wt%PCL (80 kDa)	Methylene chloride (MC), MC/ Dimethylformamide (DMF)	...	...	...	5500, 200	[71]
Yoshimoto et al.	2003	10 w/v% PCL (80 kDa)	Chloroform	13	6	...	400 -700	[72]
Li et al.	2003	14 w/v% PCL (80 kDa)	(DMF)/tetrahydrofuran (THF) 1 : 1	12	0.4	20	700	[73]
Shin et al.	2004	10 w/v% PCL (80 kDa)	Chloroform	13	6		...	[74]
Shin et al	2004	10 w/v% PCL (80 kDa)	Chloroform /methanol 1 : 1	12	6	30	250	[75]
Ishii et al.	2005	10 w/v% PCL (80 kDa)	Chloroform /methanol 1 : 1	12	6	...	250	[76]
Li et al.	2005	14 w/v% PCL (80 kDa)	DMF/THF 1 : 1	12	0.4	20	500-700	[77]
Li et al.	2005	14 w/v% PCL (80 kDa)	DMF/THF 1 : 1	12	0.4	20	700	[78]
Pham et al.	2006	8–15 w/v% PCL (80 kDa)	Chloroform /methanol 5 : 1 to 7 : 1	19-27	3.5-18	18-33	2-10μm	[79]
Luong-Van et al.	2006	8 w/v% PCL (80 kDa)	Dichloromethane/methanol 7:3	0.8 kV/cm	0.5	...	810	[80]
Li et al.	2007	14 w/v% PCL (80 kDa)	DMF/THF 1 : 1	15	...	20	438	[81]
Kolambkar et al.	2007	13 wt/v% PCL (80 kDa)	Dichloromethane/DMF 40:60	14	0.75	15	591	[82]
Prabhakaran et al.	2008	12 w/v% PCL (80 kDa)	Chloroform/methanol 1 : 3	12	1	12	350	[83]
Wong et al.	2008	PCL (80 kDa)	Acetone & DMF/chloroform	...	...	...	250 nm to 2.5 μm	[84]
Pektok et al.	2008	15 w/v% PCL (80 kDa)	Chloroform/methanol 7 : 3	20	12	20	1900	[85]
Nisbet et al.	2008	10 w/v% PCL	Chloroform/methanol 3 : 1	20	0.397	15	750	[86]
Ghasemi et al.	2008	10 w/v% PCL (80 kDa)	MC/ DMF 4:1	12	...	20	418	[35]
Nottelet et al.	2009	5–15w/v% PCL (80 kDa)	Acetone, Chloroform/acetone 7 : 3,Chloroform/ ethanol 7:3	15-25	12-24	15-25	500-2500	[87]
Martins et al.	2009	17 w/v% PCL,	Chloroform/DMF 7 : 3	9-10	1	20	...	[88]
Li et al.	2009	14 w/v% PCL (80 kDa)	DMF/THF 1 : 1	12	...	20		[89]
Piskin et al.	2009	40 w/v% PCL ([Mw 84 kDa: YMw 14 kDa 20 : 80)	Chloroform /DMF 1 : 1	15	...	10	600-800	[90]
Chen et al.	2009	10–20 w/v% PCL (80 kDa)	Acetone	10-25	3	7.5-25	400-1100	[91]
Nisbet et al.	2009	13 w/v% PCL	Chloroform/methanol 75 : 25	15	0.6	12	350-450	[92]
Wise et al.	2009	10 w/v% PCL (80 kDa)	MC/DMF 75 : 25	1 KV/ cm	1		500	[93]
Merrell, et al.	2009	15% w/v PCL(80 kDa)	Chloroform/ methanol 3:1	25	2	10	300-400	[94]
Lowery et al.	2010	PCL (80 kDa)	Chloroform, methanol & DMF	13-37	0.05-0.1	32-48	730 to 10530	[95]
Ruckh, et al.	2010	12 w/v% PCL (80 kDa)	Choroform /methanol 4 : 1	21	2.8	10	372	[96]
Wu et al.	2010	10 w/v% PCL (80 kDa	Chloroform/DMF 10 : 1	18	0.4	15	300-500	[97]
Zhu et al.	2010	10–25% PCL (80 kDa)	Chloroform /DMF 2 : 1	15-20	1	10	100nm-10μm	[98]
Cao et al.	2010	9.5 and 14% PCL(65 kDa)	TFE / dH2O 5 : 1	16-18	1.5	13-14	313, 506	[99]
Puppi et al.	2010	15w/v% PCL (189 kDa)	Acetone	25	1-16	15	1.5–2.5 μm	[59]
Puppi et al.	2010	15w/v% *PCL (64 &189 kDa)	Acetone	25	16	15-18	...	[100]
Jha et al.	2011	50–275 mg mL_1 PCL (65 kDa)	TFE	22	2-20	10-30	400-1500	[101]
Gholipour et al.	2011	5w/v% PCL (80 kDa)	MC/DMF 4:1	10-20	0.5	20	164-220	[102]
Kołbuk et al.	2012	7-14% PCL (80 kDa)	Chloroform/DMF 1:1& Chloroform/ methanol 3:1	7.5-15	0.2	15	...	[103]
Ruckh et al.	2012	12% w/v% PCL	Chloroform/methanol. 3:1	18-21	2.3–2.6	10-11.5	300-500	[104]

Luong-Van et al. [80] incorporated heparin into electrospun PCL fiber mats for assessment as a controlled delivery device. The fiber diameter was found to be dependent on the concentration of heparin added, while increasing heparin concentration lead to a decreased fiber diameter, which can be attributed to an increased ionic charge of the spinning solution *(Figure 4)*. A sustained release of heparin could be achieved from the fibers over 14 days with the release diffusion controlled during this time. Merrell et al. [94] have investigated the feasibility and potential of PCL nanofibers as a delivery vehicle for curcumin for wound healing applications. The fibers showed sustained release of curcumin for 72 h and could be made to deliver a dose much lower than the reported cytotoxic concentration while remaining bioactive. The in vivo wound healing capability of the curcumin loaded PCL nanofibers was demonstrated by an increased rate of wound closure in a streptozotocin-induced diabeticmicemodel. In another study, nanofiber PCL scaffolds were loaded with two concentrations of rifampicin (RIF), and the RIF release kinetics and bactericidal efficacies of the scaffolds were evaluated compared to RIF-free control scaffolds.

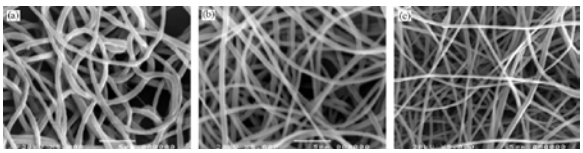


FIGURE. 4. SEM micrographs of electrospun PCL fibers containing different amounts of heparin (a) 0 wt%, (b) 0.05 wt%, and (c) 0.5 wt% [80].

There were significant differences between the RIF release profiles, though both scaffolds showed an initial burst release, and RIF release was completed after 8 hours. Approximately, 50% of the loaded RIF remained entrapped within the scaffolds [104]. Kanawung et al. [109] used electrospinning to fabricate ultrafine fiber mats from PCL and PCL solution that contained diclofenac sodium (DS) as the model drug. The effects of solution and process parameters (i.e., solution concentration, applied electrical potential, and collection distance) on morphological appearance and size of the as-spun PCL were investigated. Incorporation of the model drugs caused the resulting as-spun fibers to be larger in their diameters. As shown in *Figure 5*, the cumulative release of the model drug from drug-loaded as-spun PCL fiber mats increased monotonically with increasing immersion it became practically constant at long immersion times.

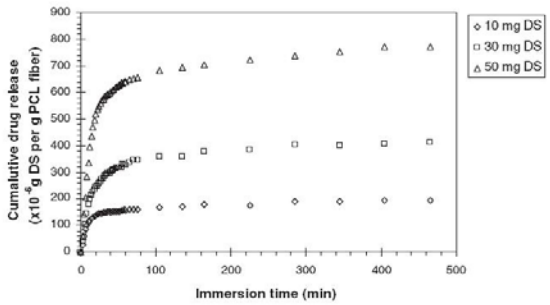


FIGURE 5. Cumulative amount of DS released from DS-loaded PCL fiber mats that were electrospun from PCL solutions loaded with 10, 30 and 50 mg of DS over an immersion period of 465 min [109].

In another attempt, Tammaro et al. [110] have prepared new fibrous composites by using electrospinning technique, obtained by fixing an anti-inflammatory drug, diclofenac sodium, into a lamellar inorganic compound, and incorporating the obtained nanohybrid into a biodegradable PCL. The structure, morphology, and thermal behavior of the electrospun fibers were analyzed. The release of the active diclofenac molecules was found much slower in comparison to the release of the fibers in which the drug was directly incorporated into the polymer. Liu et al. [111] produced PCL electrospun fibers containing ampicillin sodium salt and twisted them into nanofiber yarns. The fiber diameters and crystallinity, the *in vitro* antimicrobial properties of the yarns, and the *in vitro* release of ampicillin from yarns containing various ampicillin concentrations were studied. *Figure 6* shows the smooth surface of a fiber.

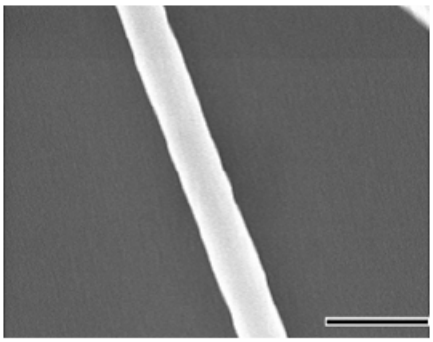


FIGURE 6. Representative SEM image showing the smooth surface of a fiber (The scale bar represents 500 nm.) [111].

Tissue Engineering

Tissue engineering can be defined as: "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ" [112]. It is the use of a combination of cells, engineering and materials methods, and suitable biochemical and physio-chemical factors to improve or replace biological functions. Powerful developments in the multidisciplinary field of tissue engineering have yielded to a novel set of tissue replacement parts and implementation strategies. Scientific advances in biomaterials, stem cells, growth and differentiation factors, and biomimetic environments have created unique opportunities to fabricate tissues in the laboratory from combinations of engineered extracellular matrices scaffolds, cells, and biologically active molecules. To fulfill the diverse needs in tissue engineering, various materials have been exploited as scaffolds for tissue regeneration. As scaffold candidates, the following characteristics are desirable: (i) three dimensional and highly porous structures with an interconnected pore network for cell growth and flow transport of nutrients and metabolic waste; (ii) biocompatible and bioresorbable with a controllable degradation and resorption rate to match cell/tissue growth *in vitro* and/or *in vivo;* (iii) suitable surface chemistry for cell attachment, proliferation and differentiation and (iv) mechanical properties to match those of the tissues at the site of implantation [113]. Polymeric biodegradable scaffolds combine advantages of synthetic and natural materials. The physical properties of synthetic polymers, such as mechanical strength and degradation rate, can be manipulated according to requirements, with fewer batch-to-batch variations than usual with natural materials. Amongst the

different classes of biodegradable polymers, PCL is suitable for scaffold fabrication. PCL is an incredibly versatile bioresorbable polymer and by way of its superior rheological properties it can be used by almost any polymer processing technology to produce an enormous array of scaffolds. A number of fabrication technologies have been applied to process PCL into 3D polymeric scaffolds of high porosity and surface area. Cell-invasive fiber-based scaffolds can be produced using methodologies developed for the textile industry, but with structures specifically designed for tissue engineering applications. Tissue engineering textiles have a relatively high surface area and their 'value added' application, from an industry with established techniques, is an advantage. Additionally, textiles are typically formed into thin meshes and therefore the permeability is high, allowing the necessary nutrients to reach the seeded cells. Traditional fabrication of non-woven textiles is based on the production of continuous micron diameter; fibers by extruding a polymer melt or polymer solution through a spinneret which is then mechanically drawn onto a winder, or a series of winders, and collected onto a spool. The fiber of the diameter is determined by the extrusion rate and the speed(s) of the winder(s) with a constant drawing rate paramount for attaining uniform diameter, continuous fibers [12]. Van Lieshout *et al* produced multifilament double-bed knitted, fibrin- covered PCL scaffolds to potentially function as aortic valves. On testing, it demonstrated good durability, proper opening and it showed coaptation upon closing, but had higher associated leakage compared to those of tested porcine valves [114]. Electrospinning is of great interest as a scaffold fabrication technique, since the resulting fiber diameters are in the size range (submicron to nanometer) of the extracellular matrix (ECM) microstructures, particularly the higher-ordered collagen microfibrils [115]. The flexibility of the electrospun fibers, due to the very high aspect ratio (length/diameter), is also beneficial, allowing seeded cells to remodel their surroundings. A plethora of research papers have focused on specific applications of PCL scaffolds in various tissue engineering applications. *Table V* reviews some studies, investigated the fabrication of PCL scaffold in various tissue engineering applications.

TABLE V. Fabrication of PCL scaffold in various tissue engineering applications.

Workers	Year	Brief method and outcome	Refs
Yoshimoto, et al	2003	Microporous, non-woven PCL scaffolds were made by electrospinning. Mesenchymal stem cells (MSCs) derived from the bone marrow of neonatal rats were cultured, expanded and seeded on electrospun PCL scaffolds.	[72]
Li et al.	2003	Three-dimensional, nanofibrous PCL scaffold composed of electrospun nanofibers for its ability to maintain chondrocytes in a mature functional state was evaluated.	[73]
Shin et al.	2004	A highly porous, degradable PCL scaffold with an extracellular matrix-like topography was produced by electrospinning. Bone formation from MSCs on a novel nanofibrous scaffold in a rat model was assessed.	[74]
Ishii et al.	2005	The formation of thick cardiac grafts *in vitro* and the versatility of PCL electrospun mesh for cardiac tissue engineering was demonstrated.	[76]
Li et al	2005	A nanofibrous scaffold made of PCL was fabricated, and its ability to support *in vitro* chondrogenesis of MSCs was examined.	[77]
Li et al	2005	A three-dimensional nanofibrous scaffold fabricated from PCL for its ability to support and maintain multilineage differentiation of bone marrow-derived human mesenchymal stem cells (hMSCs) was tested.	[78]
Pham et al.	2006	Bilayered constructs consisting of microfiber scaffolds with varying thicknesses of nanofibers on top were generated and evaluated for their potential to affect rat marrow stromal cell attachment, spreading, and infiltration.	[79]
Li et al.	2006	Six commonly used poly (α-hydroxy esters) were used to prepare electrospun fibrous scaffolds, and their physical and biological properties were also characterized.	[116]
Shao et al	2006	To evaluate the repair potential in large osteochondral defects on high load-bearing sites, a hybrid scaffold system which comprised 3D porous PCL scaffold for the cartilage component and tricalcium phosphate-reinforced PCL scaffold for the bone portion were fabricated.	[117]
Van Lieshout et al	2006	Multifilament double-bed knitted fibrin- covered PCL scaffolds to potentially function as aortic valves were produced.	[114]
Van Lieshout et al	2006	Two types of scaffolds; an electrospun valvular scaffold and a knitted valvular scaffold were developed for tissue engineering of the aortic valves and were compared in a physiologic flow system and in a tissue-engineering process.	[119]

Li, et al	2007	The fabrication of biodegradable nanofibrous scaffolds composed of aligned fibers via electrospinning onto a rotating target was reported and their mechanical anisotropy as a function of the production parameters was characterized.	[81]
Oh et al.	2007	PCL cylindrical scaffolds with gradually increasing pore size along the longitudinal direction were fabricated by a novel centrifugation method to investigate pore size effect on cell and tissue interactions.	[115]
Pektok et al.	2008	The degradation and healing characteristics of small diameter PCL vascular grafts, produced via electrospinning, in the rat systemic arterial circulation was investigated.	[32]
Choi et al.	2008	PCL/collagen nanofibers of different orientations, to engineer functional muscle tissue for restoring large skeletal muscle tissue defects were produced.	[121]
Guarino et al.	2008	Scaffolds comprising PLLA fibers embedded in a porous PCL matrix were obtained by synergistic use of phase inversion/particulate leaching technique and filament winding technology.	[122]
Bregy et al.	2008	The use of fused diode laser soldering of vascular tissue using PCL scaffolds doped with bovine serum albumin (BSA) and Indocyanine green (ICG) was investigated.	[123]
Chen et al.	2009	A vacuum seeding technique on PCL electrospun scaffolds was used to prevent congregate and proliferate of cells on the surface of scaffold.	[91]
Nisbet, et al.	2009	The extent of microglial and astrocytic response was measured following implantation of electrospun PCL scaffolds into the caudate putamen of the adult rat brain.	[92]
Wise et al	2009	Electrospun and oriented PCL scaffolds were created, and hMSCs were cultured on these scaffolds. Cell viability, morphology, and orientation on the fibrous scaffolds were quantitatively determined as a function of time.	[93]
Li et al	2009	Cell-seeded nanofibrous PCL scaffolds for cartilage repair using 7 mm full-thickness cartilage defects in a swine model was evaluated. Biodegradable nanofibrous scaffolds seeded with MSCs could effectively repair cartilage defects in vivo, and that this approach is promising for cartilage repair.	[89]
Balguid et al.	2009	Electrospun sheets comprising PCL with different fiber diameters (3-12 μm) were investigated for penetration depth using human venous myofibroblastsas as a means to optimize cell delivery during cardiovascular tissue engineering applications.	[125]
Ruckh et al.	2010	Nanofiber PCL scaffolds were fabricated by electrospinning, and their ability to enhance the osteoblastic behavior of MSCs in osteogenic media was investigated.	[96]
Wu et al.	2010	A novel electrospinning technique was demonstrated to fabricate small diameter 3-D nanofibrous tubular scaffold with controllable nanofiber orientations so as to regulate the macroscopic mechanical property of the scaffolds and benefit cell responses along different directions for vascular grafts applications.	[97]
Cao et al.	2010	The biocompatibility with regard to scaffold architecture and topographical effect of PCL nanofibrous scaffolds on the in vivo and *in vitro* foreign body reaction was investigated.	[99]
Puppi et al.	2010	Three-dimensional electrospun microfibrous meshes of (*PCL) as potential scaffolds for tissue engineering applications was developed. Cell culture experiments employing MC3T3-E1 osteoblast like cells showed good cell viability adhesion and collagen production on the *PCL scaffolds.	[100]
Jha, et al	2011	The structural and functional properties of three-dimensional (3D) nerve guides fabricated from PCL using the air gap electrospinning process was describe.	[101]
Puppi et al.	2011	The cytocompatibility of the wet-spun *PCL and the influence of the scaffold architecture on cell behavior were performed with pre-osteoblast cells.	[61]
Puppi et al.	2012	Three-dimensional polymeric scaffolds, based on wet-spinning of PCL and PCL/ hydroxyapatite (HA) solutions, was developed. The developed scaffolds showed good reproducibility of the internal architecture characterized by highly porous, aligned fibers with an average diameter in the range 200–250 μm.	[64]
Ruckh et al.	2012	PCL nanofiber scaffolds were fabricated to include both 10 or 20% (w/w) rifampicin (RIF), and the RIF release kinetics and bactericidal efficacies of the scaffolds were evaluated compared to RIF-free control scaffolds.	[104]
Diban et al.	2013	Hallow fibers were successfully manufactured from blends of PCL/PLGA by phase separation. These have adequate elongation characteristics to be applied in small-caliber blood vessel regeneration. The PCL/PLGA85/15 ratio yielded a miscible blend after processing, whereas higher PLGA contents in the blend led to separation of the polymer phases.	[123]

CONCLUSION

Featured with excellent characteristics, such as biodegradability, biocompatibility, mild undesirable host reactions, three-dimensional and directional porous structures, PCL fiber is broadly studied and used in different biomaterials. Therefore investigating of production of PCL fiber by various methods can be of much importance. This article presented a review on the production of PCL fiber by various methods including melt spinning, solution spinning and electrospinning. Correlations between structure and properties of the fibers and applications of them in biomedical domains such as sutures, drug loaded fibers and scaffold for use in tissue engineering were also discussed.

REFRENCES

[1] Bikiaris D N, Papageorgiou G Z, Achilias D S, Pavlidou E and Stergiou A. "Miscibility and enzymatic degradation studies of poly(e-caprolactone)/poly(propylene succinate) blends". *European Polymer Journal,* Vol 43, 2007, pp. 2491–2503.

[2] Charuchinda A, Molly R, Siripitayananon J, Molloy N and Sriyai M. "Factors influencing the small-scale melt spinning of poly(ε-caprolactone) monofilament fibres". *Polymer International*, Vol 52, pp. 1175–1181.

[3] Cipitria A, Skelton A, Dargaville T R, Dalton P D and Hutmacher D W. "Design, fabrication and characterization of PCL electrospun scaffolds—a review". *Journal of Materials Chemistry*, Vol 21, 2011, pp. 9419–9453.

[4] Goodson J M, Holborow D, Dunn R L, Hogan P and Dunham L. "Monolithic tetracycline containing fibers for controlled delivery to periodontal pockets". *J Periodontol*, Vol 54, 1983, pp. 575-579.

[5] Barber F A, Click J N. "The Effect of Inflammatory Synivial Fluid on the Breaking Strength of New Long Lasting Sutures". *J. Arthrosc. Relat. Surg,* Vol 8*,* 1992, pp. 437–441.

[6] Nakamura T, Shimizu Y, Matsui T, Okumura N, Hyon S H and Nishiya K. "A novel bioabsorbable monofilament surgical suture made from (caprolacton , L Lactide) copolymer", in Degradation Phenomena on Polymeric Biomaterials, Springer: Berlin, 1992, pp. 153-162.

[7] Tomihata K, Suzuki M, Oka T, Ikada Y, "A new resorbable monofilament suture". *Polymer Degrad. Stability*, Vol 59, 1998. pp. 13-18.

[8] Bezwada R S, Jamiolkowski D D, Lee I Y, Agarwal V, Persivale J, Erneta M, Trenka-Benthin S, Suryadevara J, Yang A and Liu S. "Monocryl suture, a new ultra-pliable absorbable monofilament suture". *Biomaterials*, Vol 16, 1995, pp. 1141-1148.

[9] Hutmacher D W, Schantz T, Zein I, Ng K W, Teoh S W and Tan K C, "Mechanical properties and cell cultural response of polycaprolactone scaffolds designed and fabricated via fused deposition modeling". *J Biomed Mater* Res, Vol 55, 2001, pp. 203-216.

[10] Meek M F, d.D.W., Bartels H L, Pennings A J, Robinson and P.a.S. JM, "Peripheral nerve regeneration and functional nerve recovery after reconstruction with a thin-walled biodegradable poly(DL-lactide-e -caprolactone) nerve guide". Cells Mater, Val 7, 2007, pp. 53-62.

[11] Pego A P, Poot A A., Grijpma D W and Feijen J. "Copolymers of trimethylene carbonate and epsilon-caprolactone for porous nerve guides: Synthesis and properties". *J Biomater Sci Polym Ed*, Vol 12, 2001, pp. 35-53.

[12] Woodruff M A, Hutmacher DW. "The return of a forgotten polymer – Polycaprolactone in the 21st century". *Prog. Polym. Sci*, Vol 35, 2010, pp. 1217–1256.

[13] Dash T K, KonkimallaK V B. "Poly-ϵ-caprolactone based formulations for drug delivery and tissue engineering: A review." *Journal of Controlled Release*, Vol 158, 2012, pp. 15-33.

[14] Labet M and Thielemans W "Synthesis of polycaprolactone: a review". *Chemical Society Reviews*, Vol 38, 2009, pp. 3484–3504.

[15] Storey R F, Taylor A. "Effect of stannous octoate concentration on the ethylene glycolinitiated polymerization of epsilon-caprolactone". *Abstr Pap Am Chem Soc*, Vol 211, 1996, pp. 114.

[16] Okada M. "Chemical syntheses of biodegradable polymers". *Progress in Polymer Science*, Vol 27, 2002, pp. 87-133.

[17] Hayash T. "Biodegradable polymers for biomedical uses. *Progress in Polymer Science*, Vol 19, 1994, pp. 663-702.

[18] Pillai, Chennakkattu K S and Sharma C P. "Review Paper: Absorbable Polymeric Surgical Sutures: Chemistry, Production, Properties, Biodegradability, and Performance". *Journal of Biomaterials Applications*, Vol 25, 2010, pp. 291-366.

[19] Liu C B, Gong C Y, Huang M J, Wang J W, Pan Y F, Zhang Y D, Li G Z, Gou M L, Tu M J, Wang K, Wei Y Q and Qian Z Y. "Thermoreversible gel–sol behavior of biodegradable pcl-peg-pcl triblock copolymer in aqueous solutions". *J. Biomed. Mater. Res. B Appl. Biomater*. Vol 84, 2008, pp. 165-175.

[20] Kalambur S, Rizvi S S H. "Rheological behavior of starch–polycaprolactone (pcl) nanocomposite melts synthesized by reactive extrusion". *Polym. Eng. Sci,* Vol 46, 2006, pp. 650–658.

[21] Wan Y, Lu X, Dalai S and Zhang J, "Thermophysical properties of polycaprolactone/ chitosan blend membranes", *Thermochim. Acta*, Vol 487, 2009, pp. 33-38.

[22] Ma Z, Haddadi A, Molavi O, Lavasanifar A, Lai R and Samuel J. "Micelles of poly(-ethylene oxide)-b-poly(epsilon–caprolactone) as vehicles for the solubilization, stabilization, and controlled delivery of curcumin". *J. Biomed. Mater. Res. A*, Vol 86, 2008, pp. 300-310.

[23] Sheikh F A, Barakat N, Kanjwal M A, Aryal S, Khil M S, Kim H Y. "Novel selfassembled amphiphilic poly(epsilon–caprolactone)-grafted-poly(vinyl alcohol) nanoparticles: hydrophobic and hydrophilic drugs carrier nanoparticles". *J. Mater. Sci. Mater. Med*, Vol 20, 2009, pp. 821–831.

[24] Chen C, Cai G, Zhang H, Jiang H and Wang L. "Chitosan-poly(epsilon–caprolactone)-poly(ethylene glycol) graft copolymers: synthesis, self-assembly, and drug release Behavior". *J. Biomed. Mater. Res. A*, Vol 96, 2010, pp. 116–124.

[25] K. Gorna, Gogolewski, S. "In vitro degradation of novel medical biodegradable aliphatic polyurethanes based on epsilon–caprolactone and pluronics with various hydrophilicities". *Polym. Degrad. Stab*, Vol 75, 2002, pp. 113-122.

[26] Pulkkinena M, Malin M, Böhmd J, Tarvainen T, Wirth T, Seppälä J, Järvinen K. "In vivo implantation of 2,2'-bis(oxazoline)-linked poly-epsilon–caprolactone: proof for enzyme sensitive surface erosion and biocompatibility". *Eur. J. Pharm. Sci*. Vol 36, 2009, pp. 310-319.

[27] Woodward C S, "The intracellular degradation of poly (epsilon-caprolactone". *Journal of biomedical materials research*, Vol 19, 1985, pp. 437-44.

[28] Gunatillake P A, Adhikari A. "Biodegradable synthetic polymers for tissue engineering". *European Cells and Materials*, Vol 5, 2003, pp. 1-16.

[29] Middleton J C and Tipton A J. "Synthetic biodegradable polymers as orthopedic devices". *Biomaterials,* Vol 21, 2000, pp. 2335-46.

[30] N. BÖLGEN1, Y.Z.M.L., K. ACATAY2, I˙. VARGEL 3 and and E. PI ¸SKIN 1, In vitro and in vivo degradation of non-woven materials made of poly(ε-caprolactone) nanofibers prepared by electrospinning under different conditions. J. Biomater. Sci. Polymer Edn,, 2005. 16: p. 1537–1555.

[31] Lam C X F, Hutmacher D W, Schantz J, Woodruff M A and Teoh S H. "Evaluation of polycaprolactone scaffold degradation for 6 months in vitro and in vivo". *Journal of Biomedical Materials Research Part A*, 2008, pp. 906-919.

[32] Pektok E, Nottelet B, Jea, Tille J C, Gurny R, Kalangos A, Walpoth B H. "Degradation and Healing Characteristics of Small-Diameter Poly(-Caprolactone) Vascular Grafts in the Rat Systemic Arterial Circulation". *Circulation*. Vol 118, 2008, pp. 2563-2570.

[33] Lam C X F, Savalani M M, Teoh S H and Hutmacher D W. "Dynamics of in vitro polymer degradation of polycaprolactone-based scaffolds: accelerated versus simulated physiological conditions". *Biomed. Mater*, Vol 3, 2008, pp. 1-15.

[34] Wan, Y., Ying W, Hua C, Xiaoying D and Siqin. "Compressive mechanical properties and biodegradability of porous poly(caprolactone)/chitosan scaffolds". *Polymer Degradation and Stability*, Vol 93, 2008, pp. 1736-1741.

[35] Ghasemi-Mobarakeh L, Prabhakaran M P, Morshed M, Nasr-Esfahani M H, Ramakrishna, Se. "Electrospun poly (ε-caprolactone)/gelatin nanofibrous scaffolds for nerve tissue engineering". *Biomaterials*, Vol 29, 2008, pp. 4532-4539.

[36] Tillman B W, Yazdani S K, Lee S J, Geary R L, Yoo J J and Atala A. "The in vivo stability of electrospun polycaprolactone-collagen scaffolds in vascular reconstruction". *Biomaterials*, Vol 30, 2009, pp. 583–588.

[37] Johnson J, Niehaus A, Nichols S, Lee D, Koepsel J, Anderson D and Lannutti J, "Electrospun PCL in vitro: a microstructural basis for mechanical property changes". J. Biomater. Sci. Polymer Edn, Vol 20, 2009, pp. 467–481.

[38] Vieiraa A C, Marquesb A T, Guedesb R M and Titac V. "Material model proposal for biodegradable materials". *Procedia Engineering*, Vol 10, 2011, pp. 1597–1602.

[39] Krishnanand K, Deopura B L and Gupta B. "Determination of intrinsic birefringence values of polycaprolactone filaments". *Polym Int*, Vol 62, 2013, pp. 49–53.

[40] Meng Q, Hu J. "Study on poly (ε-caprolactone)-based shape memory copolymer fiber prepared by bulk polymerization and melt spinning". Polymers for Advanced Technologies, Vol 19, 2008, 131-136.

[41] Mochizuki M, Havashi T, Nakatama K and MASUDA T. "Studies on biodegradable poly (hexane-6-lactone) fibers. Part 2: environmental degradation". *Pure Appl. Chem*, Vol 71, 1999, pp. 2177- 2188.

[42] Mochizuki M, Nakajima K, Qian R, Jiang B Z, Hirami M, Hayashi T, Masuda T and Nakajima A. "Studies on biodegradable poly(hexano-6-lactone) fibers. Part 1. Structure and properties of drawn PCL fibers". *Pure Appl. Chem*, Vol 69, 1997, pp. 2567-2575.

[43] Charuchinda A, Molloy R, Siripitayananon J, Molloy N and Sriyai M "Poly (-caprolactone) melt-spun monofilament fibers". *Polymer International,* Vol 52*,* 2003, pp. 1175-1181.

[44] Douglasa p, Andrewsb G, Jonesb D and Walkera G. "Analysis of in vitro drug dissolution from PCL melt extrusion". *Chemical Engineering Journal,* Vol 164, 2010, pp. 359–370.

[45] Perale G, Casalini T, Barri V, Mu¨ ller M, Maccagnan S and Masi M. "Lidocaine Release from Polycaprolactone Threads". Journal of Applied Polymer *Science*, Vol 117, 2010, pp. 3610-3614.

[46] An J, Chua C K, Leong K F, Chen C H and Chen J P. "Solvent-free fabrication of three dimensionally aligned polycaprolactone microfibers for engineering of anisotropic tissues". *Biomed Microdevices*, Vol 14, 2012, pp. 863–872.

[47] Puglia, R.S.L.B.M.S.G.G.G.P.A.M., "Combining in the melt physical and biological properties of poly(caprolactone) and chlorhexidine to obtain antimicrobial surgical monofilaments". *Appl Microbiol Biotechnol*, Vol 97, 2013, pp. 99-109.

[48] Fourne, F. "Synthetic Fibers – Machines and Equipment, Manufacture, Properties". ohio: hanser/gardner. 1999, 930.

[49] Arbab S, Noorpanah P, Mohammadi N, Soleimani M. "Designing index of void structure and tensile properties in wet-spun polyacrylonitrile (PAN) fiber. I. Effect of dope polymer or nonsolvent concentration". *Journal of Applied Polymer Science*, Vol 109, 2008, pp. 3461-3469.

[50] Arbab S, Mohammadi N, Noorpanah P. "The synergistic effect of dope concentration and jet-drawing on structure development of wet-spun poly (acrylonitrile)". *epolymer*, 2008, 80, pp. 1-11.

[51] Arbab S, Noorpanah P, Mohammadi N, Zeinolebadi A. "Simultaneous effects of polymer concentration, jet-stretching, and hot-drawing on microstructural development of wet-spun poly(acrylonitrile) fibers". *Polymer Bulletin*, Vol 66, 2011, pp. 1267-1280.

[52] Polacco, G., et al., Biodegradable hollow fibres containing drug-loaded nanoparticles as controlled release systems. *Polymer International*, 2002. 51(12): p. 1464-1472.

[53] Williamson M R, Adams E F, Coombes A G A. "Cell attachment and proliferation on novel polycaprolactone fibers having application in soft tissue engineering". *European Cells and Materials*, Vol 4, 2002, pp. 62-63.

[54] Williamson M R, Coombes A G A. "Gravity spinning of polycaprolactone fibres for applications in tissue engineering". *Biomaterials,* Vol 25, 2004, pp. 459–465.

[55] Williamson M R, Changb H I, Coombes A G A. "Gravity spun polycaprolactone fibres: controlling release of a hydrophilic macromolecule (ovalbumin) and a lipophilic drug (progesterone)". *Biomaterials*, Vol 25, 2004, pp. 5053–5060.

[56] Chang H I, Lau Y C, Yan C, Coombes A G A. "Controlled release of an antibiotic, gentamicin sulphate, from gravity spun polycaprolactone fibers". *Journal of Biomedical Materials Research Part A*, Vol 84, 2008, pp. 230-237.

[57] Chiono V, Ciardelli G, Vozzi G, Sotgiu M G, Vinci B, Domenici C, Giusti P. "Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/ poly(e-caprolactone) blends for tissue engineering applications in the form of hollow fibers". *Journal of Biomedical Materials Research Part A,* Vol 85, 2008, PP. 938-953.

[58] Tuzlakoglu K, Pashkuleva I, Rodrigues M T, Gomes M E, Van Lenthe G H, Mu¨ ller R, Reis R L. "A new route to produce starch-based fiber mesh scaffolds by wet spinning and subsequent surface modification as a way to improve cell attachment and proliferation". *Journal of Biomedical Materials Research Part A*, 2008: p. 369-377.

[59] Puppi P, Piras A M, Chiellini F, Chiellini E, Martins A, Leonor I B, Neves N and Reis R. "Optimized electro- and wet-spinning techniques for the production of polymeric fibrous scaffolds loaded with bisphosphonate and hydroxyapatite". Journal of tissue engineering and regenerative medicine, Vol 5, 2011, pp. 253–263.

[60] Yilgor p, Sousa R A, Reis A L, Hasirci N and Hasirci V. "Effect of scaffold architecture and BMP-2/BMP-7 delivery on in vitro bone regeneration". *J Mater Sci: Mater Med,* Vol 21, 2010, pp. 2999-3008.

[61] Puppi D, Dinucci D, Bartoli C, Mota C, Migone C, Dini F, Barsotti G, Carlucci F and Chiellini F. "Development of 3D wet-spun polymeric scaffolds loaded with antimicrobial agents for bone engineering" . *Journal of Bioactive and Compatible Polymers*, Vol 26, 2011, pp. 478–492.

[62] [62]. Wang Z, Wu H, Liao C, Zhou N, Cheng W, Wan Y. "Sustained release of ketoprofen from fibrous chitosan-poly(ε-caprolactone) membranes". *Carbohydrate Polymers*, Vol 84, 2011, pp. 624-630.

[63] Neves S C, Teixeira L S M, Moroni L, Reis R L, Blitterswijk C A V, Alves N M, Karperien M, Mano J F. "Chitosan/Poly(3-caprolactone) blend scaffolds for cartilage repair". Biomaterials, Vol 32, 2011, pp. 1068-1079.

[64] Puppi D, Mota C, Gazzarri M, Dinucci D, Gloria A, Myrzabekova M, Ambrosio L and Chiellini F. "Additive manufacturing of wet-spun polymeric scaffolds for bone tissue engineering". *Biomed Microdevices*, Vol 14, 2012, pp. 1115–1127.

[65] Williamson M R, Adams E F, Coombes A G A. "Gravity spun polycaprolactone fibres for soft tissue engineering: Interaction with fibroblasts and myoblasts in cell culture". *Biomaterials,* Vol 27, 2006, pp. 1019-1026.

[66] Shen X X, Zheng Y, Ma Z H, Zhu L M, Branford-White C. "Wet-Spinning Medicated PAN/PCL Fibers for Drug Sustained Release" *Bioinformatics and Biomedical*, Vol 13, 2008, 1375 - 1378

[67] Gupta B, Revagade N and Hilborn J. "Poly (lactic acid) fiber: An overview". *Progress in Polymer Science*, Vol 32, 2007, pp. 455-482.

[68] Chandra R, Rustgi R. "Biodegradable polymers. Progress in Polymer Science", Vol 23, 1998, 1273-335.

[69] Nair L S and Laurencin C T. "Biodegradable polymers as biomaterials". *Progress in Polymer* Science, Vol 32, 2007, pp. 762-798.

[70] Frazza E J, Schmitt E E. "A new absorbable suture". J Biomed Mater Res Symposium, Vol 1, 1971, pp. 43-58.

[71] Leea K H, Kimb H Y, Khilb M S, Rab Y M, Lee D R, "Characterization of nano-structured poly(1-caprolactone) nonwoven mats via electrospinning". *Polymer*, Vol 44, 2003, pp. 1287–1294.

[72] H. Yoshimoto, Y M Shina Y M, Teraia H, Vacanti J P. "A biodegradable nanofiber scaffold by electrospinning and its potential for bone tissue engineering". *Biomaterials*, Vol 24, 2003, pp. 2077–2082.

[73] Li W J, Danielson K J, Alexander P G, Tuan R S, "Biological response of chondrocytes cultured in threedimensional nanofibrous poly(-caprolactone) scaffolds". *Journal of Biomedical Materials Research Part A*. Vol 67, 2003, pp. 1105-14.

[74] Shin M, Yoshimoto H and Vacanti J P. "In vivo bone tissue engineering using mesenchymal stem cells on a novel electrospun nanofibrous scaffold". *Tissue Eng Part A*. Vol 10, 2004, pp. 33–41.

[75] Shin M, Ishii O, Sueda T, Vacanti J P. "Contractile cardiac grafts using a novel nanofibrous mesh". *Biomaterials*, Vol 25, 2004, pp. 3717–3723.

[76] Ishii O, Shin M, Sueda T, Vacanti J P. "In vitro tissue engineering of a cardiac graft using a degradable scaffold with an extracellular matrix-like topography". *J. Thorac. Cardiovasc. Surg,* Vol 130*,* 2005, pp. 1358–1363.

[77] Li W J, Tuli R, Okafor C, Derfoul A, Danielson K G, Hall D J, Tuan R S. "A three-dimensional nanofibrous scaffold for cartilage tissue engineering using human mesenchymal stem cells". *Biomaterials*, Vol 26, 2005, pp. 599–609.

[78] Lia W J, Tuli R, Huang X, Laquerriere P, Tuan R S. "Multilineage differentiation of human mesenchymal stem cells in a three-dimensional nanofibrous scaffold". *Biomaterials*, Vol 26, 2005, PP. 5158–5166.

[79] Pham Q M, Sharma U and Mikos A G. "Electrospun poly (ε-caprolactone) microfiber and multilayer nanofiber/microfiber scaffolds: characterization of scaffolds and measurement of cellular infiltration". *Biomacromolecules*, Vol 7, 2006, pp. 2796–2805.

[80] Luong-Vana E, Grøndahla L, Chuad K N, Leongd K W and Nurcombeb V, Cool S M. "Controlled release of heparin from poly(e-caprolactone) electrospun fibers". *Biomaterials*, 2006, 27: p. 2042–2050.

[81] Li W J, Mauck R L, Cooper J A, Yuan X, Tuan R S. "Engineering controllable anisotropy in electrospun biodegradable nanofibrous scaffolds for musculoskeletal tissue engineering". *J. Biomech*, Vol 40, 2007, pp. 1686–1693.

[82] Kolambkar Y M. "Electrospun nanofiber meshes for the repair of large bone defects", in Department of Biomedical Engineering, Georgia Institute of Technology, 2007.

[83] M. P. Prabhakaran, e.a., "Surface modified electrospun nanofibrous scaffolds for nerve tissue engineering". Nanotechnology, Vol 19, 2008, pp. 455102.

[84] Wong S C, Baji A, Leng S. "Effect of fiber diameter on tensile properties of electrospun poly (3-caprolactone)". *Polymer*, Vol 49, 2008, pp. 4713–4722.

[85] Pektok E, Nottelet B, Tille J C, Gurny R, Kalangos A, Moeller M, Walpoth B H. "Degradation and healing characteristics of smalldiameter poly (3-caprolactone) vascular grafts in the rat systemic arterial circulation". *Circulation*, Vol 118, 2008, pp. 2563–2570.

[86] Nisbet D R, Yu L M Y, Zahir T, Forsythe J S, Shoichet M S. "Characterization of neural stem cells on electrospun poly (3-caprolactone) submicron scaffolds: evaluating their potential in neural tissue engineering". *J. Biomater. Sci. Polym. Ed*, Vol 19, 2008, pp. 623–634.

[87] Nottelet B, Pektok E, Mandracchia D, Tille J C, Walpoth B, Gurny R, Möller M. "Factorial design optimization and in vivo feasibility of poly (3-caprolactone)-micro- and nanofiber-based small diameter vascular grafts". *J. Biomed. Mater. Res., Part A*. Vol 89, 2009, pp. 865–875.

[88] Martins A, Pinho E D, Faria S, Pashkuleva I, Marques A P, Reis R L, Neves N M. "Surface modification of electrospun polycaprolactone nanofiber meshes by plasma treatment to enhance biological performance". *Small*, Vol 5, 2009, pp. 1195–1206.

[89] Li W J, Chiang H, Kuo T F, Lee H S, Jiang C C, Tuan R S. "Evaluation of articular cartilage repair using biodegradable nanofibrous scaffolds in a swine model: a pilot study". *J. Tissue Eng.* Regener. Med, Vol 2, 2009, p. 1–10.

[90] Pişkin E, Işoğlu I A, Bölgen N, Vargel I, Griffiths S, Cavuşoğlu T, Korkusuz P, Güzel E, Cartmell S. "In vivo performance of simvastatin-loaded electrospun spiral-wound polycaprolactone scaffolds in reconstruction of cranial bone defects in the rat model". *J. Biomed. Mater. Res., Part A*, Vol 90, 2009, pp. 1137–1151.

[91] Chen M, Michaud H, Bhowmick S. "Controlled vacuum seeding as a means of generating uniform cellular distribution in electrospun polycaprolactone (PCL) scaffolds". *J. Biomech. Eng*, Vol 131, 2009, pp. 074521.

[92] Nisbet D R, Rodda A E, Horne M K, Forsythe J S, Finkelstein D I. "Neurite infiltration and cellular response to electrospun polycaprolactone scaffolds implanted into the brain". *Biomaterials*. Vol 30, 2009, pp. 4573–4580.

[93] Wise J K, Yarin A L, Megaridis C M, Cho M, "Chondrogenic Differentiation of Human Mesenchymal Stem Cells on Oriented Nanofibrous Scaffolds: Engineering the Superficial Zone of Articular Cartilage". *Tissue Engineering Part A*. Vol 15, 2009, pp. 913-21.

[94] Merrel J G, McLaughlin S W, Tie L, Laurencin C T, Chen A F and Naird L S. "Curcumin Loaded Poly(ε-Caprolactone) Nanofibers: Diabetic Wound Dressing with Antioxidant and Anti-inflammatory Properties". *Clinical and Experimental Pharmacology and Physiology*, Vol 36, 2009, pp. 1149–1156.

[95] Lowery J L, Datta N, Rutledge G C. "Effect of fiber diameter, pore size and seeding method on growth of human dermal fibroblasts in electrospun poly (3-caprolactone) fibrous mats". *Biomaterials*, Vol 31, 2010, pp. 491–504.

[96] Ruckh T T, Kumar K, Kipper M J, Popat KC. "Osteogenic differentiation of bone marrow stromal cells on poly (3-caprolactone) nanofiber scaffolds". Acta Biomaterials, Vol 6, 2010, pp. 2949–2959.

[97] Wu H, Fan J, Chu C C, Wu J. "Electrospinning of small diameter 3-D nanofibrous tubular scaffolds with controllable nanofiber orientations for vascular grafts". *J. Mater. Sci.: Mater. Med*. Vol 21, 2010, pp. 3207–3215.

[98] Zhu Y, Cao Y, Pan J, Liu Y. "Macro-alignment of electrospun fibers for vascular tissue engineering". *J. Biomed. Mater. Res., Part B*. Vol 92, 2010, pp. 508–516.

[99] Cao H, McHugh K, Chew S Y, Anderson J M. "The topographical effect of electrospun nanofibrous scaffolds on the in vivo and in vitro foreign body reaction". *J. Biomed. Mater. Res., Part A*, Vol 93, 2010, pp. 1151–1159.

[100] Puppi D, Detta N, Piras A M, Chiellini F, Clarke D A, Reilly G C, Chiellini E. "Development of Electrospun Three-arm Star Poly(ε-caprolactone) Meshes for Tissue Engineering Applications". *Macromol. Biosci*. Vol 10, 2010, pp. 887–897.

[101] Jha B S, Colello R J, Bowman J R, Sell S A, Lee K D, Bigbee J W, Bowlin G L, Chow W N, Mathern B E, Simpson D G. "Two pole air gap electrospinning: fabrication of highly aligned, three-dimensional scaffolds for nerve reconstruction". Acta Biomaterialia, Vol 7, 2011, pp. 203–215.

[102] Khanging A G, and Bahrami S H. "Solvents on Poly (ε-Caprolactone) Nanofibrous Webs Morphology". *Journal of Nanomaterials*, Vol 2011, pp. 1-10.

[103] Kolbuk D, Sajkiewicz P, Kowalewski T A. "Optical birefringence and molecular orientation of electrospun polycaprolactone fibers by polarizing-interference microscopy". *European Polymer Journal*, Vol 48, 2012, pp. 275–283.

[104] Ruckh T T, Oldinski R A, Carroll D A, Mikhova K, Bryers J D, Popat K C. "Antimicrobial effects of nanofiber poly (caprolactone) tissue scaffolds releasing rifampicin". J *Mater Sci: Mater Med*, Vol 23, 2012, pp. 1411-1420.

[105] Middleton J C, Tipton A J. "Synthetic biodegradable polymers as orthopedic devices". *Biomaterials*, Vol 21, 2000, pp. 2335-46.

[106] Bezwada R S, Jamiolkowski D D, Lee I Y, Agarwal V, Persivale J, Trenka-Benthin S, Erneta M, Suryadevara J, Yang A, Liu S. "Monocryl Suture, A New Ultra-Pliable Absorbable Monofilament Suture". *Biomaterials*. Vol 16, 1995, pp. 1141–1148.

[107] Merkli A, Tabatabay C, Gurny R, Heller J, "Biodegradable polymers for the controlled release of ocular drugs". *Progress in Polymer Science*, Vol 23, 1998, pp. 563-80.

[108] Sinha V R, Bansal K, Kaushik R, Kumria R, Trehan A, "Poly-epsilon-caprolactone microspheres and nanospheres: an overview". *Int J Pharm*., Vol 278, 2004, pp. 1-23.

[109] Kanawung K, K. Panitchanapan, Puangmalee S, Utok W, Kreua-Ongarjnukool N, Rangkupan R and Supaphol P. "Preparation and characterization of polycaprolactone/diclofenac sodium and poly(vinyl alcohol)/tetracycline hydrochloride fiber mats and their release of the model drugs". *Polym. J.* Vol 39, 2007, pp. 369–378.

[110] Tammaro L, Russo G and Vittoria V. "Encapsulation of DiclofenacMolecules into Poly (ε-Caprolactone) Electrospun Fibers for Delivery Protection". Journal of Nanomaterials, 2009.

[111] Liu H, Leonas K K, Zhao Y. "Antimicrobial Properties and Release Profile of Ampicillin from Electrospun Poly (ε-caprolactone) Nanofiber Yarns". *Journal of Engineered Fibers and Fabrics,* Vol 5*,* 2010, pp. 10-19.

[112] Langer R, Vacanti J P."Tissue engineering". *Science*, Vol 260, 1993, pp. 920-6.

[113] Hutmacher D W. "Scaffolds in tissue engineering bone and cartilage". *Biomaterials*, Vol 21, 2000, pp. 2529-43.

[114] Van Lieshout M, Peters G, Rutten M, Baaijens F. "A knitted, fibrin-covered polycaprolactone scaffold for tissue engineering of the aortic valve". *Tissue Eng*. Vol 12, 2006, pp. 481-7.

[115] Choi J S, Lee S G, Christ G J, Atala A, Yoo J J. "The influence of electrospun aligned poly (epsilon-caprolactone)/collagen nanofiber meshes on the formation of self-aligned skeletal muscle myotubes". *Biomaterials*, Vol 29, 2008, pp. 2899-906.

[116] Li W J, Cooper JA Jr, Mauck R L, Tuan R S. "Fabrication and characterization of six electrospun poly (alpha-hydroxy ester)-based fibrous scaffolds for tissue engineering applications". *Acta Biomaterialia,* Vol 2, 2006, pp. 377-85.

[117] Shao X, Goh J C, Hutmacher D W, Lee E H, Zigang G., "Repair of large articular osteochondral defects using hybrid scaffolds and bone marrow-derived mesenchymal stem cells in a rabbit model". *Tissue Eng Part A*, Vol 12, 2006, pp. 1539-51.

[118] Van Lieshout M I, Vaz C M, Rutten M C, Peters G W, Baaijens F P. "Electrospinning versus knitting: two scaffolds for tissue engineering of the aortic valve". *Journal of Biomaterials Science-Polymer Edition*, Vol 17, 2006, pp. 77-89.

[119] Oh SH, Park I K, Kim J M, Lee J H. "In vitro and in vivo characteristics of PCL scaffolds with pore size gradient fabricated by a centrifugation method". *Biomaterials*. Vol 28, 2007, pp. 1664-71.

[120] Guarino V, Causa F, Taddei P, di Foggia M, Ciapetti G, Martini D, Fagnano C, Baldini N, Ambrosio L. "Polylactic acid fibre-reinforced polycaprolactone scaffolds for bone tissue engineering". *Biomaterials*. Vol 29, 2008, pp. 3662-70.

[121] Bregy A, Bogni S, Bernau V J, Vajtai I, Vollbach F, Petri-Fink A, Constantinescu M, Hofmann H, Frenz M, Reinert M. "Solder Doped Polycaprolactone Scaffold Enables Reproducible Laser Tissue Soldering". *Lasers in Surgery and Medicine*, Vol 40, 2008, pp. 716-25.

[122] Balguid A, Mol A, van Marion M H, Bank R A, Bouten C V, Baaijens F P. "Tailoring Fiber Diameter in Electrospun Poly (epsilon-Caprolactone) Scaffolds for Optimal Cellular Infiltration in Cardiovascular Tissue Engineering". *Tissue Engineering Part A*. Vol 15, 2009, pp. 437-44.

[123] Diban N, Haimi S,Bolhuis-Versteeg L, Teixeira S, Miettinen S, Poot A, Grijpma D, Stamatialis D. "Hollow fibers of poly(lactide-co-glycolide) and poly(e-caprolactone) blends for vascular tissue engineering applications". *Acta Biomaterialia*, Vol 9, 2013, 6450–6458.

AUTHORS' ADDRESSES

Bahareh Azimi
Parviz Nourpanah
Mohammad Rabiee
Shahram Arbab
Textile Engineering Department
Amirkabir University of Technology
424 Hafez Ave
Tehran,
IRAN

Received: 5 June 2020 | Revised: 15 August 2020 | Accepted: 1 December 2020

DOI: 10.1111/jocd.13883

ORIGINAL CONTRIBUTION

JCD Journal of Cosmetic Dermatology WILEY

Efficacy study of the new polycaprolactone thread compared with other commercialized threads in a murine model

Seung Woo Cho MD[1] | Byung Ho Shin PhD[1] | Chan Yeong Heo MD, PhD[1,2] | Jung Hee Shim PhD[1,3]

[1]Department of Plastic and Reconstructive Surgery, Seoul National University Bundang Hospital, Seongnam, Korea

[2]Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, Seoul, Korea

[3]Department of Research Administration Team, Seoul National University Bundang Hospital, Seongnam, Korea

Correspondence
Jung Hee Shim, Department of Research Administration Team, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Seongnam-si, Gyeonggi-do 13620, Korea.
Email: xmylife@empas.com

Chan Yeong Heo, Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, 103 Daehak-ro (Yeongeon-dong), Jongnogu, Seoul 03080, Korea.
Email: lionheo@snu.ac.kr

Abstract

Background: Polydioxanone (PDO) threads, poly-L-lactic acid (PLLA) threads, and polycaprolactone (PCL) threads have been used for lifting and antiaging purposes. The new PCL threads that have less residual monomer compared to the previous PCL are developed.

Aims: The efficacy of threads regarding collagen synthesis and wrinkle improvement was evaluated in vivo model.

Methods: In this study, threads were inserted into 30 six-week-old male SKH-1 hairless mice. One of four threads was implanted at either side of the spine of each mouse. Biopsy specimens obtained at 1, 4, and 8 weeks were examined using hematoxylin and eosin (H&E) and Herovici's stain. Additionally, immunoblot analysis was performed using primary antibody for collagen type III and transforming growth factor-β (TGF-β) and visualized by chemiluminescence and densitometric quantification. Finally, skin replicas were used to calculate total wrinkle area (mm^2).

Results: Neocollagenesis was significantly increased by 50% in the new PCL and pre-existing PCL groups at 8 weeks (p value < 0.001). Additionally, new-PCL-implanted mice showed a significant increase in collagen type III and TGF-β expressions at 8 weeks (p value < 0.001). The number of inflammatory cells was also increased in the skin of PCL-implanted mice at 8 weeks. Finally, wrinkles were reduced about 20% in the new PCL group at 8 weeks.

Conclusions: The new PCL thread exhibited a superior skin rejuvenation effect. This suggests that the material processing technology can be applied not only to the thread but also to various products such as dermal filler and cosmetics.

KEYWORDS

collagen, PCL, TGF-β, thread lifting, wrinkle

Jung Hee Shim and Chan Yeong Heo contributed equally to this article as corresponding authors.

1 | INTRODUCTION

Skin has an intact epidermis with layers that acts as a solid barrier to outside influences. It is composed of abundant components such as collagen, elastin, and glycosaminoglycans. As one grows older, the synthesis of collagen in skin reduces, especially type I and III collagen which results in uneven focal ptosis and laxity of the soft tissues around whole areas including infraorbital, buccal, mental, and submental parts.[1,2]

A lot of facial rejuvenation techniques were developed to reverse or delay aging process such as lasers, fillers, botulinum toxin, fat grafts, and other soft tissue augmentation procedures.[3-7] Various face lift surgeries have been the traditional methods of facial rejuvenation since the early 20th century.[8] However, surgical methods with incisions have some disadvantages compared to nonsurgical methods such as difficulty of the techniques, high cost, long operation time and recovery periods, and surgical scars.[9] With the advent of various facial rejuvenation techniques, minimally invasive methods have gained popularity.[9] Especially, the thread lift is a safe and effective technique that lifts sagging skin on the face and neck using threads that are absorbed biologically. The evolution of thread lifting procedure is now in its third decade since Sulamanidze first proposed lifting using Aptos threads.[10] Sulamanidze developed the first barbed (short) suture technique using the "Aptos" thread in the late 1990s.[10] In 2002, the Woffles (long) thread, also known as Waptos was developed.[11] This thread was used as a suture suspension sling to lift facial soft tissues to the deep temporal fascia.[11] Isse reported an endo-progressive face lift suture in 2005.[12] This suture was fixed to the temporal fascia with a thread created by modifying the "Aptos" thread. Most of the techniques mentioned above involve a polypropylene thread which is nonabsorbable. Some have warned the dangers of nondegradable threads. They have a risk of migration, extruding from the skin, and may be visible under facial skin.[13] Nowadays, the use of lifting threads made from biocompatible and biodegradable materials has received global attention.

The absorbable threads make skin lifted immediately through mechanical effects.[14] And these threads stimulate neocollagenesis process of tissues, which results in the production of new collagen.[11,12] About 6 months after beginning of the implantation, the threads will degradate through hydrolysis.[15] After this, synthetic absorbable thread-induced collagen synthesis will last about 2 ~ 3 months.[8]

There have been biodegradable thread materials such as polycaprolactone (PCL) and poly-L-lactic acids (PLLA) starting with polydioxanone (PDO).[10,12,16] The PCL thread has received the most attention recently among them.[15] PCL is very flexible and highly elastic substance; thus, it causes less pain and discomfort compared to PDO and PLLA. PCL is biodegradable and decomposed into CO_2 and H_2O. Its safety is proven from various biodegradable medical devices approved by the US Food and Drug Administration (FDA).[17] Threads made from PCL are slowly absorbed into the body within 1 ~ 1.5 years compared to PDO (6 ~ 8 months) and PLLA (12 months).[18] For functional improvement of the collagen synthesis and wrinkle improvement, the new PCL thread with less residual monomers and a higher molecular weight has been developed expecting prolonged durability and enhanced efficacy.

There have been no other studies comparing antiaging effects on tissues of commercial threads focusing on collagen synthesis and wrinkle improvement. This study was performed to determine the efficacy of the new PCL thread compared to other commercial threads in vivo model. This preliminary study will provide guidance for future investigations.

2 | MATERIALS AND METHODS

2.1 | Insertion of threads and experimental plan

All animal experimental procedures were approved by the Animal Care and Use Committee of the hospital (permit number: 54-2017-003). 30 six-week-old male SKH-1 hairless mice (Orient Bio Inc) about 21-30 g were used in this study. Before the thread insertion, the mice were quarantined for a week and allowed free access to food and water to adapt to the laboratory environment. The mice were housed at a controlled temperature of 24°C, a relative humidity of 55%, and a 12-hour light cycle. One of four threads was implanted at either side of the spine (column) of each mouse. Mice were randomly allocated into the following five groups with 12 columns each; the new PCL (Glo-One) group, the PCL (Ultra-V) group, the PDO (Meta Biomed, Osong) group, PLLA (APROMEDION, Seoul, Korea) group, and a negative control group. All threads were 50 mm in length and 0.3 mm in diameter. After anesthesia with isoflurane, the dorsal skin of mice was disinfected with alcohol. Each thread was subcutaneously inserted under the dorsal skin on either side of the spine. Each thread was inserted 2 cm laterally from the spinal cord. Tissue samples from surrounding subcutaneous tissue, along with the thread, were harvested at 1, 4, and 8 weeks after implantation (3 × 9 cm size). Each sample was divided into three equal segments, each of which was used for staining, wrinkle measurement, and Western blotting, respectively.

2.2 | Histology

The specimens obtained from the dorsal skin were fixed in 10% buffered formalin (pH 7.1), embedded in paraffin, and sectioned at 6-10 μm for light microscopy. Sections were stained with hematoxylin-eosin (H&E) and Herovici's stain for collagen and connective tissue. The polychromatic Herovici's stain distinguishes young, newly formed type III collagen fibers (blue), from the mature, dense type I collagen fibers (red), making this stain very useful in the investigation of collagen synthesis.

The amount of type III collagen fibers in Herovici-stained sections was measured using an image analysis program (ImageJ software, National Institutes of Health, USA) and expressed as the percentage area occupied by each fiber around inserted thread. In

H&E-stained sections (100 × magnification), the number of inflammatory cells, which appear as blue dots around the thread, was measured using an image analysis program (ImageJ software, National Institutes of Health).

2.3 | Immunoblot analysis

The dorsal skin of thread inserted area was washed with ice-cold PBS and lysed in a RIPA buffer (Cell Signaling Technology) containing protease inhibitor cocktails (Roche Applied Science) for 60 minutes on ice. The skin was homogenized, followed by centrifugation at 16 000 g for 30 minutes at 4°C. Protein concentration was determined by the Bradford method. Protein samples were separated on an 8%-16% Tris-glycine gel (Invitrogen, USA), blotted onto polyvinylidenedifluoride (PVDF) membrane (Bio-Rad, Hercules). Primary antibodies used were as follows: transforming growth factor-β (TGF-β), type III collagen (Abcam). Blots were probed with anti-goat or anti-rabbit IgG-HRP and visualized by ECL chemiluminescence (GE Healthcare). Membranes were exposed to BioMax Light Kodak films. Densitometric quantification of the bands was performed using an image analyzer system (Multi Gauge version 2.3 software). These experiments were performed in triple.

2.4 | Wrinkle analysis

Lee and colleagues measured wrinkles using a SILFLO impression material (FLEXICO, England) and the Visioline® VL650 (Courage & Khazaka, Koln, Germany) in a hairless mouse.[19] Wrinkles were measured by similar methods in this study. Skin replicas were obtained from the dorsal skin using a SILFLO impression material. The Visioline® VL650 was used to assess the skin surface. Total wrinkle area (mm^2) was calculated. The analyses using Visioline® VL650 were performed in Daegu Technopark, Korea.

2.5 | Statistical analysis

All quantitative data were presented as mean ± SEM based on data derived from four experiments at each group. Statistical comparisons were carried out using the analysis of variance (ANOVA). In all analyses, $P < .05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Gross observation

After implantation of the threads into each mouse, changes in the weight and morphology of the skin were evaluated at 1, 4, and 8 weeks. Mice exhibited no gross changes of the skin in the insertion area of each thread during the experimental period. All experimental groups had no noticeable change in body weight (Figure 1).

3.2 | Neocollagenesis

All groups induced predominantly young collagen in the dermal layer of mice at all of the time points examined. The amount of type III collagen was significantly increased in the new PCL group compared to the other groups at 4 weeks. The amount of new collagen was significantly increased about 50% in both PCL thread groups compared with the PDO or PLLA thread group at 8 weeks (Figure 2). Values represent means ± SEM from three independent experiments. (* $P < .001$) (Young collagen: blue, mature collagen: red).

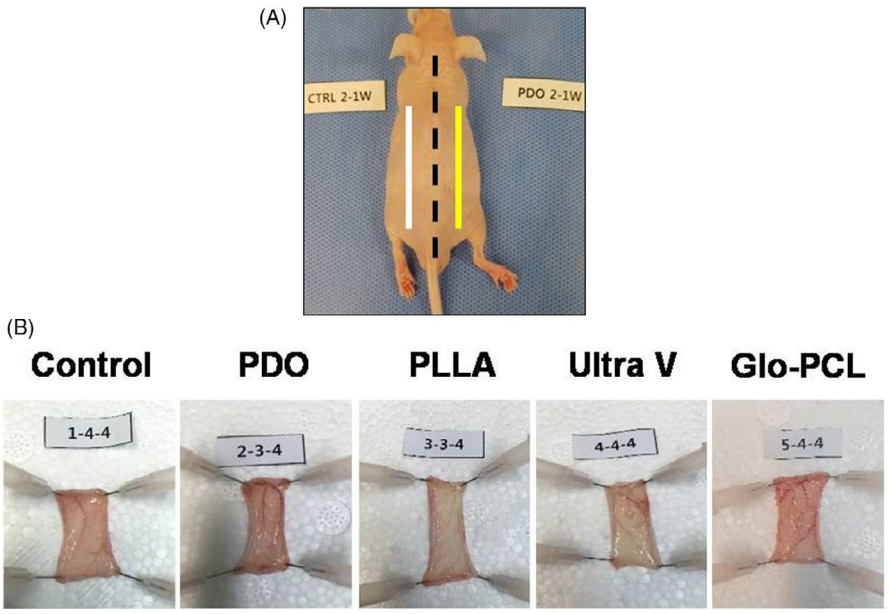


FIGURE 1 Thread implantation in mice and harvested tissues. A, Each thread was inserted at subcutaneous layer 2 cm laterally from the midline. B, Tissue samples were harvested along with the threads at 1, 4, and 8 weeks after implantation (3 × 9 cm size), followed by division into three equal segments. Each figure shows a segmented sample

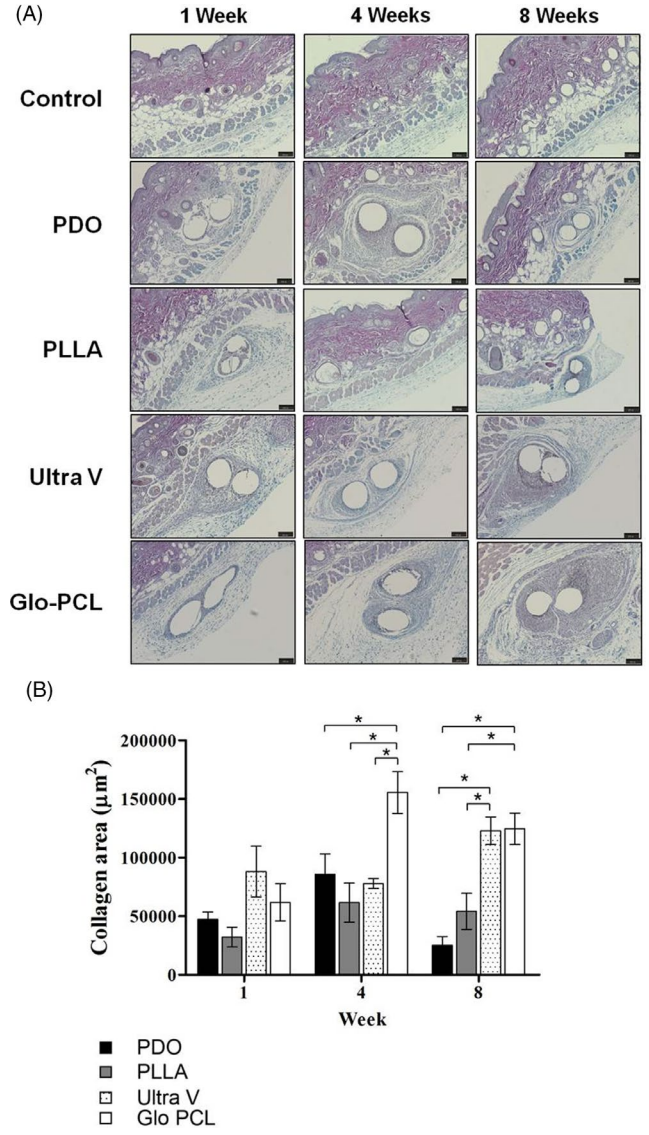


FIGURE 2 Histological evaluations of collagen fibers. A, Young, newly formed collagen fibers appearing blue through Herovici's staining were selectively stained and quantified. Black bar = 500 μm. B, Statistical analyses were performed to compare cross-sectional area of young collagen in each group at 1, 4, and 8 weeks. (* $P < .001$)

3.3 | Collagen synthesis mediated by TGF-β

The expressions of TGF-β and type III collagen were measured. There were no significant differences among the groups at 1 week. At 4 weeks, although there were no significant differences of type III collagen among the groups, significant increases of TGF-β were observed in the new PCL group. Though it is not statistically significant, type III collagen showed about 1.5-fold increases in the new PCL group relative to that of nonimplanted mouse at 4 weeks. Especially, mice with the new PCL showed significant increases (above 250% and 300%) in TGF-β and type III collagen expressions at 8 weeks, even though there was no statistically significant difference between the PCL groups. (* $P < .001$) However, the PDO and PLLA groups showed similar levels of TGF-β and type III collagen relative to nonimplanted mouse (Figure 3).

3.4 | Inflammation

The number of inflammatory cell was significantly increased only in the new PCL group at 4 weeks. At 8 weeks, there was statistically significant increase in the number of inflammatory cells in both PCL groups compared with the PDO and PLLA groups (above 200%) (Figure 4).

3.5 | Wrinkle analysis

There was no significant difference of the total wrinkle areas among the groups. However, wrinkles were reduced about 20% in the new PCL group at 8 weeks (Figure 5).

4 | DISCUSSION

Aging of facial skin results from elastic tissue and collagen degradation, which develops fine-to-deep wrinkles.[9,20] In addition to decreased elasticity, gradual thinning of subcutaneous fat layer causes volume depletion and sagging of mid-face.[20] Many facial rejuvenation techniques were developed to reverse or delay this aging process. As minimally invasive techniques replace surgical methods of facial rejuvenation, thread lifting has gained in popularity.[9] In recent years, biodegradable materials have been used to make threads.[21]

Polydioxanone (PDO) is a synthetic polymer of multiple repeating ether-ester units that is slowly hydrolyzed to a 2-hydroxyethoxyacetic monomer over 6 months and work by triggering fibroblasts to produce more collagen in a targeted area.[16] After PDO threads, poly-L-lactic acids (PLLA) threads were developed. They are made from a polymer derived from lactic acid that has been widely used as orthopedic pins and sutures.[22] PLLA threads produce collagen over a longer period than PDO threads. They have cones to hang to the tissue and increase the volume of saggy areas helping not only to provide a lift but to restore shape to the facial area.[22] Polycaprolactone (PCL) threads are the latest monofilament suspension threads of synthetic origin (caprolactone).[13] They regenerate collagen for a longer period than PDO and PLLA threads. The breakdown process of threads produces small molecular weight molecules which gradually induce the production of collagen and hyaluronic acid by the skin. As a result, skin becomes more moisturized, revitalized, and firm.[23] The new PCL thread used in this experiment was developed changing the ratio of the solvent during the polymerization. It resulted in reduction of the amount of residual monomer compared to the previous PCL. This means the new PCL thread has a higher polymer concentration and a higher molecular weight which helps resist against tensile stress.[24]

The threads have lifting effects immediately through mechanical effects by increasing the tonus of tissues, followed by

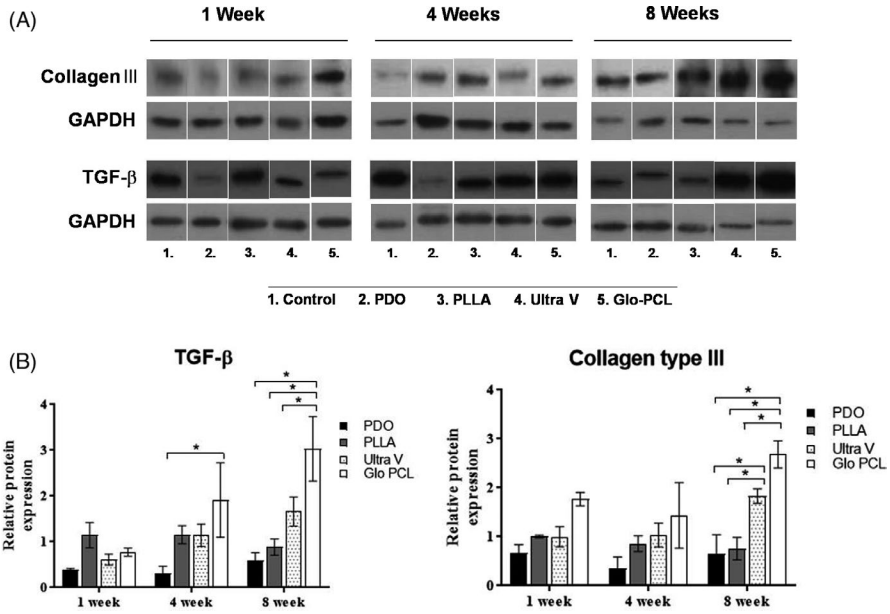


FIGURE 3 Quantitative evaluation of type III collagen and TGF-β expressions. A, Immunoblot analysis was performed to evaluate type III collagen and TGF-β expressions at 1, 4, and 8 weeks. B, Densitometric quantification of the bands was performed by an image analyzer system using Multi Gauge version 2.3 software

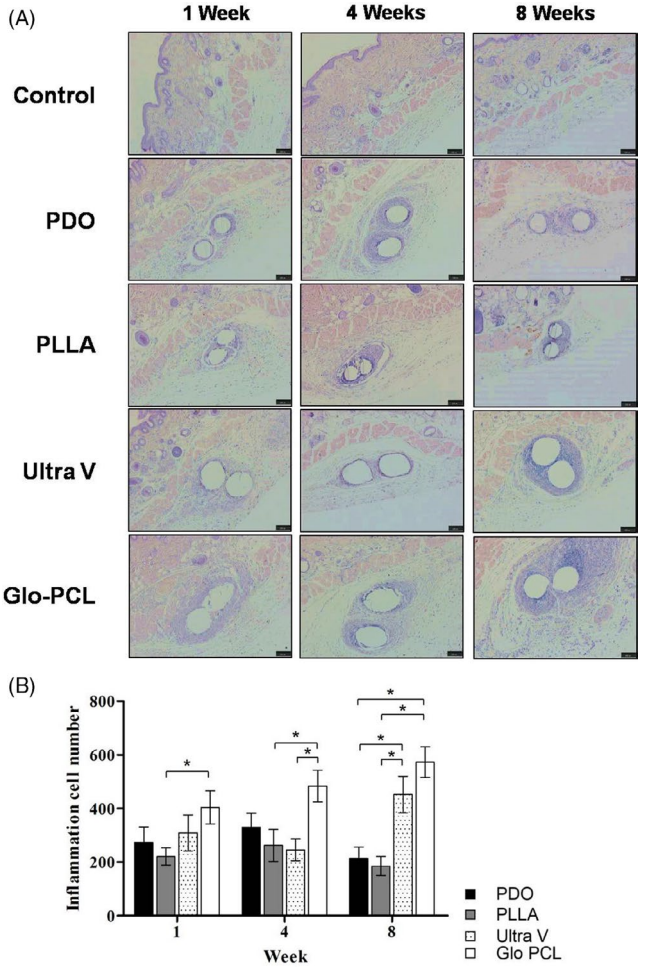


FIGURE 4 Histological evaluations of inflammatory cells. A, Hematoxylin-and-eosin-stained sections of samples were obtained at 1, 4, and 8 weeks. Black bar = 500 μm. B, The number of inflammatory cells in each group of mouse was measured

neocollagenesis by fibroblasts.[14] Collagen is essential for contiguous formation of the interstitium in the skin and a major structural component of the skin that prevents wrinkle formation.[25] Though there are several studies comparing the shapes of threads such as Cog, monofilament, and multifilament threads focusing on the mechanical effects, few studies have investigated the materials of threads focusing on the production of collagen.[16,26] However, the new PCL has a high molecular weight and was expected to have more lifting effect by producing more collagen for a longer period. Therefore, this study was designed to determine whether there are any differences in neocollagenesis among the thread materials. In previous animal studies, the thickest capsule formation around the thread was observed and the tensile strength was maximum at 4 weeks.[26,27] Thus, in this study, histological and molecular changes were investigated for 8 weeks after the implantation of PDO, PLLA, and PCL threads to evaluate the aspect of collagen production with residual tensile strength.

After thread insertion, the biostimulatory reaction starts with subclinical inflammation by macrophages and multinucleated giant cells.[28] It continues to microparticle encapsulation followed by collagen production by fibroblasts.[28] Consiglio and colleagues implanted PLLA threads in the abdominal region, which were removed at 1, 3, 6, and 12 months, followed by histological evaluation.[29] Intense inflammatory cell infiltration was normally observed at 1 and 3 months in a similar way with this study. Kapicioglu and colleagues inserted Cog threads and PLLA threads 2 cm lateral to the spinal cord of rats.[22] Skin samples were analyzed at 1, 3, and 6 months using light microscope and transmission microscope. They revealed that dermis thickness, numbers of fibroblasts, and numbers of collagen fibrils were significantly increased with threads like this study. However, there was no significant difference between Cog groups and PLLA groups unlike this study. In the present study, histopathologic review

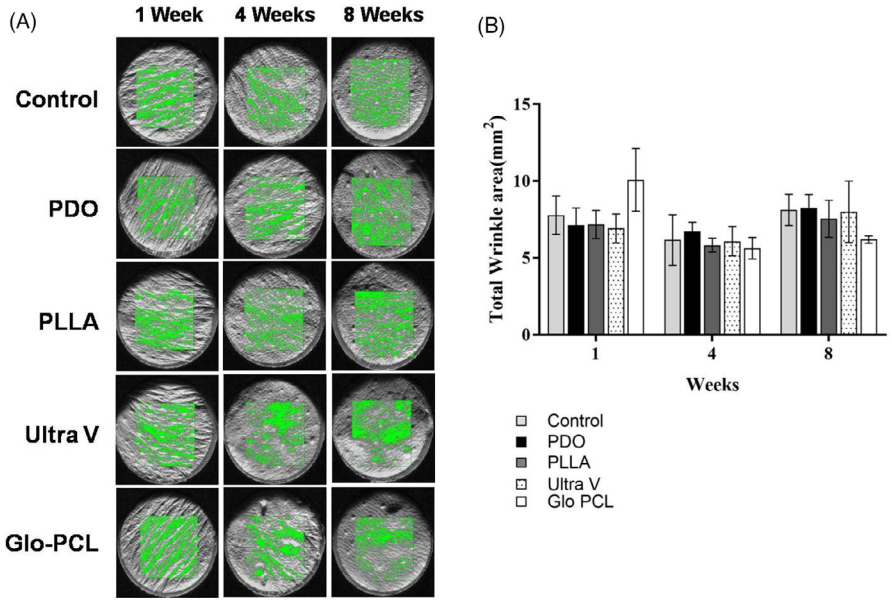


FIGURE 5 Evaluation of total wrinkle areas from skin replicas. A, Skin replicas were obtained from the dorsal skin of mice using a SILFLO impression material. B, Total wrinkle area (mm^2) of each group was measured

revealed that inflammatory reaction was induced after the implantation of all kinds of threads as in the previous study.[27] However, the number of inflammatory cells was significantly increased in the new PCL group at 4 weeks (Figure 4). The new PCL has a higher molecular weight and this helps to resist against tensile stress.[24] It means pre-existing PCL threads may start to degradate earlier than the new PCL threads resulting in lower level of biostimulation at earlier stage such as 4 weeks. Furthermore, it also explains higher expressions of TGF-β and type III collagen in the new PCL group at 4 weeks, though they are not statistically significant among the thread inserted groups (Figure 3). Because inflammation induces fibroblast to activate TGF-β pathway, both TGF-β and type III collagen expressions were increased.[28] Eventually, the amount of young collagen stained blue in Herovici's stain was significantly increased in the new PCL group at 4 weeks (Figure 2).

At 8 weeks, the pre-existing PCL and the new PCL groups showed a significantly higher level of inflammatory cells after implantation compared with the other groups. However, there was no significant difference between the PCL groups (Figure 4). Therefore, it is assumed that biostimulation reached at almost same level in both PCL groups considering the similar level of inflammatory cells. It is also explaining increased expressions of TGF-β and type III collagen in both PCL groups (Figure 3). Consequently, newly formed collagen fibers were increased in both groups (Figure 2).

Previous studies have demonstrated an increase in collagen production with the expression of various signaling molecules.[30] Among them, TGF-β pathway is considered to play a key role in wound healing process, stimulating fibroblasts proliferation in the dermis, followed by the synthesis of several proteins including collagen.[31] Therefore, the findings of present study are strengthened by correlating TGF-β expression with the level of newly synthesized collagen fibers. In addition to the filling effect of collagen fibers, it is postulated that the immediate lifting effect by mechanical anchorage is sequentially reinforced with fibrous tissues around the thread caused by initial inflammation.

In spite of an increase in collagen production, total wrinkle area was not significantly decreased in all groups at every time point (Figure 5). It can be assumed that reinforcement of mechanical anchorage and filling effect of collagen fibers are not enough to show significant difference on the surface of the skin in 8 weeks. Nonetheless, a longer period of study is needed because there were differences of expressions of TGF-β and type III collagen at 8 weeks between among the groups and it may induce greater differences as time goes by.

This study has some limitations. First, present study included a small number of samples and a relatively short period of investigation. Second, all threads used in this study were monofilaments. Further research with other shapes of threads for a longer period is required to demonstrate its clinical effectiveness.

5 | CONCLUSIONS

Here, the efficacy of the new PCL threads in SKH-1 hairless mouse has been confirmed. First, collagen synthesis was significantly increased in the new PCL group. The new PCL thread showed a significant increase at 4 weeks and both PCL groups demonstrated significant increases compared with the other groups at 8 weeks. Second, wrinkle areas of the skin were decreased in the new PCL group at 8 weeks compared with threads of various materials. However, there should be a long-term assessment of the effects for its clinical effectiveness.

The new PCL thread exhibited a skin rejuvenation including neocollagenesis and wrinkle improvement compared with other types of threads. Furthermore, the material processing technology can be applied not only to the thread but also to various products such as dermal filler and cosmetics.

CONFLICT OF INTEREST

This study was funded by Glo-one from 2015 to 2017. This included all materials, subjects, and students fee. Glo-one started its thread lifting business in 2017. Since 2017, the study was conducted independently. We previously secured our rights to publish free and independently. The funding source had no involvement in the collection, analysis, and interpretation of data; in writing of the report; and in the decision to submit the article for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Seung Woo Cho https://orcid.org/0000-0001-8266-8415

REFERENCES

1. Varani J, Dame MK, Rittie L, et al. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. *Am J Pathol*. 2006;168(6):1861-1868.
2. Atiyeh BS, Dibo SA, Costagliola M, et al. Barbed sutures "lunch time" lifting: evidence-based efficacy. *J Cosmet Dermatol*. 2010;9(2):132-141.
3. Papadavid E, Katsambas A. Lasers for facial rejuvenation: a review. *Int J Dermatol*. 2003;42(6):480-487.
4. Romagnoli M, Belmontesi M. Hyaluronic acid-based fillers: theory and practice. *Clin Dermatol*. 2008;26(2):123-159.
5. Sundaram H, Signorini M, Liew S, et al. Global Aesthetics Consensus: Botulinum Toxin Type A-Evidence-Based Review, Emerging Concepts, and Consensus Recommendations for Aesthetic Use, Including Updates on Complications. *Plast Reconstr Surg*. 2016;137(3):518e-e529.
6. Frame JD. The Past, Present, and Future of Facial Fat Grafting. *Atlas Oral Maxillofac Surg Clin North Am*. 2018;26(1):1-6.
7. Newman J. Review of soft tissue augmentation in the face. *Clin Cosmet Investig Dermatol*. 2009;2:141-150.
8. Kim J, Zheng Z, Kim H, et al. Investigation on the Cutaneous Change Induced by Face-Lifting Monodirectional Barbed Polydioxanone Thread. *Dermatol Surg*. 2017;43(1):74-80.
9. Dulguerov N, D'Souza A. Update on treatment rationale and options for the ageing face. *Curr Opin Otolaryngol Head Neck Surg*. 2011;19(4):269-275.
10. Sulamanidze M, Sulamanidze G. APTOS suture lifting methods: 10 years of experience. *Clin Plast Surg*. 2009;36(2):pp. 281–306, viii.
11. Wu WT. Barbed sutures in facial rejuvenation. *Aesthetic Surg J*. 2004;24(6):582-587.
12. Lee S, Isse N. Barbed polypropylene sutures for midface elevation: early results. *Arch Facial Plast Surg*. 2005;7(1):55-61.
13. Rezaee Khiabanloo S, Jebreili R, Aalipour E, et al. Outcomes in thread lift for face and neck: A study performed with Silhouette Soft and Promo Happy Lift double needle, innovative and classic techniques. *J Cosmet Dermatol*. 2019;18(1):84-93.
14. de Benito J, Pizzamiglio R, Theodorou D, et al. Facial rejuvenation and improvement of malar projection using sutures with absorbable cones: surgical technique and case series. *Aesthetic Plast Surg*. 2011;35(2):248-253.
15. Savoia A, Accardo C, Vannini F, et al. Outcomes in thread lift for facial rejuvenation: a study performed with happy lift revitalizing. *Dermatol Ther*. 2014;4(1):103-114.
16. Suh DH, Jang HW, Lee SJ, et al. Outcomes of polydioxanone knotless thread lifting for facial rejuvenation. *Dermatol Surg*. 2015;41(6):720-725.
17. Azimi B, Nourpanah P, Rabiee M, et al. Poly (ε-caprolactone) Fiber: An Overview. *J Eng Fiber Fabr*. 2014;9(Issue 3):74-90.
18. Wong V. Hanging by a thread: choosing the right thread for the right patient. *J Dermatol Cosmetol*. 2017;1(4):86-88.
19. Lee KO, Kim SN, Kim YC. Anti-wrinkle effects of water extracts of teas in hairless mouse. *Toxicol Res*. 2014;30(4):283-289.
20. Nkengne A, Bertin C. Aging and facial changes–documenting clinical signs, part 1: clinical changes of the aging face. *Skinmed*. 2012;10(5):284-289.
21. Abraham RF, DeFatta RJ, Williams EF 3rd. Thread-lift for facial rejuvenation: assessment of long-term results. *Arch Facial Plast Surg*. 2009;11(3):178-183.
22. Kapicioğlu Y, Gül M, Saraç G, et al. Comparison of Antiaging Effects on Rat Skin of Cog Thread and Poly-L-Lactic Acid Thread. *Dermatol Surg*. 2019;45(3):438-445.
23. Hyaluronic acid dermal fillers in the management of recurrent angular cheilitis: a case report. *Br Dent J*. 2018;225(3):217.
24. Fernández J, Amestoy H, Sardon H, et al. Effect of molecular weight on the physical properties of poly(ethylene brassylate) homopolymers. *J Mech Behav Biomed Mater*. 2016;64:209-219.
25. Weber L, Kirsch E, Müller P, et al. Collagen type distribution and macromolecular organization of connective tissue in different layers of human skin. *J Invest Dermatol*. 1984;82(2):156-160.
26. Jang HJ, Lee WS, Hwang K, et al. Effect of cog threads under rat skin. *Dermatol Surg*. 2005;31(12):1639-1644; discussion 44.
27. Kurita M, Matsumoto D, Kato H, et al. Tissue reactions to cog structure and pure gold in lifting threads: a histological study in rats. *Aesthetic Surg J*. 2011;31(3):347-351.
28. Stein P, Vitavska O, Kind P, et al. The biological basis for poly-L-lactic acid-induced augmentation. *J Dermatol Sci*. 2015;78(1):26-33.
29. Consiglio F, Pizzamiglio R, Parodi PC, et al. Suture With Resorbable Cones: Histology and Physico-Mechanical Features. *Aesthetic Surg J*. 2016;36(3):NP122-NP127.
30. Lee SH, Roh MR, Jung JY, et al. Effect of subdermal 1,444-nm pulsed neodymium-doped yttrium aluminum garnet laser on the nasolabial folds and cheek laxity. *Dermatol Surg*. 2013;39(7):1067-1078.
31. El-Domyati M, El-Ammawi TS, Medhat W, et al. Expression of transforming growth factor-beta after different non-invasive facial rejuvenation modalities. *Int J Dermatol*. 2015;54(4):396-404.

How to cite this article: Cho SW, Shin BH, Heo CY, Shim JH. Efficacy study of the new polycaprolactone thread compared with other commercialized threads in a murine model. *J Cosmet Dermatol*. 2021;20:2743–2749. https://doi.org/10.1111/jocd.13883