Poly (ε-caprolactone) Fiber: An Overview

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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].

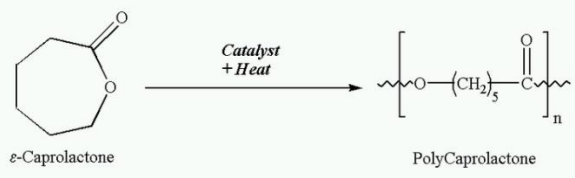

FIGURE 1. Ring opening polymerization of ε-caprolactone to polycaprolactone.

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.

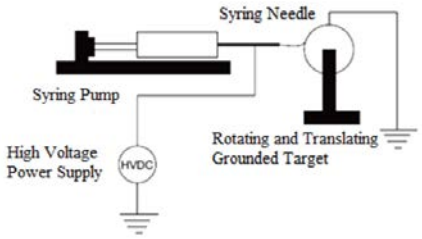

FIGURE 2. Schematic of electrospinning system [67].

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].

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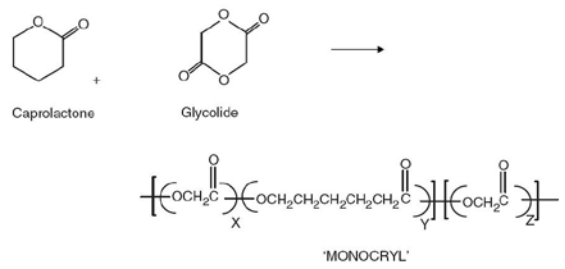
Spinning temperature (°C)	Ram speed (mm min-1)	Extrusion rate (m min-1)	Take-up rate (m min-1)	On-line draw ratio	Fiber diameter (mm)
85	2	0.12	0.6	5	0.91
90	2	0.12	0.6	5	0.81
100	2	0.12	0.6	5	0.80
110	2	0.12	0.6	5	0.80
120	2	0.12	0.6	5	0.79
85	0.5	0.03	0.6	20	0.50
85	1	0.06	0.6	10	0.66
85	2	0.12	0.6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

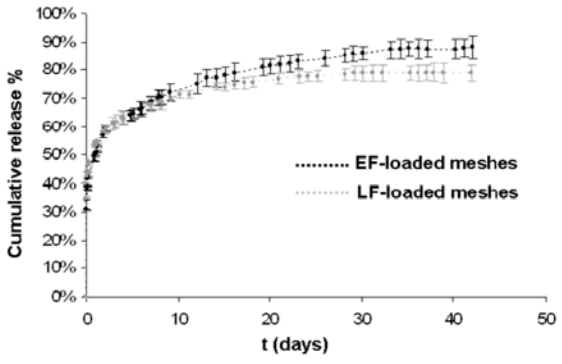


FIGURE 3. Cumulative percent release of EF and LF from *PCL meshes during in vitro drug release studies (37°C, PBS, pH 7.4). Error bars corresponding to _ standard deviation values calculated on three replicates for each time point [61].

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.

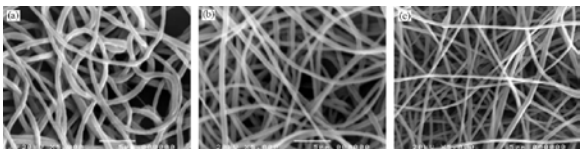


FIGURE. 4. SEM micrographs of electrospun PCL fibers containing different amounts of heparin (a) 0 wt%, (b) 0.05 wt%, and (c) 0.5 wt% [80].

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.

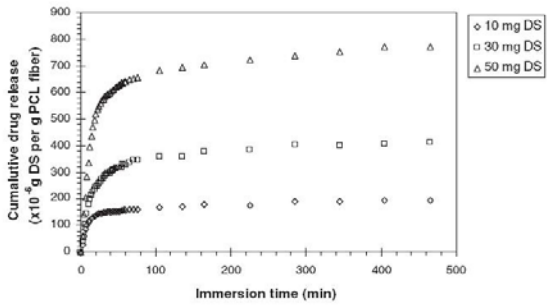


FIGURE 5. Cumulative amount of DS released from DS-loaded PCL fiber mats that were electrospun from PCL solutions loaded with 10, 30 and 50 mg of DS over an immersion period of 465 min [109].

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.

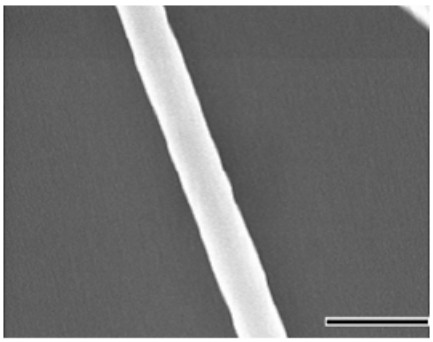


FIGURE 6. Representative SEM image showing the smooth surface of a fiber (The scale bar represents 500 nm.) [111].

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.

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