Polycaprolactone

PCL is a biodegradable polymer used in many FDA-approved surgical implants and drug delivery devices for tissue engineering and regenerative medicine applications.

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Volume 2

Geetha Manivasagam, ... Asokami Rajamanikam, in Encyclopedia of Biomedical Engineering, 2019

Polycaprolactone

PCL is a synthetic polyester polymer and has been extensively investigated for bone tissue engineering. PCL lacks bioactivity and has high degradation rate that can be manipulated by changing molecular weight, crystallinity, or by modifying the structure of PCL with hydrophilic polyethylene glycol, ceramics, or making copolymers with PLA or PGA. PCL modified by coating with HAp, TCP, gelatin and calcium phosphate, bone sialoprotein, or collagen promotes osteoblast and endothelial cell adhesion, migration, and proliferation. PCL and PGA composite scaffolds supported genetically modified human cells and have shown the regeneration of cementum like tissue, ligament, and bone structures suggesting their potential role in periodontal regeneration.

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Biomaterials and Clinical Use

K. Miller, ... L.J. Soslowsky, in Comprehensive Biomaterials, 2011

6.618.5.2.1.4 Poly(caprolactone)

Poly(caprolactone) (PCL) is a semicrystalline polymer that degrades at a much lower rate than PLA. PCL is very popular as a base polymer for long-term drug delivery applications as it has a degradation time of two to three years.[142] The degradation rate can be altered by adding other copolymers and is one strategy for improving its potential as a bioscaffold. PCL is considered to be nontoxic. PCL has an approximate strength of 0.4 GPa and a degradation time of over 24 months.[142] PCL scaffolds have been developed that possess a calcium phosphate gradient between the top and bottom surface of the mat. A gradient in mineral composition within the construct has functional consequences in PCL and PLGA scaffolds, which lead to spatial gradients in mechanical properties and cell proliferation.[148] Mineralized PLGA scaffolds have lower strain in the loading direction at the mineralized end of the scaffold than the unmineralized end.[148] These graded constructs could significantly enhance tendon to bone healing, which remains a major obstacle in tendon and ligament healing in sites such as the rotator cuff and ACL.

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Polymer Design and Development

Christopher K. Arakawa, Cole A. DeForest, in Biology and Engineering of Stem Cell Niches, 2017

3.1.4 Polycaprolactone

Polycaprolactone (PCL) is a widely used hydrolytically degradable polymer synthesized through a ring-opening polymerization of □-caprolactone. As the polymer is both hydrophobic and semicrystalline, complete degradation of the polymer can take as long as 3–4 years, making PCL a popular choice in long-term implants, bone tissue engineering, and slow releasing drug delivery applications.[87] The greatest attribute of PCL, however, is its versatility in processing and chemical properties. Its low melting temperature allows for great malleability, 3D printing capacity, heat molding, and shape memory.[88] Even more importantly, its excellent solubility in common organic solvents and ability to readily form polymer–polymer blends allows PCL to be mixed with faster degrading polymers to tune both mechanical properties and degradation time.[89] The solubility properties of PCL have been most notably utilized in electrospinning to generate sheets, tubes, and sponges with nano-topography consisting of parallel- or randomly oriented fibers.[90] Although cell

adhesion is poor on PCL surfaces, collagen coating of PCL is often used to promote cell attachment.

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Volume 1

Ohan S. Manoukian, ... Sangamesh G. Kumbar, in Encyclopedia of Biomedical Engineering, 2019

Polycaprolactone

Polycaprolactone (PCL) is a synthetic, biodegradable polymer. PCL nanofibers can be aligned to mimic an extracellular matrix structure (Manoukian et al., 2017). The average diameter of the nanofibers is 500–900 nm (Engel et al., 2008). PCL was first synthesized in the 1930s, but was not commonly used due to its slow degradation rate and inability to bear heavy loads. It regained popularity after the emergence of tissue engineering in the 1990s (Woodruff and Hutmacher, 2010). The molecular structure is shown in Fig. 23. When combined with collagen type I, it is capable of withstanding a high-pressurized environment for an extended period of time. The addition of collagen increases the burst pressure and allows PCL to become stronger as a result (Sell et al., 2009). Natural biomaterials can be added to PCL to enhance polycaprolactone's mechanical properties and stability while avoiding the need to crosslink and introduce harmful crosslinking agents (Cooper et al., 2011).

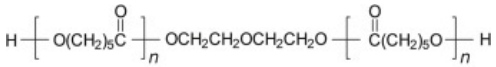

Fig. 23. Chemical structure of PCL (Costa et al., 2013).

PCL was determined to be biocompatible after both short-term and long-term studies did not elicit any adverse reactions from the host tissue. Fibrous scaffolds of electrospun PCL blended with gelatin demonstrate exceptional biocompatibility with bone marrow stromal cells. PCL composites also support the growth of adipose-derived stem cells and human coronary artery endothelial cells (Sell et al., 2009). Chitosan–PCL composite scaffolds have also been shown to be compatible with Schwann cells in nerve studies (Cooper et al., 2011).

It takes more than a year for polycaprolactone to degrade noticeably, and the total degradation time is up to 4 years. PCL is biodegraded by bacteria and fungi. In the human body, degradation is a two-step process. During the first year, ester groups are hydrolytically cleaved. Next, intracellular degradation occurs (Woodruff a nd Hutmacher, 2010). Degradation is ultimately dependent on the molecular weight and crystallinity of the polymer or composite (Lam et al., 2008b). The slow

degradation of this synthetic polymer is beneficial for neural regeneration as nerves regenerate slowly (Cooper et al., 2011).

PCL is a versatile polymer that has been implemented into various biomedical research studies. For example, PCL or PCL/hydroxyapatite scaffolds have been created using a precision extrusion deposition process. They support the growth and migration of primary fetal bovine osteoblasts and have the correct mechanical properties, pore size, and interconnectivity for bone tissue engineering (Shor et al., 2007). Nonwoven meshes of PCL incorporated with beta-tricalcium phosphate nanoparticles form a composite that mimics the structure of bone tissue at the bone–cartilage interface (Erisken et al., 2008). PCL scaffold porosity can be created and tuned using selective laser sintering to make scaffolds similar to trabecular bone (Eshraghi and Das, 2010). Electropsun scaffolds of PCL/collagen type I composites have also been successfully implanted as an artery in a rabbit model. The composite demonstrated mechanical properties such as tensile strength and elasticity comparable to native arteries. Moreover, the PCL/collagen type 1 composite did not cause platelet adhesion which prevented undesirable clotting (Sell et al., 2009). Nanofiber scaffolds of PCL, collagen type I, and collagen type II support growth and attachment of human coronary artery endothelial cells (Sell et al., 2009) (Fig. 24). In terms of neural regeneration, aligned chitosan–PCL composite fibrous scaffolds resulted in Schwann cells aligning in a bipolar fashion along the direction of the aligned fibers, and thus making these scaffolds appropriate for the reconstruction of nervous tissue (Cooper et al., 2011).

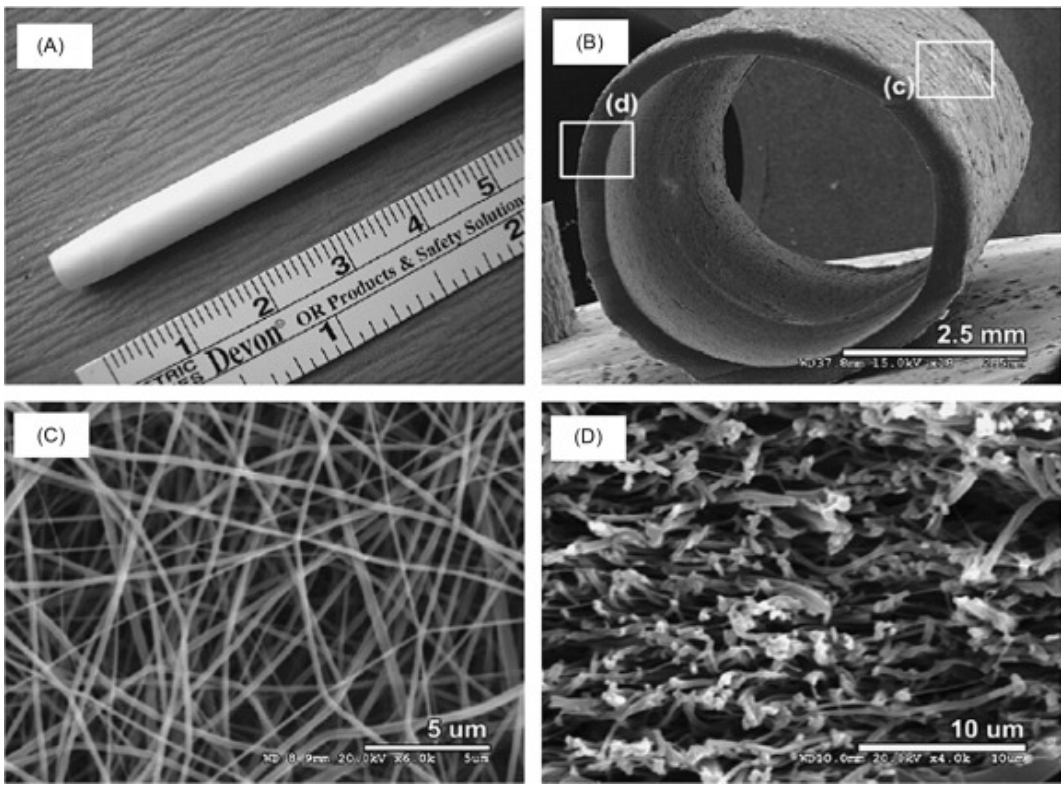

Fig. 24. Electrospun PCL/collagen composite scaffolds: (A) The gross appearance of scaffold; SEM images of (B) the entire PCL/collagen composite (18x), (C) the scaffold surface (6000x), and (D) the scaffold's cross-sectional appearance (4000x).Reproduced from Sell, S. A., McClure, M. J., Garg, K., Wolfe, P. S., Bowlin, G. L. (2009). Electrospinning of collagen/biopolymers for regenerative medicine and cardiovascular tissue engineering. *Advanced Drug Delivery Reviews* **61** (12), 1007–1019.

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Polymeric Biomaterials as Tissue Scaffolds

Jacqueline M. Bliley, Kacey G. Marra, in Stem Cell Biology and Tissue Engineering in Dental Sciences, 2015

11.3.1.3 Poly(Caprolactone)

Poly(caprolactone) (PCL) is another synthetic, biodegradeable material commonly used in tissue engineering applications. This semi-crystalline polymer (~ 50%) has a melting point between 59° C and 64° C, and has a relatively longer degradation period than either poly(glycolide) or poly(lactide). Synthesis of PCL is via ring opening polymerization of linear caprolactone monomers (Figure 11.4). Bulk degradation of PCL occurs *in vivo*, with the main products of caproic acid, succinic acid, valeric acid, and butyric acid. The acidic by-products of PCL degradation have been shown to have a negative effect on cell culture systems when clearance of these products was prevented [12]. However, PCL and copolymers thereof have been used in medical implants with little to no negative effects observed on local tissues [13]. PCL has an extensive degradation profile, normally degrading in about 1-2 years. This makes PCL uniquely apt to reconstruct defects that have a lengthy repair time (e.g., nerve). In addition, its long degradation time is particularly useful in the development of prolonged drug delivery systems. The caprolactone polymer is also one of the most flexible synthetic polymers, and usually will be combined with copolymers to increase the flexibility of the resulting biomaterial. Furthermore, increasing porosity of the caprolactone composite can modify flexibility of the polymer [14].

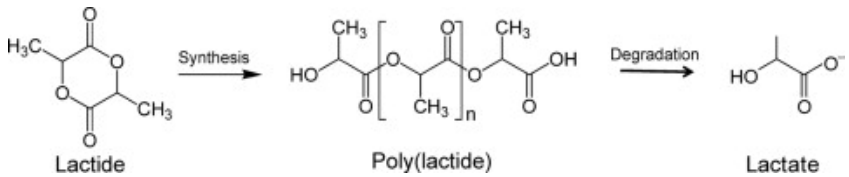

Figure 11.4. Synthesis of poly(caprolactone).

Copolymers of poly(caprolactone) have been used in a number of different clinical indications. Poliglecaprone 25 sutures consist of caprolactone and glycolide copolymers with a resorption rate of about 100 days *in vivo* [15]. In addition, a poly (dl-Lactide-□-caprolactone) nerve conduit is commercially available for the repair of peripheral nerve defects [16].

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Design and fabrication of nanocomposites for musculoskeletal tissue regeneration

N. Narayanan, ... M. Deng, in Nanocomposites for Musculoskeletal Tissue Regeneration, 2016

1.2.1.3 Polycaprolactone

Polycaprolactone (PCL), a hydrophobic polymer with semicrystalline structure, is made of caprolactone subunits linked together by the process of ring-opening polymerization. These polymers have longer degradation time than PLGA and PLA (Woodruff and Hutmacher, 2010). FDA has approved PCL for sutures with a trade name of Maxon™. PCL is soluble in a wide variety of organic solvents; therefore, it can be blended with other polymers (Sarasam and Madihally, 2005; Marra et al., 1999; Ghasemi-Mobarakeh et al., 2008). Bernstein et al. (2010) developed nanocomposites using PCL and tricalcium phosphates for potential bone tissue regeneration applications. The mixture of the polymer and the ceramic was cold-sintered to obtain the nanocomposites. The fabricated nanocomposites showed the ability to form apatite layer when incubated in SBF. In another study, Lee et al. (2007) synthesized nanocomposite materials by grafting PCL from the surface of functionalized nHA crystals. The authors reported favorable protein adsorption on the surface of the synthesized nanocomposites.

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Polymers for a Sustainable Environment and Green Energy

H.-J. Endres, A. Siebert-Raths, in Polymer Science: A Comprehensive Reference, 2012

10.19.2.2 Polycaprolactone

PCL is a polyester prepared by ring-opening polymerization of □-caprolactone using a catalyst such as stannous octanoate and not produced from renewable resources, that is, it belongs, as PVA does, to the group of biodegradable biopolymers with synthetic origins (**Figure 6**).

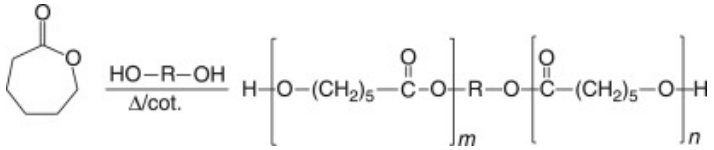

Figure 6. Ring-opening polymerization of polycaprolactone.

Its main basic building blocks are esters and ethene groups. The ratio of these and their distribution in the polymer, the DP as well as possibly even more components polymerized with it, essentially determine the crystallinity and properties of different types of PCL. High mobility in the chain segments and low intermolecular interaction, however, generally result in very low melting and glass transition temperatures and rather waxy consistency.

In principle, PCL has mechanical properties similar to other conventional, non-degradable synthetic polymers. It is nontoxic and its molecular mass of less than 15 000 g mol^{-1} means the material is brittle. At high molecular masses in the 40 000 g mol^{-1} range, it is semicrystalline structured and soft, that is, it has especially high elasticity. To be sure, it is sharply defined, but its very low melting point of □60 °C limits its applicability significantly. PCL is compatible with almost all plastics, especially with starch or lignin.

PCL's oxygen permeability is fairly comparable with that of polyethylene, that is, it cannot be used as a good oxygen barrier material. By contrast, with PE, however, it absorbs moisture and its water vapor permeability is especially high due to the polar ester groups in its molecular structure.

One of its positive properties is its very good chemical and solvent resistance. PCL is insoluble in aliphatic hydrocarbons, alcohols, and glycol. It is soluble in most aromatic and chlorinated hydrocarbons as well as in polar solvents.

PCL is a favorite choice as a blend component for softening and hydrophobizing other biopolymers. Degradation investigations performed as early as the 1970s detected generally good, that is, rapid and complete degradation behavior. Here, the PCL types with smaller molecular masses degrade somewhat better than the PCL types with higher molecular mass numbers. When PCL biologically degrades aerobically, it first hydrolyzes to hydroxy capronic acid that further oxidizes to adipic acid. After further intermediate stages, the final products of CO_2 and water finally arise via the citric acid cycle.

The increasing use of PCL in biodegradable devices in tissue engineering and regenerative medicine has created a need for long-term degradation data obtained under physiological conditions. Recent studies revealed that PCL and PCL-composite scaffolds degrade very differently under these different degradation conditions, while still undergoing hydrolysis. Molecular weight and mass loss results differ due to the different degradation pathways followed (surface degradation pathway for accelerated conditions and bulk degradation pathway for simulated physiological conditions). Ultimately, polymer degradation was shown to be chiefly governed by molecular weight, crystallinity susceptibility to hydrolysis, and device architecture considerations while maintaining its thermodynamic equilibrium.[15]

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Biodegradable Block Copolymers and Their Applications for Drug Delivery

Vandana Soni, ... Rakesh K. Tekade, in Basic Fundamentals of Drug Delivery, 2019

11.5.1.4 Poly(e-Caprolactone)-Poly (Ethylene Glycol) (PCL-PEG) Block Copolymers

PCL is the first-generation member of synthetic aliphatic polyesters. The biodegradability is very much advantageous to use this material as resorbable materials, especially for the controlled drug release. Though the presence of various shorter chain polyglycolides and derivatives has decreased the popularity, its copolymer derivatives are providing a new way with advanced functions to be explored for the delivery system. The properties of PCL like slow crystallization kinetics and low melting temperatures in the physiological range have made this material very striking for the design of tunable biomaterials. Various advantages such as slow degradation rates make PCL valuable for greater stability of implants and prolonged drug release, thus playing an important role in biomedical applications (Sisson et al., 2013).

PEG has low cytotoxicity and high water-solubility thus is widely used for biomedical applications, including drug carriers. These polyester-polyether block copolymers are gaining interest for the controlled delivery of drugs, especially in the field of biomedical applications. These block copolymers are amphiphilic, meaning they have both hydrophobic and hydrophilic parts. The solubility profile of PEG allows its use as a common constituent of the hydrophilic outer shell. The hydrophobic core of the micelle is able to entrap lipophilic drugs through hydrophobic interaction and the outer hydrophilic shell offers a guard for the drugs, providing a long-term

circulation in vivo. Yan et al. prepared the amphiphilic PCL-PEG-PCL block copolymers and used this as a vehicle for the delivery of Ginkgolide B as a novel method for brain-targeting. Ginkgolide B shows very low bioavailability to the brain. The synthesis of the amphiphilic PCL-PEG-PCL copolymer as micelles overcomes this limitation of Ginkgolide B and enhances its solubility in water as well as circulation time in vivo. The PCL-PEG-PCL tri-block copolymer synthesis was performed by a ring opening polymerization of e-CL while polyethylene oxide was used as an initiator (Yan et al., 2017).

In another study performed by Danafar, PCL-PEG-PCL was used in the form of polymersomes for the delivery of clavulanic acid, a suicide inhibitor of bacterial beta-lactamase enzymes. In this study, a reliable drug delivery system using PCL-PEG-PCL was synthesized and the release profile of the clavulanic acid (CLV) from the drug-loaded polymersomes was evaluated. CLV encapsulated within PCL-PEG-PCL NPs were prepared by a double emulsion technique (w/o/w), leading to the formation of PCL-PEG-PCL polymersomes which were found to be in uniformity and spherical with loading efficiency 16.00%±1.45% and particles size of 113 nm. In vitro release study shows the sustained release of CLV from prepared polymersomes (Danafar, 2016.).

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Polymeric Biomaterials in Tissue Engineering and Regenerative Medicine

Xiaoyan Tang, ... Xiaojun Yu, in Natural and Synthetic Biomedical Polymers, 2014

21.3.1.6 Polycaprolactone

PCL is a semicrystalline polyester. Similar to poly(dioxanone), it can be made from ring-opening polymerization of “e-caprolactone.” The homopolymer is easy to process. It has a melting point of 59-64 °C and a glass-transition temperature of – 60 °C and can be blended with a wide range of polymers to form miscible solutions. The homopolymer is increasingly used in research labs for various applications due to its slow degradation rate, good permeability, and nontoxicity. Compared to other polymers, it has a relatively long degradation time of up to 2 or 3 years [153,161]. As for its copolymers, e-caprolactone has been used with glycolide to form a monofilament suture (MONOCRYLs) for commercial use. Further applications such as a drug/vaccine carrier and a long-term contraceptive with zero-order drug release are discussed in various papers [179].

Also, in recent years, PCL has been widely studied as materials for tissue engineering applications. Yoshimoto prepared electrospun PCL as a potential candidate scaffold for bone tissue engineering [180]. PCL blended with PLLA, PLGA/HA, and gelatin electrospun sheets was studied and characterized [36,181,182]. Advanced 3D prototyped blend composites made for hard-tissue engineering were investigated based on PCL/organic-inorganic hybrid fillers [183].

> Read full chapter

Electrospun biomaterials for dermal regeneration

E.A. Growney Kalaf, ... S.A. Sell, in Electrospun Materials for Tissue Engineering and Biomedical Applications, 2017

9.2.2.1 Polycaprolactone

PCL is a synthetic, biodegradable polymer that has been widely used in biomedical applications, especially drug delivery. This semicrystalline polymer is somewhat hydrophobic and can be utilized both as a homopolymer and in combination with other polymers, such as PLA or PGA, to create a copolymer (Fig. 9.9). With a fairly slow resorption time of 24 months and a nonacidic degradation environment, PCL is an ideal material for extended drug delivery [94]. Additionally, the degradation of PCL is enhanced by lipases and can occur by bulk or surface degradation [95].

Fig. 9.9. Chemical structure of PCL.

The degradation of PCL in vivo is broken up into two stages. During the first stage, the longer of the two, the ester group, is cleaved via a hydrolytic reaction. Following this cleavage, the polymer is rapidly broken down through intracellular degradation in the phagosomes of macrophages and giant cells, and the molecular weight is decreased to 3000 or less [96].

Typical parameters under which PCL (6–12% w/v) is electrospun include flow rates between 0.1 and 1 mL/min and high applied voltages ranging from 22.5 to 36.76 kV. A working distance of approximately 35 cm is commonly used for all other parameters [96–98].

Previous studies have examined these electrospun PCL scaffolds for a dermal application. The average fiber diameter has been created to range from 284 ± 48 to 8320 ± 720 nm, and all studies found the electrospun scaffold porosity to be around 85% [96–98]. This falls within the desired range of 60–90% for optimal cellular infiltration [98]. The elastic modulus of these scaffolds can range anywhere from 6.7 ± 0.4 to 21.42 ± 0.04 MPa, depending on the combination of parameter values [96,98].

A separate study seeded PCL scaffolds with human fetal fibroblasts and also applied them as skin substitutes within in vivo rat wound models. Overall, the fibroblasts had poor proliferation and adhesion. Due to its slow degradation, the scaffold delayed wound contraction but did not prevent it completely. Additionally, it elicited a foreign body response including the presence of many multinucleated macrophages [96].

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