1
Biodegradable Polyesters: Synthesis, Properties, Applications

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1.1
Historical Overview on the Origin of Polymer Science and Synthesis of Polyamides and Polyesters

There are some persons who stand out prominently in any review of the history of polyesters. As early as in 1911, Meyer [1] found that the saponification of polyesters of polyacids and polyalcohols and the hydrolysis of a glycerol ester proceeds in acid and alkaline solution, and, the hydrolysis can only be detected under certain conditions with heterogeneous saponification. However, he did not mention the molecular weights of the polyesters used. Hermann Staudinger (1881–1965) is recognized as the father of polymer chemistry because of his great contributions to polymer science (Figure 1.1).

In 1920, Staudinger reported [3] that polymerization processes in the wider sense are all processes in which two or more molecules combined to a result in a product of the same composition but with higher molecular weight. These high-molecular-weight compounds are produced by two basic polymerization processes: the first was called *condensation polymerization*(nowadays, termed step-growth polymerization) in which polymers are formed by stepwise reactions between functional groups of monomers, usually containing heteroatoms such as nitrogen or oxygen; and the second called *chain-growth polymerization* (or addition polymerization), which involves double or triple carbon–carbon bonds breaking and the linking together of the other molecules. In reactions, these unsaturated monomers are able to form repeating units where the main-chain backbone usually contains only carbon atoms. In his paper entitled "Polymerization" [3], Staudinger presented several reactions that form high-molecular-weight molecules by linking together a large number of small molecules. This new concept was the base for "macromolecular chemistry" in the history of science. Staudinger noticed that the natural fibers were not comprised of small molecules as imagined earlier [4] and he gave an early formal awareness of "small" differing from "big" molecules. Thanks to his pioneering concept, in the past 90 years, the molecular architectures of synthetic polymers and biopolymers have become clearly known and most synthetic polymers can be designed, characterized, and

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Figure 1.1 Hermann Staudinger who was born on 23 March 1881 at Worms, Germany and died on 8 September 1965 at Freiburg, Germany [2].

tailored with high precision. But in his time, his concepts about macromolecules were doubted by the scientific community, although he presented key experimental evidence to support the existence of high-molecular-weight polymers. Most scientists were very reluctant to accept the existence of large compounds with molecular weights exceeding 5000 Da. Instead, micelle-type aggregates, as observed for soap molecules, were considered to account for the unusual properties of such materials. Moreover, some scientists were convinced that the size of a molecule could never exceed the size of the unit cell, as measured by X-ray crystallography [5]. A well-known effort was that of a natural rubber, which was selected as the model system by Staudinger because Carl Harries and Rudolf Pummerer had suggested that natural rubber consisted of aggregated small cyclic polyisoprene units via "partial valencies" associated with the double bonds. Such aggregates should have been destroyed when the double bonds were removed by hydrogenation. Staudinger's hydrogenation experiments showed that hydrogenated rubber was very similar to normal unsaturated rubber, indicating the existence of high-molecular-weight polymers whether the double bonds were hydrogenated or not. During the late 1920s [6–9], Staudinger provided additional evidence based on viscometry to confirm that molecular weights remained unchanged during chemical modification of polymers. Staudinger continued to encounter very strong opposition from leading organic chemists for nearly two decades. For instance, Heinrich Wieland, 1927 Nobel laureate in chemistry, wrote to Staudinger, "Dear colleague, drop the idea of large molecules; organic

molecules with a molecular weight higher than 5000 do not exist. Purify your products, such as rubber, then they will crystallize and prove to be low molecular compounds!" [5].

Staudinger continued the promotion of his concepts of polymer sciences, despite his colleagues' mistrust of many of his methods and results. He eloquently defended his ideas against all attacks using his ingenuity, persistence, and pronounced enthusiasm. By the end of the 1920s and during the 1930s, Staudinger's macromolecular concept found increasing acceptance by other chemists. Finally, on 10 December 1953, Staudinger was rewarded for his concept of macromolecules and his prolonged effort to establish the science of large molecules, when he was awarded the Nobel Prize for chemistry [5].

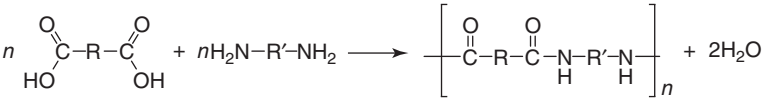
1.1.1 Synthesis of Polyamides

Wallace Carothers (1896–1937) who is another great polymer giant must not be neglected here. In the 1930s, Carothers formally reported laboratory and theoretical studies for the condensation polymerization and made synthetic polymers of Nylon and glycol esters [10, 11] (Figure 1.2). Among the discoveries of synthetic polymers, Carothers' most significant achievement was the synthesis of

Figure 1.2 Wallace Carothers who was born on 27 April 1896 in Burlington, Iowa, United States and died on 29 April 1937 at Philadelphia, Pennsylvania, United States [12].

Nylon. Nylon is a generic term for a family of synthetic polymers known generically as aliphatic polyamides, first produced in 1935 at DuPont's research facility at the DuPont Experimental Station led by Carothers. As one of the most popular thermoplastics, Nylon has different chemical structures and trade names such as nylon-6,6, nylon-6, nylon-6,9, and nylon-11.

There are two typical approaches for the synthesis of nylon. The first approach includes combining molecules with an acid (COOH) group on each end are reacted with two chemicals that contain amine (NH_2) groups at each end. This process creates nylon-6,6, made of hexamethylene diamine with six carbon atoms and adipic acid. The second approach consists of a compound having an acid at one end and an amine at the other and this compound is polymerized to form a chain with repeating units of $(–NH–[CH_2]_n–CO–)_x$. For instance, nylon-6 is made from a single six-carbon substance called *caprolactam*. In this equation, if $n = 5$, then nylon-6 is the assigned name (this may also be referred to as *polymer*). The numerical suffix specifies the number of carbons donated by the monomers: the diamine first and the diacid next. The most common nylon polymer is nylon-6,6 which refers to the one in which the diamine (hexamethylene diamine) and the diacid (adipic acid) each donate six carbons to the polymer chain. It is difficult to get equimolar proportions between the two involved monomers exactly correct, and deviations can lead to chain termination at molecular weights less than a desirable 10 000 Da. To overcome this problem, a crystalline, solid "nylon salt" can be formed at room temperature, using an exact 1 : 1 equimolar ratio of the acid and the base to neutralize each other. Heated to 285 °C, the salt reacts to form nylon polymer. However, it is impossible to spin the chains into yarn at above 20 000 Da. To overcome this difficulty, some acetic acid must be added to react with a free amine end group during polymer propagation to limit the molecular weight. The general reaction is



Two molecules of water are given off and the nylon is formed. Its properties are determined by the R and R′ groups in the monomers. In nylon-6,6, R = 4C and R′ = 6C alkanes, but one also has to include the two carboxyl carbons in the diacid to get the number it donates to the chain. In Kevlar, both R and R′ are benzene rings.

In early discovery of polymers, of course there were a lot of arguments on the basics of polymer science and unclear concepts and terms. Carothers criticized Berzelius [10, 13] about his misleading concept on polymers as the term *polymers* indicated the presence of the same atoms in the same proportions. Carothers described a "condensation" that requires as starting materials compounds in which at least two functional groups are present in the same molecule (e.g., hydroxy acids, HO–R–COOH, might lead to polyesters, $HO[RCOO]_xRCO–$; and amino acids to polyamides, $NH_2[RCONH]_yRCO–$.) [10]. In addition, he

suggested the possible condensation products via intra- or interpolymerization with bifunctional monomers as limited atomic ring or high-molecular-weight chains [10]. In 1929, Carothers and Arvin [14] prepared some esters by heating a variety of acids and 5% excess of glycol for about 3 h at 175–185° and then at 200–250° and 0.2 mmHg for 3 h. Some solid esters had molecular weights ranging from 2300 Da to the highest of 5000 Da as polymers and in the final chemical structure of the polyesters it was assumed that HO groups were present at each end of the chain because of the presence of one more molecule of glycol than that of acid. Carothers, who analyzed the hydroxy-acids of the series, found that $HO(CH_2)_xCOOH$ might condense with them, but in most cases the bifunctional reaction led to a lower-atomic-number ring lactone. Higher-molecular-weight condensed substances were only synthesized by the oxidation of the corresponding cyclic ketones with persulfuric acid [15]. In 1930, Carothers *et al.* [11] synthesized powder-like polymeric ethyl oxalates in at least two forms by heating; these polyesters had higher melting points (soluble form m.p. 159 °C and insoluble form m.p. 172 °C) than the monomer ethyl oxalate (m.p. 144 °C). The material with m.p. 172 °C was insoluble in all common organic solvents. Most importantly, they found that the polymeric ethyl oxalateswere all not stable and purified polymers were partially depolymerized during standing. It was found that the monomer of ethyl oxalate crystals was also not stable in ambient condition.

1.1.2 Initial Knowledge about Polyesters

A brief introduction to commonly used polyesters would be in order here. The most well-known and daily used man-made polyester is polyethylene terephthalate (PET)(more often written as poly(ethylene terephthalate), whose chemical structure is shown in Figure 1.3). PET is a thermoplastic polymer resin of the polyester family and is used in the form of synthetic fibers. This polyester is generally nonbiodegradable. Whinfield synthesized PET in 1941 and called it *terylene* [16] and Hardy [17] characterized teryleneusing a couple of methods (Figure 1.3).

The general chemical formula for polyesters can be summarized in short form as $–(COOR)_x–$ but the R groups are different and bring in varying properties to the final polyesters. PET has an aromatic ring in its main-chain structure, as a result of which it is not readily biodegradable. In contrast to PET, the aliphatic polyesters listed in Table 1.1 are readily biodegradable and there are no aromatic rings in their main chain structures. However, chemical composition is not the only determining factor for polymer biodegradability.

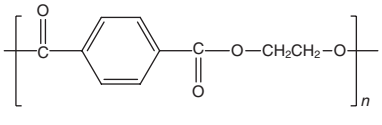


Figure 1.3 Poly(ethylene terephthalate).

Table 1.1 Number of publications in the past 110 years in terms of "biodegradable polyester," "poly(lactic acid)," and "poly(ethylene terephthalate)".

Recorded publication time period/year	Biodegradable polyester	PLA	PET	Publication ratio of PET/PLA
1900–1909	0	0	0	—
1910–1919	0	0	0	—
1920–1929	0	0	0	—
1930–1939	0	1	2	2
1940–1949	0	13	7	0.538
1950–1959	0	21	394	18.8
1960–1969	0	14	3 123	223.1
1970–1979	56	73	6 879	94.2
1980–1989	169	340	10 600	31.2
1990–1999	3 223	2 877	24 675	8.58
2000–2009	8 572	17 611	53 606	3.04

From Scifinder Scholar searching.

1.2 Publication Trend of Representative Biodegradable and Nonbiodegradable Polyesters in the Past Century

Before 1970, the concept of a biodegradable polyester as a whole was not found in literature although we do know that biodegradable polyesters had been studied for sometime [18–20].

Poly(lactic acid) (PLA), a representative biodegradable polyester, has been studied intensively as shown in Table 1.1 for about 80 years. Studies on biodegradable polyesters such as PLA have increased considerably since the new millennium. Nowadays, aliphatic polyesters such as PLA, poly(caprolactone) (PCL), and poly(ethylene succinate) are commercially produced and their output continues to increase. Table 1.1 shows clearly that while the number of publications on PLA as well as PET has been on the increase, the relative ratio of publications on PLA to PET is quite high.

1.3 Biodegradable Polyesters

Today it is known that aliphatic polyesters such as PLAs, PCL, and poly(hydroxybutyrate) (PHB) and their copolymers are biodegradable in the human body as well as in the environment [21]. However, few researchers knew of biodegradable polyesters in the 1960s. The earliest publication on biodegradable polyesters was from Bowman [22] in 1961; it is resulted in a US patent for synthesis of a

homopolymer of glycolic acid which is suitable for use as a binder in explosives. In 1962, Bowman showed that this polymer could be used as a binder for solid propellants [23]. Poly(glycolic acid) (PGA)was found easily thermally degraded [24] and its poor thermal and hydrolytic stabilities were problematic for any permanent application. Choju *et al.* [25] mentioned that this PGA homopolymer is an unstabilized polymer and weight loss under heating begins at 240 °C [25]. It was later realized that one could take advantage of the hydrolytic sensitivity of PGA to make polymeric devices which can degrade in the human body [23, 26]. Schmitt and Polistina [27] made use of the hydrolytic degradation of PGA to make absorbable surgical dressings. This degradability also made PGA the first bioresorbable suture material [28, 29]. In Li's review [30], it was summarized that people tend to use the word "degradable" as a general term and reserve "biodegradable" for polymers which are biologically degraded by enzymes introduced *in vitro* or generated by surrounding living cells. A polymer able to degrade, and to have its degradation by-products assimilated or excreted by a living system, is then designated as "bioresorbable." Most degradable and biodegradable polymers contain hydrolyzable linkages, namely, ester, orthoester, anhydride, carbonate, amide, urea, and urethane, in their backbones. The ester bond-containing aliphatic polyesters are particularly interesting because of their outstanding biocompatibility and variable physical, chemical, and biological properties. The main members of aliphatic polyesters, their acronyms, and chemical structures are listed in Table 1.2. Among the aliphatic polyesters, PLA, PGA , and PCL are the most investigated [30, 31].

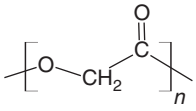
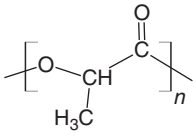
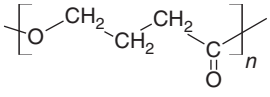
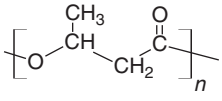
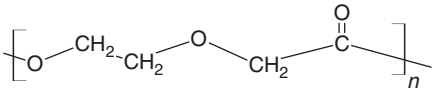
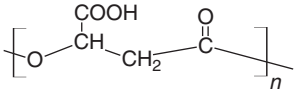
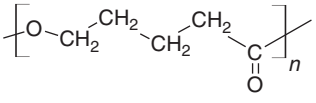
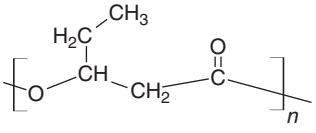
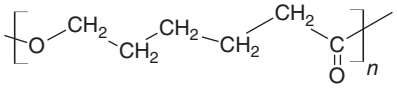
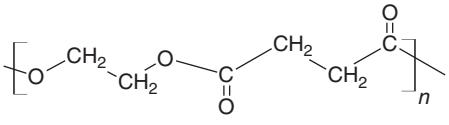
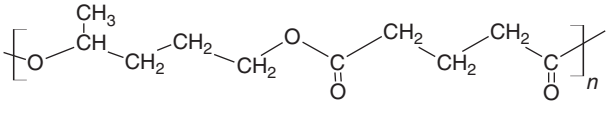
1.3.1
Biodegradable Aliphatic Polyesters and Their Copolymers

Biodegradable polyesters can degrade in the environment because of the characteristics of their main-chain structure and a certain extent of hydrophilicity and crystallinity. Latest investigations have shown that the hydrophilic/hydrophobic balance of polyester molecules seems to be crucial for the enzyme to bind to the substrate and the subsequent hydrolytic action of the enzyme. Interestingly, lipases are not able to hydrolyze polyesters having an optically active carbon such as PHB and PLLA (poly-L-lactide) [32]. Lipases are an important group of esterases for biodegradation of aliphatic polyesters. These enzymes are known to hydrolyze triacylglycerols (fat) to fatty acid and glycerol. It seems probable that lipase can hydrolyze aliphatic polyestersin contrast to aromatic polyesters because the flexibility of the main chain and the hydrophilicity of aliphatic polyesters is so high that it allows intimate contact between the polyester chain and the active site of lipases. This is in marked contrast to the rigid main chain and hydrophobicity of aromatic polyesters [32].

1.3.1.1 **Poly(lactic acid)**

Lactic acid is the smallest optically active organic molecule of natural origin with either L(+) or D(−) stereoisomers; it is produced by animals, in plants, and

Table 1.2 The main members of aliphatic polyesters, their acronyms, and chemical structure.

Polymer	Acronym	Chemical structures
Poly(glycolic acid) or poly(glycolide)	PGA	
Poly(lactic acid) or poly(lactide)	PLA	
Poly(4-hydroxybutyrate)	4PHB	
Poly(3-hydroxy butyrate) or poly(hydroxy butyrate)	PHB	
Poly(para-dioxanone)	PDO	
Poly(beta-malic acid)	PMLA	
Poly(valerolactone)	PVL	
Poly(hydroxy valerate)	PHV	
Poly(ε-caprolactone)	PCL	
Poly(ethylene succinate)	PES	
Poly(ε-decalactone)	PDL	

by microorganisms in nature [33]. The first report on the isolation of lactic acid was in 1780 [34]. The dimerization of lactic acid monomers into a form of lactide followed by ring-opening polymerization was reported by Carothers *et al.* [18], who found that the ability of lactic acid to undergo reversible polymerization is generally characteristic of six-membered cyclic esters. The ester rings of five atoms or more than six atoms do not polymerize under the action of heat. The polymers formed from six-membered cyclic esters are linear polyesters and, at least in certain instances, the chains are open and terminated by HO and COOH groups. Both the polymerization and the depolymerization take place with a process of ester interchange [18]. It was known [14, 18] that the polymer based on lactyl units was instable in humid atmosphere and the application of this kind of polymers was not considered as meaningful earlier than the 1960s. In the 1960s, their biodegradability and nontoxicity for use in medical applications became apparent [35]. Research on lactic acid-based polymers intended for medical applications has markedly increased since then and boomed in the last two decades in many other areas of interest [36–43]. Polylactides have been of significant research interest due to their biocompatibility and biodegradability, leading to applications in medical science and biotechnology.

Synthesis PLA is a thermoplastic aliphatic polyester which is formed by condensation polymerization of lactic acid, as mentioned in the preceding. Lactic acid is isolated from tapioca, corn and other plant root starches, sugarcanes , or other resources. Bacterial fermentation is normally used to produce lactic acid from starch or sugar. However, lactic acid cannot be straight away be polymerized into a useful material as one condensation reaction by two lactic acids generates one molecule of water. The generated water degrades the oligomer chain to result in low-molecular-weight lactide. Two lactic acid molecules then undergo a single esterification and get catalytically cyclized to form a cyclic dilactate ester. Although dimerization also generates water, it can be separated before polymerization owing to a significant drop in polarity (Figure 1.4).

The polymerization of lactic acid to lactide or high-molecular-weight lactic acid-based polymers can be conducted in several ways:

1) Lactic acid through condensation polymerization to produce lower-molecular-weight PLA (degree of polymerization (DP) is normally less than 100).

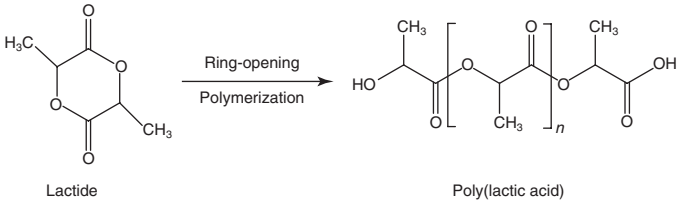


Figure 1.4 Synthesis of poly(lactic acid) via ring opening.

2) Lactic acid can be polymerized in solution to produce high-molecular-weight PLA.
3) PLA at low DP depolymerizes to lactide either through ring-opening polymerization with stannous octoate as catalyst and $SnCl_2$ or through copolymerization with comonomers in solution to obtain high-molecular-weight PLA copolymers [24]. In this way, the reaction does not generate additional water and hence, a wide range of molecular weights is obtainable;
4) Lactic acid reacts with diacid or diol to form telechelic polylactic acid, then through further a linking reaction it forms high-molecular-weight lactic acid copolymers [33, 44, 45]. Polymerization of a racemic mixture of L- and D-lactides usually leads to the synthesis of poly-DL-lactide (PDLLA)which is amorphous. Use of stereospecific catalysts can result in heterotactic PLA which is found to show crystallinity [46, 47]. The degree of crystallinity and many associated properties are greatly controlled by the ratio of D to L enantiomers in the polymer [48].

Chemical and Physical Properties Owing to the chirality of lactic acid, different forms of polylactide exist as PLLA [49], poly-D-lactide (PDLA) [50], PDLLA [51], and poly(L-lactide-*co*-D,L-lactide) (PLDLLA) [52]. Poly(lactide)s such as PLA and lactide copolymers are biodegradable and nontoxic to the human body and the environment. They have been used as biomedical materials for tissue regeneration, matrices for drug delivery systems, and alternatives for commercial polymeric materials to minimize the impact on the environment. With stereocomplex formation between enantiomeric PLA, numerous studies have been carried out with respect to the formation, structure, properties, degradation, and applications of the PLA stereocomplexes. Stereocomplexation enhances the mechanical properties, the thermal resistance, and the hydrolysis-resistance of PLA-based materials. These improvements arise from a peculiarly strong interaction between L-lactyl unit sequences and D-lactyl unit sequences. Stereocomplexation opens a new way for the preparation of biomaterials such as hydrogels and particles for drug delivery systems. PLA stereocomplexation, and the structure, properties, degradation, and applications of a variety of stereocomplexed PLA materials have been studied [32, 50–58] (Table 1.3).

Table 1.3 Thermal analysis data for PLLA, PDLA, PDLLA, and PLDLLA [32, 50–58].

Samples	PLLA	PDLA	PDLLA	PLDLLA
T_g (°C)	62.1; 50–65	50–60	50–60	50–55
T_m (°C)	106–122;170–190	165–187	Amorphous	—
Density (g cm^{-3})	1.25–1.29	1.24	1.27	1.3
Tensile strength (MPa)	0.08–1	—	0.04–0.05	32
Young's modulus (GPa)	2.7–16	3.2–7.9	1.5–1.9	2.3
Elongation at break (%)	30–40	—	5–10	5

PLA is the product resulting from polymerization of L,L-lactide. PLLA has a crystallinity of around 37%, a glass transition temperature between 50 and 65 °C, a melting temperature between 173 and 178 °C and a tensile modulus between 2.7 and 16 GPa [33, 58]. PLLA can be processed like most thermoplastics into fiber and film. The melting temperature of PLLA can be increased by 40–50 °C and its heat deflection temperature can be increased from approximately 60 °C to up to 190 °C by physically blending a PLLA with PDLA. PDLA and PLLA form a highly regular stereocomplex with increased crystallinity. The temperature stability is enhanced when a 50 : 50 blend is used, but even at lower concentrations of 3–10% of PDLA, there is still a significant improvement [50, 57, 59]. PDLA acts as a nucleating agent in a blend of PLLA in the formation of crystalline structure [60, 61]. Thus PDLA helps in increasing the crystallization rate. Biodegradation of PDLA is slower than for PLA because the former has the higher crystallinity. The differences in the degradation behavior of the amorphous and crystalline PLAs can be explained by assuming a simple hydrolysis as the main degradation mechanism [62]. PDLA is optically transparent and this is very useful in poly(lactide) blends [63, 64]. PLDLLA has been used as scaffold for bone engineering [65].

Applications Polylactide-based polymers are available for controlled drug releases, implantable composites, bone fixation parts, packaging, and paper coatings, sustained release systems for pesticides and fertilizers, and compost bags [66]. Histological studies indicate that the PLA is nontoxic, nontissue reactive, and biodegradable, and neither the polymer nor its degradation products are retained in any of the vital organs of the animals. PLA is suitable for sutures, vascular grafts, and other surgical implants. The polymer implant, however, degrades slowly *in vivo*, losing 12–14% in three months. Kulkarni *et al.* [35] reported that high-molecular-weight PLA made from the cyclic lactide intermediate is suitable for casting films or spinning fibers. The films are quite permeable to water vapor and can soften in the presence of water. Sinclair and Gynn [67] prepared polymers/copolymers using glycolic and lactic acid-based compound for implant devices in managing maxillofacial trauma. In 1973, Sinclair [68] extended polymers of lactic and glycolic acids as ecologically beneficial, biodegradable polyesters encapsulating materials for slow release of herbicide in soil. PLA prepared from D,L-lactic acid via a D,L-lactide intermediate was mixed with ground urea, and compression-molded at 130 °C into pellets containing 25% urea. In sand, the pellets showed a slow biodegradation of the polymer to lactic acid and a urea-release rate 0.1–1% per day.

Fibrillated and self-reinforced (SR) poly(L-lactide) rods 4.5 mm in diameter were used for fixing right femoral, cortical bone osteotomies of rabbits and observed for 3–48 weeks. None of the rods broke during this period. The rods were also tested mechanically. About 25% of the initial 136 MPa shear-strength of the rods was left after 24 weeks. The results show that fibrillated SR-PLLA rods are strong enough to be used in intramedullary nailing of femoral cortical bone osteotomies in rabbits [69].

As a food-packaging material, PLA is safe for its intended use as a polymer for fabricating articles that will hold and/or package food [70, 71]. A 70 wt% PLLA and 30 wt% polyethylene glycol (PEG, mol wt 18 500) can be compression-molded to make a blend which was made into a highly transparent, exudation-free, flexible, craze-free sheet [72]. PLA blended with biodegradable starch ester compound can even make high-impact-resistant thermoplastic, biodegradable starch materials. Such materials are highly desirable in the packaging industry [73]. A compostable biodegradable coating of paper or paperboard consists of an outer layer containing polylactide and an adhesive layer , which binds the outer layer to the paper or paperboard, of biodegradable polymer material (e.g., polyesters) that is coextruded with the polylactide. The coated paper is used as packaging for food stuffs and for disposable dishes such as containers for frozen foods, disposable drinking cups, heat-sealed cartons, and packaging wraps [74].

1.3.1.2 Polyglycolide or Poly(glycolic acid)

Poly(glycolide) or poly(glycolic acid) is a biodegradable, thermoplastic polymer and the simplest linear, aliphatic polyester. In 1954 Higgins *et al.* [75] patented a hydroxyacetic acid or its esters form homopolymers from which tough films and fibers can be prepared. Since then PGA has been known for its thermal processability and biodegradability but also for its hydrolyticity, which limited its applications for years. PGA is degraded by enzyme [76] or is highly hydrolytic in water with high pH $\geq$ 10. However, at near-neutral pHs, the hydrolyticity of PGA is reduced markedly [77]. Currently, monomers of lactic acid, ε-caprolactone, trimethylene carbonate, homopolymer or copolymers of poly(glycolide), poly(lactic-co-glycolic acid) (PLGA), poly(glycolide-*co*-caprolactone), and poly(glycolide-*co*-trimethylenecarbonate) are widely used as a material for the synthesis of absorbable sutures and are being evaluated in the biomedical field.

Synthesis As early as in 1949, Sporzynski *et al.* [78] published their synthesis routes for poly(glycolide). Not only for synthesis, Sporzynski and his coworkers also described the physical properties of PGA as the yellow powders with melting point at 217 °C. They found PGA was depolymerized to 10% glycolide; the presence of copper increased the yield of glycolide. In 1967, Chujo *et al.* [79] systematically studied the ring-opening polymerization within which the polymerization behavior of glycolide in the presence of various catalysts and the cationic copolymerization reaction of glycolide with various comonomers were examined. A schematic representation is shown in Figure 1.5.

In homopolymerization, an anionic polymerization catalyst such as KOH gives brittle and highly colored polymers in low yield. A Lewis acid such as SbF_3 gives a tough and colorless polymer almost quantitatively. Antimony oxide is almost as good as SbF_3. The temperature has substantial effects on viscosity and the time to reach 100% yield. Ferric chloride–propylene oxide complex also gives a high-molecular-weight polymer in good yield. Glycolide is easily copolymerized

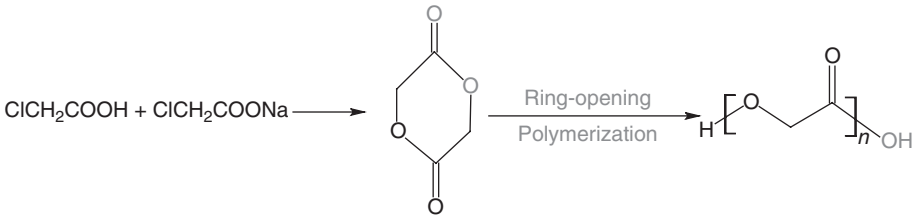


Figure 1.5 Ring-opening polymerization to make poly(glycolide).

with lactide, 1,3-dioxolane, 1,3,5-trioxane, and beta-propiolactone, and moderately copolymerized with epichlorohydrin and styrene oxide to give a product with small reduced viscosity. Chujo *et al.* [25] then published their results on the properties of PGA from ring-opening polymerization. They had found that the melting point for PGA as a crystalline homopolymer was in the range of 227 – 230 °C, after it was copolymerized with lactide in a ring-opening reaction, dissolved in a γ-butyrolactone and treated with toluene diisocyanate, in such way that a highly polymeric and crystalline copolymer was made to overcome the instability of homopolymer PGA under heat. The resulting copolymer had the highest tensile yield strength (116.5 MPa) and highest value (2068 MPa) of modulus of rigidity among all the thermoplastics known then. The copolymer of glycolide-β-propiolactone decomposed remarkedly, indicating the influence of the chain end on the heat stability of the copolymer.

Chemical and Physical Properties PGA can be easily crystallized as spherulites and hedrites in a hedritic rosette [80]. Braided sutures from melt-extruded, stretched, and heat-set PGA fibers were chosen for their high strength, excellent handling properties, minimal tissue reactivity, and a similar but more reproducible absorption rate than catgut, as comparing to nylon-4, poly(β-hydroxybutyric acid), poly(ethylene oxide), oxidized regenerated cellulose, and poly(vinyl alcohol) as absorbable sutures. However, one of the two PGA polymorphs from ring-opening polymerization is readily degradable in the presence of moisture [21]. In 1973, using thermogravimetric, gas evolution analysis together with kinetic study, Cooper *et al.* [81] confirmed that the degradation of PGA was a first-order reaction mainly via an intramolecular ester interchange mechanism [81], as shown in Figure 1.6 (Table 1.4).

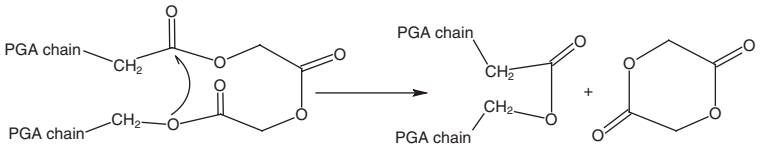


Figure 1.6 Intramolecular ester interchange mechanism of poly(glycolide) degradation (the intramolecular arrow indicates the direction in which the ester interchange occurs).

Table 1.4 Thermal and mechanical properties of poly(glycolide) [21, 50].

Property	PGA
T_g(°C)	40
T_m(°C)	225–230
Density(g cm^{-3})	1.5–1.69
Tensile strength (GPa)	0.08–1
Young's modulus (GPa)	4–14
Elongation at break (%)	30–40

Applications Currently, polyglycolide and its copolymers (poly(lactic-co-glycolic acid), poly(glycolide-*co*-caprolactone), and poly(glycolide-*co*-trimethylene carbonate)) are widely used as materials for the synthesis of absorbable sutures [82–88]. In most cases, PGA is copolymerized with other organic acids such as with PLA to make a PLA–PGA copolymer for improving its property [89]. PGA–PLA copolymers have been known to be *biodegradable* and *histocompatible* for the past 40 years. Their physicochemical and biological properties have been found suitable, in many instances, for sustaining drug release *in vivo* for days or months [89, 90]. Microencapsulation technique is chosen frequently for its unique properties because microcapsules can be made using different traditional and nontraditional techniques containing core materials ranging from biological proteins to synthetic drugs [90]. Lima and Rodrigues Junior [91] reviewed the development of a biocompatible delivery system using poly(-DL-lactide-*co*-glycolide) microspheres as a controlled release antigen for parenteral administration offers several advantages in terms of immune adjuvanticity over other compounds. It was found that, in contrast to other carriers, microspheres are more stable, thus permitting administration by the oral or parenteral route.

Nanotechnology has been applied in drug delivery system in recent years using biodegradable polymer as key carrier materials. Biodegradable nanoparticles formulated from biocompatible poly(D,L-lactide-*co*-glycolide) has shown the potential for sustained intracellular delivery of different therapeutic agents [92]. Drug delivery into the brain using poly(lactide-*co*-glycolide) microspheres attracted attention. For brain drug administration, locally controlled drug release by way of an implantable polymeric device was developed as macroscopic implants needing open surgery for implantation. To avoid surgery implantation, poly(lactide-*co*-glycolide) microspheres were shown to be safe and promising for drug delivery into the brain. Poly(lactide-*co*-glycolide) is biodegradable and biocompatible with brain tissue. Owing to their size, these microspheres can be easily implanted by stereotaxy in discrete, precise, and functional areas of the brain without causing damage to the surrounding tissues. Brain tumor treatments were developed using this approach [93]. Biodegradable nano/microparticles of poly(DL-lactide-*co*-glycolide) and PLGA-based polymers are widely investigated as carriers for controlled delivery of macromolecular therapeutics such as proteins, peptides, vaccines, genes, antigens, and growth factors. These devices

are mainly produced by emulsion or double-emulsion technique followed by solvent evaporation or spray-drying. Drug encapsulation, particle size, molecular weight (MW), ratio of lactide to glycolide in PLGA, and surface morphologies could influence the release characteristics. Encapsulation efficiency and release rates through nano/microparticle-mediated drug delivery devices can be optimized to improve their therapeutic efficacy [94].

Owing to their absorbability, poly(glycolide) devices were used in trauma and bone surgery [95]. Ultra-high-strength implants are manufactured from PGA and/or PLA polymers using self-reinforcing techniques. The implants are available for stabilization of fractures, osteotomies, bone grafts, and fusions, as well as for reattachment of ligaments, tendons, meniscal tears, and other soft tissue structures. As these implants are completely absorbed, the need for a removal operation is overcome and long-term interference with tendons, nerves, and the growing skeleton is avoided. This kind of implants does not interfere with clinical imaging [96].

1.3.1.3 Poly(caprolactone)

PCL is an aliphatic polyester composed of hexanoate repeat units. It is a semicrystalline polymer with a degree of crystallinity which can reach 70%. The physical, thermal, and mechanical properties of PCL depend on its molecular weight and its degree of crystallinity [97]. As early as in 1921, Windaus *et al.* [98] found that the degradation of certain cholesterol derivatives led to obtain hydroaromatic acids of the glutaric acid series which are very difficult to oxidize and do not undergo a smooth thermal degradation. In the presence of silver salt, a good yield of lactone such as γ-caprolactone is obtained. In 1934, Van Natta *et al.* [99] published the first paper on synthesis of ε-caprolactone and its polymer where ε-caprolactone on heating can be converted to a polymer of high molecular weight. The process is not easily reversible. Berens [100] introduced a way to make a PCL polyester copolymer with haloethylene. The copolymers consist of a mixture of 50–98 wt% haloethylene and 2–50 wt% of a PCL polyester. Polyester polyols with OH end groups and MW 300–3000 are prepared by ring-opening polymerization of ε-caprolactone in the presence of water, alkylene oxides, transesterification, or alkoxylation catalysts Bu_2SnO, and possibly diepoxides and tertiary amines under 30 atm pressure [101]. PCL is a biodegradable polyester with a low melting point of around 60 °C and a glass transition temperature of about −60 °C. It is prepared by ring-opening polymerization of ε-caprolactone using a catalyst such as stannous octoate [102].

PCL is commonly used in the manufacture of polyurethanes because of its imparting good water, oil, solvent, and chlorine resistance to the polyurethane produced. In 1934, Carothers *et al.* [103] prepared epsilon-caprolactone for the first time. Under the condition of heat epsilon-caprolactone is converted to a polyester of high molecular weight. The 1965, Magnus [104] published details of his study of effects of components and varying –NCO/–OH or –NCO/–NH_2 group ratio on the low-temperature properties, hydrolytic and heat stability, and solvent and chemical resistance of the polyurethane elastomers. It was found that

as the –NCO/–OH or –NCO/–NH_2 group ratio increased, the deformation of the polymer decreased, and the tensile strength and modulus increased. In 1981, stannous octoate was used as catalyst in making polyfunctional adhesives, tackifiers, fillers by ring-opening reaction of ε-caprolactone with poly(vinyl alcohol) [105]. In 1982, Busfield [106] systematically studied the mechanical properties of some PCL-based, cross-linked, crystallizable polyurethanes. It was disclosed that crystallization in these polymers is facilitated by (i) decreasing cross-link density, (ii) increasing length of PCL segment, and (iii) using a flexible aliphatic diisocyanate as linking unit. The crystallization can be easily prevented by quenching with liquid nitrogen from the melt. Therefore, the mechanical properties as Young's moduli were enhanced markedly by increasing the PCL segment length and less markedly by increasing the cross-link density. Replacing the aromatic linking units by aliphatic crosslinker decreases Young's moduli in the glassy region. In the rubbery region, Young's modulus is enhanced by having shorter PCL segment lengths or by the presence of the more rigid linking unit diphenylmethane diisocyanate and is decreased very significantly at low cross-link densities. Young's modulus is not enhanced by heavier cross-linking in the rubbery region. The above study is a good sample for structure-property of polyurethanes.

Synthesis In general, the anionic ring-opening polymerization of lactones involves a number of specific features that have to be taken into consideration for the optimization of the synthesis: for example, the nature of the propagating site, the slow initiation rate, the ability of the active sites to react with functional links [97, 98]. An alkoxide (or a carbanionic species) may attack lactones and lead to ring opening in two different ways: (i) by scission of the *O*-alkyl bond or (ii) by cleavage of the *O*-acyl linkage. In the former case, the propagating site is a carboxylate, whereas in the latter case, it is an alkoxide [107] (Figure 1.7).

Carboxylates are much weaker nucleophiles than alkoxides, and they are unable to give rise to an *O*-acyl scission upon attack of another lactone molecule. The consequence is that once the propagation site is a carboxylate, it stays as such. Only if the probability of *O*-acyl scission is equal to unity can one be sure that all propagation sites are alcoholates, even at high conversions. At various degrees of conversion, all experimental data showed that the propagating sites are alkoxides until the end of the reaction.

Normally, the polymerization is conducted at low temperature because the activation energy for chain growth is generally rather low, which means that the variation of the rate of propagation with temperature is not very large.

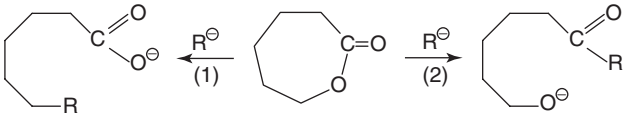


Figure 1.7 Two different ways of ring opening: (1) by scission of the *O*-alkyl bond or (2) by cleavage of the *O*-acyl linkage.

For instance, a polymerization of ε-caprolactone was carried out in two steps: (i) pretreatment of raw materials and (ii) polymerization. ε-Caprolactone was purified by distillation over calcium hydride under reduced pressure, b.p. 117 °C at 20 mbar. Tetrahydrofuran (THF) was distilled twice, over sodium first and then from a dilute solution of sodium benzophenone in THF. 1,1-Diphenyl-3-methylpentyllithium is obtained by addition of *sec*-butyllithium (BuLi) on 1,1-diphenylethylene (DPE). This initiator is prepared at −60 °C in anhydrous THF. 1,4-Dilithio-1,1,4,4-tetraphenylbutane was synthesized from lithium and DPE in THF at room temperature. The polymerizations were conducted in tight reactors, under inert atmosphere. The THF was cooled down to −90 °C, a few drops of initiator 1,1-diphenyl-3-methylpentyllithium were used to neutralize solvent impurities. Then, more amount of the initiator was added, the concentrations of which ranged from 5×10^{-4} to 10^{-3} mol L^{-1}. The initial concentration of the monomer was kept at 0.5 mol L^{-1}. The monomer (diluted in THF) was added slowly. Initiation was not instantaneous: the red color vanished after approximately 30 min. The propagation step was carried out between −20 and −10 °C. The polymerization was stopped with a few drops of acetic acid at rather low conversion (30%), after a period of 2–10 min, depending upon the desired molecular weight. The monomer conversion was determined from the size exclusion chromatography (SEC) diagrams obtained on polymerization mixtures [107].

Chemical and Physical Properties The major physical and mechanical properties of poly(caprolactone) are summarized briefly in Table 1.5. Its physical and mechanical properties depend mainly on its molecular weight and crystallinity. In general, aromatic and some polar solvents such as benzene, toluene, cyclohexanone, dichloromethane and 2-nitropropane are good solvents for PCL. Water, alcohols, petroleum ether, diethylether are poor solvents for PCL. PCL can be slightly soluble in acetonitrile, acetone, 2-butanone, ethyl acetate and dimethylformamide. PCL has high polymer-polymer miscibility with most of the other polymers such as poly(vinyl chloride), poly(styrene-acrylonitrile), poly(acrylonitrile butadiene

Table 1.5 Properties of poly(caprolactone) [97].

Property	Range
Number average molecular weight (M_n/g mol^{-1})	530–630 000
Melting temperature (T_m/ °C)	56–65
Glass transition temperature (T_g/°C)	(−65) to (−60)
Density (g cm^{-3})	1.071–1.200
Decomposition temperature (°C)	350
Inherent viscosity (η_{inh}/cm^3 g^{-1})	100–130
Intrinsic viscosity (η_{int}/cm^3 g^{-1})	0.9
Tensile strength (σ/MPa)	4–785
Young modulus (E/GPa)	0.21–0.44
Elongation at break (ε/%)	20–1 000

styrene), poly(bisphenol-A), polyethylene, polypropylene and natural rubber etc. Due to the low glass transition temperature, PCL is soft and has high flexibility. Since its low melting point (Table 1.5), PCL is readily for processing and moulding [57,97].

Applications Homopolymers of ε-caprolactone and its copolymers with dilactide or ε-decalactone were prepared for biodegradable controlled drug delivery systems [108]. Release rates from PCL and related biodegradable polyesters were studied by Pitt *et al.* [109]. They investigated several steroids from films and capsules of homopolymers and copolymers of ε-caprolactone, DL-lactic acid and glycolic acid were measured *in vitro* and *in vivo* for up to 500 days. Relatively constant release rates from capsules were observed only under certain conditions. Release from PCL and poly(ε-caprolactone-DL-lactic acid) was diffusion controlled. Release from poly(DL-lactic acid-glycolic acid) was associated with polymer degradation. Release from poly(DL-lactic acid) was very slow when diffusion controlled. Owing to the bioerosion and permeability [110], PCL and poly(DL-lactic acid) as drug carriers were applied in the long-term delivery (1 year) of levonorgestrel, a contraceptive agent, and the short-term delivery (1–2 months) of naltrexone, a narcotic antagonist.

1.4 Concluding Remarks

In this short chapter, two giant polymer scientists Staudinger and Carothers and their contributions to the origin and further development of polymer science as well as some historical records on the synthesis of polyamides and polyesters were briefly overviewed. Three well-known biodegradable polyesters, namely, PLA, PGA, and poly(caprolactone) were selected to described their synthesis, structures, properties, and applications. Owing to the similarity of the biodegradable polyesters in synthesis, properties, and applications, this chapter aims to give readers a general outline about biodegradable polyesters. A few biodegradable polyesters listed in Table 1.1 are not described in the similar detail in this chapter. Biodegradable polyesters have intensively been researched in the last two decades because of their biodegradability and superb physical properties. Recently, nanomaterials, nanotechnology, and the opportunities for wider medical applications have resulted in much more attention being directed to this class of polyesters, as can be concluded from the examples described in other chapters of this book.

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