Polylactic-*Co*-Glycolic Acid (PLGA)

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INTRODUCTION

Poly(lactide-*co*-glycolide) (PLGA) is a synthetic copolymer of lactic acid (α-hydroxy propanoic acid) and glycolic acid (hydroxy acetic acid). Lactic acid contains an asymmetric carbon atom, and therefore has two optical isomers: L(+) lactic acid and D(−) lactic acid. Lactic acid is present in nature as either an intermediate or an end product in carbohydrate metabolism. It is widely distributed in all living creatures (man, animals, plants, and microorganisms). Glycolic acid occurs in nature to a limited extent. Poly(lactide-*co*-glycolide) degrades in vivo to innocuous products. Its final degradation products are lactate (salt form of lactic acid) and glycolate (salt form of glycolic acid).

Poly(lactide-*co*-glycolide) can be synthesized by direct polycondensation of lactic acid and glycolic acid. However, the most efficient route to obtain high-molecular weight (MW) copolymers is the ring opening polymerization of lactide and glycolide. Lactide and glycolide are the cyclic diesters of lactic acid and glycolic acid, respectively, and they are prepared by thermal degradation of lactic and glycolic acid oligomers, respectively. Being a biocompatible and biodegradable polymer with adjustable properties and capable of being processed to form a variety of objects, PLGA finds extensive biomedical applications, such as sutures, orthopedic fixation devices, and drug delivery systems. Poly(lactide-*co*-glycolide) scaffolds are investigated for tissue engineering applications. The synthesis, properties, and biomedical applications of PLGA are discussed in this entry.

SYNTHESIS OF PLGA

Poly(lactide-*co*-glycolide) can be prepared by the direct polycondensation of lactic and glycolic acid (Scheme 1). The polycondensation reaction can be effected in solution or in the melt/solid state.

As a high degree of dehydration, required for the production of high-MW polymer, is difficult to achieve, polycondensation was considered to be an inadequate method to obtain high polymers.[1] However, Ajioka et al. prepared high-MW (160 kDa) poly(L-lactic-*co*-glycolic acid) by azeotropic dehydration of a solution of L-lactic acid and glycolic acid in diphenylether for 20–40 hr at 130°C using tin powder as catalyst.[2] The solvents introduce complexity of both process control and purification of the end product. Therefore, polycondensation is preferred to be effected in the melt state. The melt polycondensation system involves two equilibria: the dehydration/hydration for ester formation and the ring/chain equilibrium for cyclic diester formation. In ordinary melt polycondensation, the cyclic diesters lactide and/or glycolide (Scheme 2) are formed by depolymerization because the reaction conditions of high temperature and high vacuum can induce not only dehydration but also formation of the cyclic diesters in equilibrium with the polymer. This prevents further growth of the polymer chain, and a high-MW polymer cannot be obtained.

To overcome this problem, a melt/solid polycondensation method was recently developed (Scheme 3).[3] In the first step, oligomers are prepared by dehydration of monomers. In the second step, the oligomers are melt-polymerized under vacuum (10 Torr) using, for example, zinc acetate dihydrate or tin chloride dihydrate/*p*-toluenesulfonic acid as catalysts. A third step then follows in which condensation is continued at the solid state for 10 hr under high vacuum (0.5 Torr). It is believed that in the solid state, the polymerization reaction is favored over the depolymerization or other side reactions. With this melt/solid polycondensation method, polymers with MW comparable to the polymers produced by the ring opening polymerization of the cyclic diesters can be produced.

To prepare high-MW PLGA in a relatively short reaction time, it is necessary to proceed by ring-opening polymerization of the cyclic diesters, lactide, and glycolide (Scheme 4). Lactide and glycolide are produced by thermal degradation of lactic and glycolic acid oligomers, respectively, and are commercially available. As the lactide molecule bears two asymmetric carbon atoms, lactide exists in the form of three diastereoisomers (L-, D-, and *meso*-lactide) and a racemate (50/50 mixture of L- and D-lactides commonly referred to as DL-lactide) (Scheme 2). The ring opening polymerization reaction can be conducted at temperatures higher than the melting point of the polymer (melt polymerization), at temperatures lower than the

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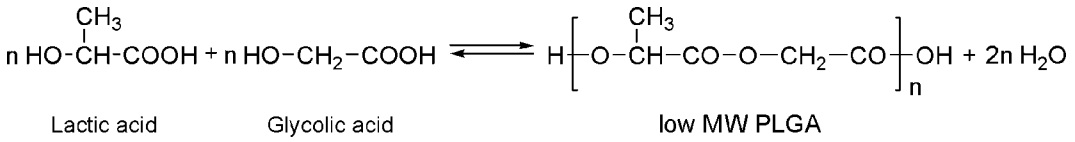


Scheme 1 Polycondensation of lactic and glycolic acid.

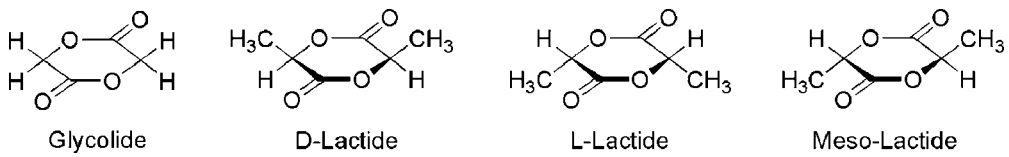
melting point of the polymer (solid-state polymerization), or in solution.

Polymers having high MW can be synthesized using a variety of catalysts, such as powdered zinc, Lewis acids (e.g., zinc chloride and antimony trifluoride), or organometallic compounds (e.g., triethyl aluminum or stannous octoate).[1,4,5] Stannous octoate is the most commonly used catalyst because of its acceptance by the U.S. Food and Drug Administration as a food stabilizer. When organometallic catalysts, such as diethyl zinc, are employed, the polymerization reaction is considered to follow a coordination mechanism.[6] The initiation of the reaction is considered to involve a nucleophilic attack of the catalyst species on one of the lactide or glycolide carbonyls leading to the opening of the ring and formation of active species. Lactide/glycolide molecules are then coordinated to the active species to create the polymer chain (Scheme 5).

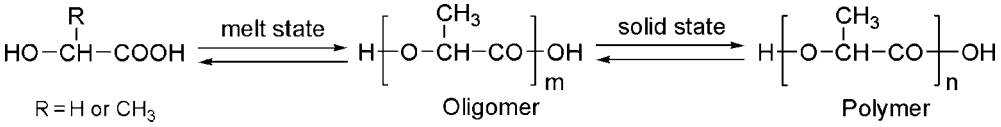
The situation with the stannous octoate-catalyzed polymerization is more complex. Based on kinetic and spectroscopic data, Kowalski, Duda, and Penczek concluded that stannous octoate is by itself neither an initiator nor a catalyst of lactide polymerization.[7] Reaction of stannous octoate with hydroxyl containing compounds (e.g., alcohols and water), added in the polymerization feed or present as impurities of stannous octoate, provides the initiating species. Chain growth proceeds by a coordination–insertion mechanism in the $\cdots$Sn–OR bond in a similar way to that shown for $\cdots$Zn–OR, as shown in Scheme 5.[7,8] Transesterification reactions toward the conclusion of polymerization (i.e., at high conversion) may cause a broadening of the MW distribution.[5,6] The polymerization was found to be first order with regard to the monomer (lactide/glycolide) concentration.[6,7] The rate of polymerization was initially increased with the concentration of stannous octoate in the polymerization feed, but after reaching a maximum it eventually decreased with further increasing stannous octoate concentration.[7]

Owing to chain growing by dimer (lactide or glycolide) addition (Scheme 5), the polymer chains that result from the ring opening polymerization of lactide and glycolide are actually polydimer chains. Thus, PLGA formed by ring-opening polymerization of lactide and glycolide is more accurately referred to as poly(lactide-*co*-glycolide). Because of the addition of pairs of repeating units during chain growth, and the existence of different stereoisomers of lactide, poly (lactide) (PLA) homopolymers and PLGA copolymers having different and rather complex configurational structures can be obtained through ring-opening polymerization. Using different mixtures of lactide stereoisomers, stereocopolymers (PLA and PLGA polymers containing L- and D-lactic acid units) having different physical and biological properties can be synthesized.[4]

Lactide and glycolide of high purity are required to obtain high-MW copolymers. The exclusion of moisture is also essential because it may cause termination of the chain growth or hydrolysis of the monomers to acidic products. Thus, the polymerization is carried out either in high vacuum or in inert atmosphere (e.g., in nitrogen). In practice, the amount and type of the catalyst determine the temperature and the time required to produce high-MW polymer in high yield. As a rule, the higher the amount of catalyst the shorter the time required to produce high-MW polymer. Also, the amount of catalyst required to produce high-MW polymer decreases as the temperature of polymerization increases.[9] When organometallic catalysts, such as triethyl aluminum and stannous octoate, are employed in lactide/glycolide polymerization, the MW of the polymer initially increases sharply with the catalyst level, and after reaching a maximum it eventually decreases with further increase of the catalyst level.[1,9,10] The ascending part of the polymer MW vs. catalyst level curve, observed at low catalyst/monomer ratios, may be attributed to the increased rate of polymerization with increasing catalyst levels. The descending part of the polymer MW



Scheme 2 Structures of glycolide and lactide.



Scheme 3 Melt/solid polycondensation of lactic and glycolic (R=H) acid.

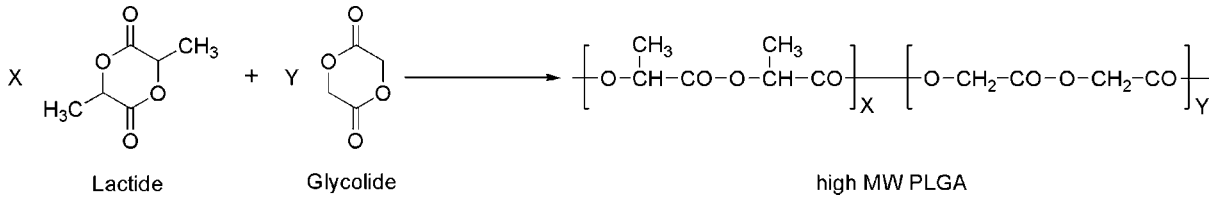
vs. catalyst-level curve, observed at high catalyst/monomer ratios, may be attributed to the formation of a higher number of initiating species at high catalyst levels. A higher number of initiating species would initiate a greater number of polymerization reactions, leading to the formation of relatively small chains, i.e., to a decreased MW of the synthesized polymer. In support of the latter consideration, Kricheldorf, Kreiser-Saunders, and Stricker, using relatively high stannous octoate proportions in L-lactide polymerizations at 180°C, found that the MWs of synthesized polymers paralleled the monomer/stannous octoate ratio.[8] As glycolide is more reactive than lactide, PLGA copolymer chains may contain blocks of glycolide units rather than a random distribution of glycolide and lactide units.[5] Indeed, PLGA copolymers produced by melt polymerization under vacuum were found to have heterogenous microstructure, based on ^{13}C-NMR spectra.[9]

The ring-opening polymerization of lactide and glycolide in bulk (melt or solid polymerization) is usually carried out at temperatures ranging between 130°C and 220°C over a period of 2–6 hr. Stannous octoate is added at 0.03–0.1% w/w proportions. Under these conditions, copolymers with molecuar weights in the range 10^4–10^5 are prepared at high conversions (higher than 90%).[5] Long reaction periods at high temperatures may cause significant depolymerization (chain unzipping) and should therefore be avoided.[9,10] It is pertinent to remember here that the cyclic diesters lactide and glycolide are prepared by thermal breakdown of low-MW PLA and PGA, respectively. For PLGA copolymers synthesized under identical conditions, increasing the glycolide content of the feed resulted in copolymer of lower MW, indicating that more severe reaction conditions are required to polymerize glycolide than lactide.[9] A pilot-scale polymerization process for the preparation of PLGA has been described in detail.[11]

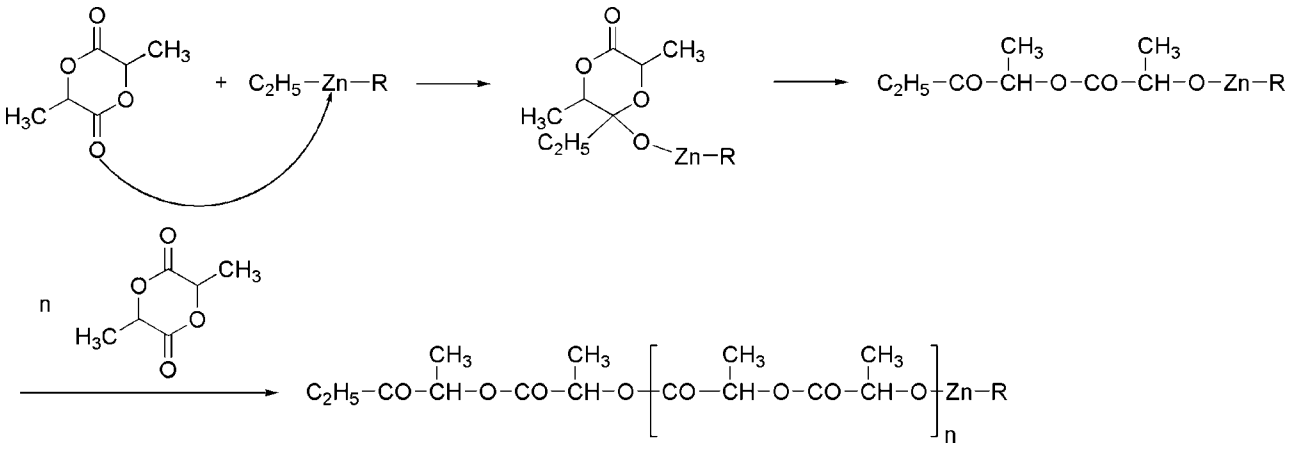
As previously mentioned, minor reactions, such as ester interchange and chain unzipping, may take place during lactide/glycolide polymerization, which lead to the formation of low-MW species (e.g., cyclic dimers, trimers, cyclic oligomers, and even monomers). These, together with unreacted monomers and catalyst residues, may adversely affect the properties of the final product, such as mechanical strength and degradation rate, and should therefore be removed by careful purification (once or twice) of the crude polymer. The purification can be effected by first dissolving the polymerization product in dichloromethane or chloroform and then precipitating the polymer in excess methanol or diethyl ether. The purified polymer is collected by filtration and dried. Alternatively, after the polymerization is complete, residual monomers are removed from the polymer melt by applying vacuum.[11] The purified polymer is stored under vacuum or is packaged under nitrogen in moisture-proof packages.

POLY(LACTIDE-*CO*-GLYCOLIDE) PROPERTIES

A distinct advantage of PLGA copolymers, and the one that characterizes this family of polymers, is that they can be designed so as to acquire specific, desired properties. A broad spectrum of performance characteristics can be obtained by careful manipulation of three key properties of the copolymer: composition (lactide/glycolide ratio), lactide stereoisomeric composition (L- or DL-lactide), and MW. The notation L-PLGA(X:Y) or DL-PLGA(X:Y) will be used in this entry to describe PLGA copolymers consisting of X mol% L- or DL-lactide, respectively, and Y mol% glycolide.



Scheme 4 Ring opening polymerization of lactide and glycolide.



Scheme 5 Coordination mechanism of polymerization of lactide.

Solubility

Solubilty in common organic solvents is important with regard to the ease of polymer characterization, processing, and application. Poly(lactide-*co*-glycolide) containing less than 50% glycolyl units (glycolic acid units) is soluble in most common organic solvents, such as halogenated hydrocarbons (chloroform and dichloromethane), ethyl acetate, acetone, dioxan, and tetrahydrofuran. Poly(lactide-*co*-glycolide) rich in glycolyl units (50% and higher) is insoluble in most organic solvents, and uncommon solvents, such as hexafluoroisopropanol, have been used in characterization and processing of PLGA with high content of glycolyl units.

Crystallinity

Crystallinity affects the rate of degradation and the mechanical properties of PLGA. Poly(lactide-*co*-glycolide) crystallinity depends on chemical composition (lactide/glycolide ratio) and stereoisomeric composition of lactide units in the copolymer.[5,12] Poly(DL-lactide-*co*-glycolide) consisting of 0–75% glycolyl units is amorphous. Poly(L-lactide-*co*-glycolide) with 25–75% glycolyl units is also amorphous. The crystallinities, glass transition temperatures, and melting points of poly(L-lactide-*co*-glycolide) copolymers are presented in Fig. 1.

Thermal Stability

Poly(lactide-*co*-glycolide) copolymers are thermoplastic materials exhibiting adequate heat stability in the absence of moisture. Thus, they can be melt processed to produce sutures, orthopedic fixation devices, and drug delivery systems. Poly(lactide-*co*-glycolide) degrades to lactide and glycolide after prolonged heating above 200°C under nitrogen or vacuum.[5] At lower temperatures, thermal degradation is a function of time and temperature and is considerably accelerated by impurities, residual monomers, and humidity.

Mechanical Properties

The mechanical properties (strength, toughness, and elasticity) of PLGA depend on composition (lactide/glycolide ratio), lactide stereochemistry, MW, and

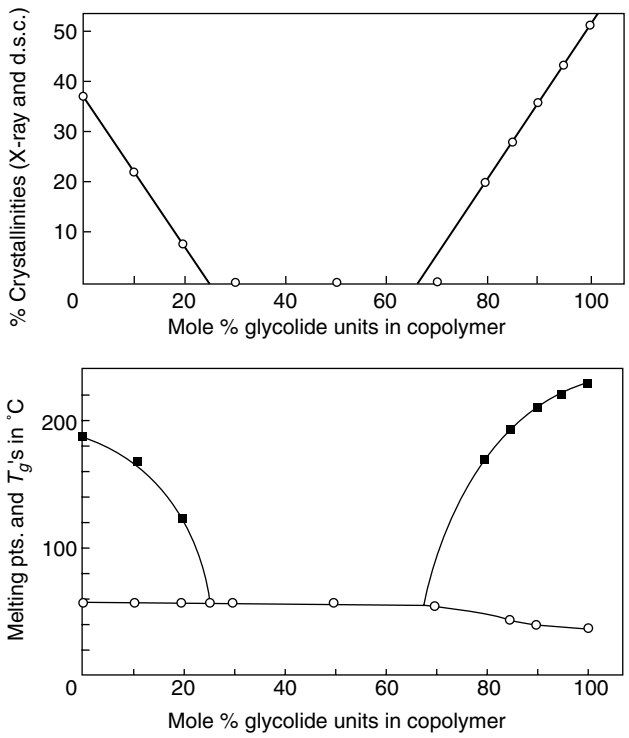


Fig. 1 Crystallinities (upper graph) and glass transition temperatures (○) and melting point (■) (lower graph) for lactide/glycolide polymers. (From Ref.[5].)

processing.[12,13] Crystalline polymers, such as poly (L-lactide) and poly(glycolide), exhibit significantly higher mechanical strength than the amorphous poly (DL-lactide) and the amorphous or less crystalline PLGA. Certain mechanical properties of commonly used lactide/glycolide polymers are presented in Table 1.

Degradation

Poly(lactide-*co*-glycolide) degrades in vitro through hydrolysis of ester bonds. The final degradation products in vitro are lactic acid and glycolic acid. Poly(lactide-*co*-glycolide) degradation has been proposed to be a two-stage process.[14] During the first stage, random hydrolytic cleavage of ester bonds occurs, leading to MW reduction. The chain scission process appears to follow first-order kinetics. The second stage is characterized by the onset of mass loss from the polymer matrix, accompanied by an increase in the rate of chain scission. Mass loss begins when the polymer has been degraded to a degree where chain fragments small enough to dissolve in the degradation medium and diffuse out from the polymer matrix have been generated. Because esterification of carboxylic acid chain ends (end-capping) to reduce the initial carboxylic end group concentration was shown to retard degradation, chain scission is believed to be autocatalyzed by the generated carboxylic acid end groups.[14,15]

After the early work on PLGA, hydrolytic degradation was regarded as homogenous (bulk erosion).[14] However, more recent research has shown that relatively large-sized PLGA devices degrade (both in vitro and in vivo) through a heterogenous process, with the degradation of the core being faster than that of the surface of the device.[16] In Fig. 2, the core of poly(DL-lactide-*co*-glycolide) (50 : 50) matrices (cylindrical tablets) was completely degraded (dissolved away, so that the matrix appeared to be centrally hollow under the electron microscope) after 20 days' incubation in phosphate buffer, pH 7.4.[17] Vert and coworkers introduced the concept of heterogenous PLGA degradation related to ''diffusion–reaction–dissolution'' phenomena: the soluble oligomers that eventually form during polymer degradation can escape faster from the surface than from the interior of the matrix, resulting in a smaller autocatalytic effect at the carboxyl-depleted surface and, consequently, a lower degradation rate at the surface than in the interior of the matrix.[16] According to the diffusion–reaction–dissolution model, relatively large PLA devices, which degrade via a heterogenous mechanism, were found to degrade faster than relatively small PLA devices that degrade via a homogenous mechanism.[16]

In vivo degradation of PLGA proceeds through hydrolysis of ester bonds, as the in vitro degradation. No involvement of the living tissues (cells and enzymes) is considered to take place during the early stages of degradation, apart from that resulting from the foreign body response. During foreign body reaction, cells accumulating around the polymer implant may produce free radicals and acidic products that could accelerate polymer hydrolysis. Enzyme-catalyzed PLGA degradation in vivo has been claimed by some investigators based on differences between the in vitro and the in vivo degradation characteristics. Although degradation has been shown to be accelerated by enzymes in vitro, no convincing data have been presented for enzymatic hydrolysis of PLGA in vivo.[18] Enzymes are not the only body constituent that could affect PLGA degradation. Phenomena like adsorption of proteins, absorption of lipids, and greater solubility of PLGA oligomers in blood may be the sources of differences between the in vitro and in vivo degradation.[19] However, when degradation has advanced to the stage that implant coherence is lost and the matrix begins to fragment, living tissues participate actively in further polymer degradation; small enough fragments (less than 10 μm) are assimilated by phagocytes and are further hydrolyzed intracellularly to monomeric anions (lactate and glycolate).[11,20] Lactate and glycolate are also the final products of PLGA extracellular hydrolysis. The

Table 1 Mechanical properties of commercially available lactide and glycolide homopolymers and copolymers

Polymer type	Tensile strength (psi $\times$ 10^{-3})	Elongation (%)	Modulus (psi $\times$ 10^{-5})
L-PLA	8–12	5–10	4–6
DL-PLA	4–6	3–10	2–4
DL-PLGA(85 : 15)	6–8	3–10	2–4
DL-PLGA(75 : 25)	6–8	3–10	2–4
DL-PLGA(65 : 35)	6–8	3–10	2–4
DL-PLGA(50 : 50)	6–8	3–10	2–4
PGA	>10	15–20	10

Information was provided by the suppliers.

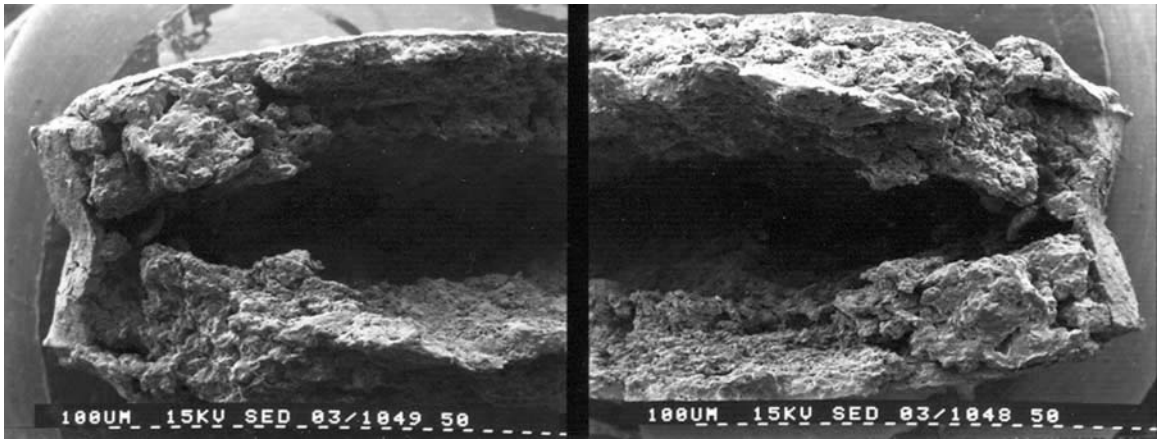


Fig. 2 Scanning electron microscope picture of a DL-PLGA (50 : 50) tablet after 20 days of incubation in phosphate buffer, pH 7.4 at 37°C. (From Ref.[17].)

final stage of in vivo degradation is elimination. During this stage, L-lactate is converted into carbon dioxide and pyruvate. Pyruvate then enters the Krebs cycle. D-Lactate is not metabolized and has only been detected in excreta.[1,21] Glycolate is excreted directly in the urine or may be oxidized to glyoxylate, which is then converted to glycine, serine, and pyruvate. Pyruvate then can enter Krebs cycle, as before, with lactate.[11] Several studies reported that PLGA degrades at similar rates in vitro (in media modeling body fluids) and in vivo. Other studies, however, found faster PLGA degradation in vivo than in vitro. This discrepancy is probably due to differences in the experimental conditions, degradation parameters measured, and types of polymers involved in these studies. From a PLGA device development perspective, an in vivo degradation rate higher to that measured in vitro in simulated body fluids should be taken into account.

The factors affecting the rate of PLGA degradation are well documented in the literature and are those related to the following.[20,22,23]

1. Polymer characteristics, such as chemical composition (lactide/glycolide ratio) monomer distribution pattern, chain-ends chemical composition, MW, MW distribution, and polymer purity (e.g., residual monomers).[24]
2. Device characteristics, such as size, shape, porosity, and presence of additives (e.g., acidic or basic compounds, plasticizers, or drugs).
3. Melt-processing, annealing, and sterilization.
4. Environment in which degradation takes place, such as site of in vivo implantation, and the pH and temperature of the degradation medium.

Chemical composition and lactide stereoisomeric composition are the most influencing factors for PLGA degradation as they determine, among other properties, the hydrophilicity and the crystallinity of the polymer. Among the first to evaluate the effect of composition on PLGA degradation rate in vivo were Miller, Brady, and Cutright.[25] They found that PLGA (50 : 50) was the fastest degrading composition, with the degradation rate being decreased when either lactide or glycolide content of the copolymer was increased (Fig. 3). Although the degradation rates reported may be a little higher than those obtained in recent years, probably due to better standardization of the experimental conditions and better characterization of polymers in more recent degradation studies, the trends shown in Fig 3 have been confirmed by studies conducted after the work of Miller, Brady, and Cutright.[25]

The effect of composition on PLGA degradation (Fig. 3) can be explained based on the combined effects

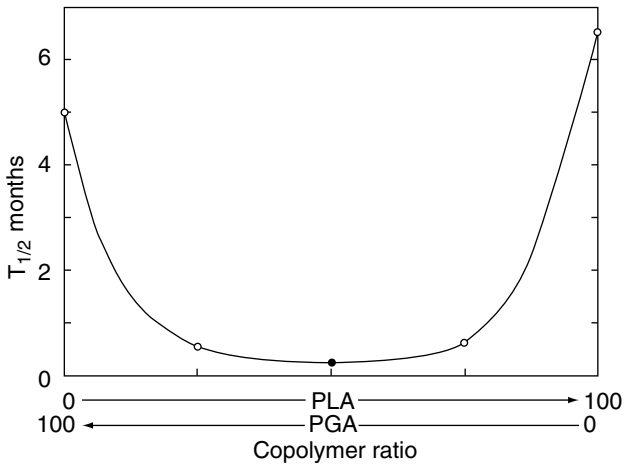


Fig. 3 Half-life in months of lactide/glycolide polymers implanted in rat tissue. (From Ref.[25].)

that the changes of composition have on copolymer hydrophilicity and crystallinity. An increase in hydrophilicity increases the rate of PLGA degradation, whereas an increase in crystallinity has the opposite effect. Hydrophilicity increases as the proportion of the more hydrophilic glycolide in the copolymer increases and crystallinity increases as the proportion of glycolide or L-lactide units exceeds 75% (Fig. 1). Increased hydrophilicity and decreased crystallinity account for the increased PLGA degradation rate as the lactide content decreases from 100 mol% to 50 mol% (Fig. 3). In addition, glycolic linkages are hydrolyzed faster than the lactic linkages and this may also contribute to the observed increase in degradation rate with increasing glycolide content of PLGA copolymers from 0 to 50 mol% glycolide (Fig 3).[22] However, with a further increase of the glycolide content, crystallinity of the copolymer increases and outweighs the effect of increased copolymer hydrophilicity on degradation. The net result is a decrease in degradation rate as the glycolide content of PLGA increases from 50 to 100 mol% (Fig 3). By changing the lactide/glycolide ratio and lactide stereoisomeric composition, polymers having in vivo degradation times from a few weeks to more than 2 yr can be produced (Table 2).

Not only the monomer proportion, but also the distribution pattern of the two monomers in the copolymer chains (copolymer ''microstructure'') may affect the degradation of PLGA copolymers that are rich in glycolide. As glycolide is more reactive than lactide, these copolymers may contain blocks of glycolide rather than a random sequence of glycolide and lactide.[5] At the same monomer ratio, the copolymers having a homogenous microstructure (random monomer sequence) are expected to degrade faster than the copolymers having a heterogenous microstructure.[26]

Poly(lactide-*co*-glycolide) degradation time increases with the average MW of the copolymer.[15,27] Apart from the average MW, the MW distribution may also affect PLGA degradation. A wide MW distribution would indicate the presence of relatively large numbers of carboxylic end groups, which can facilitate the autocatalytic degradation of the polymer chains.[20]

The chemical composition of chain ends could significantly affect PLGA degradation. The chemical composition of the chain terminus depends on the type of catalyst/initiator used in polymerization, but it can be modified after PLGA preparation. It has been reported, for example, that stannous octoate causes chain-end modification by esterification of alcoholic end groups by octanoic acid and generates hydrophobic residues.[28] Such modifications do not occur with zinc metal or zinc lactate initiators, and, as a result, these initiators provide PLGA polymers with different physicochemical and degradation properties as compared with stannous octoate. The influence of the chain-end composition on PLGA degradation has been exploited by PLGA suppliers (e.g., Boehringer Ingelheim in Germany and Alkermes in the United States), which have commercialized copolymers with free carboxyl end groups exhibiting faster degradation than normal copolymers of the same composition but with ester end groups (Table 2).

Sterilization by ionizing γ- or β-rays has been shown to cause radiation dose-dependent degradation of PLGA.[5,29] On the contrary, sterilization by ethylene oxide does not appear to adversely affect PLGA properties. Both γ irradiation and ethylene oxide have been applied to sterilize commercial PLGA devices. Recently, plasma sterilization was introduced as a sterilizing method for polyester devices. A low-temperature radiofrequency plasma treatment was applied to sterilize PLA pins. Treatment with oxygen or carbon dioxide plasmas at a power of 100 W for 15 min sterilized the pins efficiently. The method caused a slight increase of the MW of the polymer, whereas it did not adversely affect the crystallinity and the mechanical properties of the polymer.[30]

Table 2 Approximate resorption times of commercially available lactide and glycolide homopolymers and copolymers

Polymer	Biodegradation time (months)
L-PLA	>24
DL-PLA	12–16
DL-PLGA (85 : 15)	5–6
DL-PLGA (75 : 25)	4–5
DL-PLGA (50 : 50)	1–2
DL-PLGA (50 : 50) H[a]	<1
PGA	6–12

Information was provided by the suppliers.
[a]Copolymer with free carboxyl end groups.

Biocompatibility and Tissue Reactions

The biocompatibility and nontoxicity of PLGA polymers were first demonstrated with the application of these polymers in the production of biodegradable sutures. Dexon (PGA) and Vicryl L-PLGA (8 : 92) sutures have successfully been used in the clinic for more than 30 yr.

In general, host responses to a polymeric implant are affected by polymer physical and chemical properties and implant properties (volume, shape, and surface characteristics) and are considered to be tissue-dependent, organ-dependent, and species-dependent.[20] Several studies have shown that PLGA implantation in bone or soft tissues of animals causes none or only a mild inflammatory response, which diminishes with

time.[31–33] No toxicity or allergic responses were observed.

Soft tissue responses to PLGA occur in three phases.[20] The first phase includes the initiation, resolution, and organization of the acute and chronic inflammatory response. A minimal inflammatory reaction with the presence of polymorphonuclear leukocytes, lymphocytes, plasma cells, and monocytes is observed. The second phase is characterized by the presence of foreign body reactions with the accumulation of monocytes, which differentiate to macrophages, which in turn may fuse or join together to form giant cells, and fibroblast infiltration, which leads to implant encapsulation (and progressive invasion) by connective tissue. Formation of blood capillaries (neoangiogenesis), which surround and invade the implant, is also observed. The third phase is characterized by implant fragmentation and phagocytosis of small fragments by macrophages and foreign body giant cells. Also, fiber formation and neovascularization are enhanced and connective tissue replaces the resorbed polymer. The duration of the second and third phases depends on the rate of polymer degradation. The implants are finally totally resorbed and replaced by connective tissue. Similar responses are observed when PLGA is implanted intraosteally.[31,33] A mild foreign body reaction is elicited on PLGA implantation with accumulation of histiocytes and mast cells in close vicinity to the implant. A bony capsule builds around the implant with a fibrous interface separating the osteoid line from the polymer. Polymer degradation is accompanied by a fibrous and vascular invasion of the cracks that develop. The implant is progressively replaced by bone, and polymer fragments resulting from polymer degradation are surrounded by giant and mononucleated cells. Polymer debris is observed intracellularly. The implant is finally replaced by woven bone.

Clinical trials of PLGA application in man as sutures and fracture fixation devices (rods, pins, screws, and plates) have confirmed the biocompatibility of PLGA polymers.[34–36] Late-stage severe foreign body reactions in about 5–8% of patients with PGA rod implants have been reported.[11] The factors that may contribute to late-stage body reactions are numerous and complex. Polymer purity appears to be important. This is because a much lower incidence of late-stage foreign body reactions has been observed with purified melt processed PLA than with bulk PLA, which may have contained a relatively high level of residual lactide.[11] It has also been suggested that the occurrence of inflammatory reactions may depend on the anatomical region, the capacity of the tissue to

Table 3 Commercially available PLGA sutures, orthopedic fixation devices, and drug delivery systems

Trade name	Manufacturer	Application	Polymer type
Sutures and suture anchors			
Vicryl	Ethicon	Sutures	L-PLGA (8 : 92)
Polysorb	U.S. Surgical	Sutures	L-PLGA
Biologically Quiet Biosphere	Instrument Makar	Suture anchors	DL-PLGA (85 : 15)
Biologically Quiet Mini-screw	Instrument Makar	Suture anchors	DL-PLGA (85 : 15)
SD sorb 2 mm and 3 mm, SD sorb E-Z TAC	Surgical Dynamics	Suture anchors	L-PLGA (82 : 18)
Orthopedic fixation devices			
Biologically Quiet Interference Screw	Instrument Makar	Interference screw	DL-PLGA (85 : 15)
Lactosorb Screws and Plates	Biomet	Craniomaxillofacial fixation	L-PLGA (82 : 18)
Biologically Quiet Staple	Instrument Makar	ACL reconstruction	DL-PLGA (85 : 15)
SD sorb Meniscal Staple	Surgical Dynamics	Meniscus repair	L-PLGA (82 : 18)
BiosorbPDX Screws and Tacks	Bionx	Craniomaxillofacial fixation	Self-reinforced L-PLGA (80 : 20)
SmartPinPDX	Bionx	Fracture fixation	Self-reinforced L-PLGA (80 : 20)
Drug delivery systems			
Zoladex		Delivery of goserelin acetate in prostate cancer	DL-PLGA
Nutropin Depot		Delivery of human growth hormone in growth deficiencies	DL-PLGA
Trelstar Depot		Delivery of triptorelin pamoate in prostate cancer	DL-PLGA
Sandostatin LAR		Delivery of octreotide in acromegaly	DL-PLGA

ACL, Anterior cruciate ligament

clear the degradation products, and the volume of polymer implanted.[37] Tiainen et al. noted that the complications in the use of resorbable polymeric devices reported in the literature mainly concerned homopolymers (L-PLA and PGA) and not PLGA copolymers.[33]

BIOMEDICAL APPLICATIONS

Lactide/glycolide homopolymers and copolymers have been applied in the clinic as sutures, fixation devices in bone surgery (plates, screws, and pins), and drug delivery systems. Commercially available PLGA products are presented in Table 3. Poly(glycolide) and glycolide-rich poly(L-lactide-*co*-glycolide) have good fiber-forming properties and suitable (relatively fast) degradation rate to be applied as sutures.[34]

The use of PLGA in bone surgery offers significant advantages. First, implant degradation obviates the need for a second surgical event for removal. Second, the implant can be engineered to degrade at a rate that will slowly transfer load to the healing bone, resulting in a healed bone, which is strong and has no tendency to refracture on implant removal. The latter is a serious problem with metal implants, where the load is exclusively carried by the rigid implant during bone healing. Crystalline PLA and L-lactide-rich poly(L-lactide-*co*-glycolide) have appropriate mechanical properties (high strength and tensile/flexural modulus), especially when reinforced, and the degradation rate is slow enough to be applied for orthopedic fixation.[38,39] Self-reinforced, amorphous PLGA copolymers of adequate mechanical strength and appropriate rate of in vivo degradation have recently been developed as osteofixation materials in craniofacial surgery.[33]

Amorphous PLGA polymers have received wide attention as excipients in controlled drug delivery systems and as antigen carriers in the development of novel vaccines.[40–42] Apart from their established biocompatibility, the main reason behind the extensive investigation of PLGA polymers for drug delivery applications is their controlled degradation. By controlling the rate of in vivo degradation, the rate of drug release can be controlled and delivery systems with tailor-made drug release properties can be developed. For example, in the area of cancer treatment, a single once-a-month injection of a PLGA depot of goserelin provides a continuous supply of the required amount of drug for 1 mo and has replaced 30 daily injections of the drug. Currently, a number of approved drug products in the market utilize PLGA polymers (Table 3).

Tissue engineering can be used to restore, maintain, or enhance tissues and organs. Poly(lactide-*co*-glycolide) porous scaffolds have been proposed as three-dimensional templates to guide tissue regeneration.[43]

CONCLUSIONS

Poly(lactide-*co*-glycolide) copolymers represent an important family of polymers for medicine. They are biocompatible and biodegradable, degrading in vivo to innocuous products. In some cases, foreign body reactions on in vivo implantation can be minimized by careful control of polymer properties (e.g., purity or degradation rate). Poly(lactide-*co*-glycolide) properties can be tailored for the specific application by simply changing the lactide/glycolide ratio and/or lactide diastereoisomeric structure. Poly(lactide-*co*-glycolide) application in controlled drug delivery and orthopedics has grown in the last two decades and is expected to grow further in the years to come. Owing to the progress in molecular biology and genetics, an ever-increasing number of novel types of drugs (recombinant proteins and genes) will become available. Efficient in vivo administration of these drugs will require the development of novel delivery technologies involving, among others, PLGA carriers. Poly(lactide-*co*-glycolide)-based vaccines, reducing or even eliminating the need for booster immunizations or capable of inducing the appropriate type of immune responses (e.g., cytotoxic T cell responses against viral infections or cancer), will be clinically tested. Tissue engineering is the new field where PLGA copolymers are expected to make a major impact in the near future. Clinical application of PLGA scaffolds in tissue engineering is expected to be realized, when the progress in fabrication techniques and scaffolds properties will allow the PLGA scaffolds to meet important clinical design criteria, such as the ability to be fabricated during surgery and being tailored for specific applications. The scaffolds can be designed to release, at a controlled rate, growth factors that induce cellular differentiation and tissue growth in vitro or cell migration into the wound site in vivo.[44] Copolymers of PLGA with other polymers may also find significant biomedical applications in the years to come. For example, block copolymers of PLGA with poly(ethylene glycol) have been applied for the preparation of surface engineered nanoparticulate drug carriers. These carriers exhibit long-circulation properties in blood following intravenous administration and are currently being investigated for drug-targeting applications.[45]

ARTICLES OF FURTHER INTEREST

Biofunctional Polymers, p. 89.
Bone Plates and Screws, Bioabsorbable, p. 199.
Elastomers, Biodegradable, p. 484.
Poly(Glycolic Acid), p. 1246.
Poly(Lactic Acids), p. 1254.
Polymers, p. 1279.

Sutures, p. 1432.
Tissue Engineering Scaffolds, p. 1630.

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