Synthetic biodegradable polymers as orthopedic devices

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Abstract

Polymer scientists, working closely with those in the device and medical fields, have made tremendous advances over the past 30 years in the use of synthetic materials in the body. In this article we will focus on properties of biodegradable polymers which make them ideally suited for orthopedic applications where a permanent implant is not desired. The materials with the greatest history of use are the poly(lactides) and poly(glycolides), and these will be covered in specific detail. The chemistry of the polymers, including synthesis and degradation, the tailoring of properties by proper synthetic controls such as copolymer composition, special requirements for processing and handling, and mechanisms of biodegradation will be covered. An overview of biocompatibility and approved devices of particular interest in orthopedics are also covered. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Biodegradable; Bioabsorbable; Polylactide (PLA); Polyglycolide (PLG)

1. Introduction

Research in the first half of the 20th century with polymers synthesized from glycolic acid and other α-hydroxy acids was abandoned for further development because the resulting polymers were too unstable for long-term industrial uses. However, this very instability — leading to biodegradation — has proven to be immensely important in medical uses in the last three decades. Polymers prepared from glycolic acid and lactic acid have found a multitude of uses in the medical industry, beginning with biodegradable sutures first approved in the 1960s [1]. Since that time other medical devices, based on lactic and glycolic acid, as well as other materials, including poly(dioxanone), poly(trimethylene carbonate) copolymers, and poly(ε-caprolactone) homopolymers and copolymers, have been accepted for use as medical devices [2]. In addition to these approved devices, a great deal of research continues on polyanhydrides [3], polyorthoesters [4], and other materials [5,6].

Why would a medical practitioner want a material to degrade? There may be a variety of reasons, but the most basic begins with the physician's simple desire: to have a device, which can be used as an implant and will not necessitate a second surgical event for removal. In addition to not requiring a second surgery, the biodegradation may offer other advantages. For example, a fractured bone, fixated with a rigid, non-biodegradable stainless steel implant, has a tendency for re-fracture upon removal of the implant. The bone does not carry sufficient load during the healing process, because the load is carried by the rigid stainless steel. However an implant prepared from biodegradable polymer can be engineered to degrade at a rate that will slowly transfer load to the healing bone [7]. Another exciting application for which biodegradable polymers offer tremendous potential is the basis for drug delivery, either as a drug delivery system alone or in conjunction to functioning as a medical device. In orthopedic applications, the delivery of a bone morphogenic protein may be used to speed the healing process after a fracture [8], or the delivery of an antibiotic may help prevent osteomyelitis following surgery [9].

Polymer scientists, working closely with those in the device and medical fields, have made tremendous advances over the past 30 years. In this article we will focus on a number of these devices. We will also cover the chemistry of the polymers, including synthesis and degradation, how properties can be controlled by proper synthetic controls such as copolymer composition, special requirements for processing and handling, and discuss some of the commercial devices.

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Nomenclature

Abbreviations
LPLA   poly(L-lactide)
PGA   poly(glycolide)
DLPLA   poly(DL-lactide)
PDO   poly(dioxanone)
LDLPLA   poly(DL-lactide-*co*-L-lactide)
SR   self-reinforced
DLPLG   poly(DL-lactide-*co*-glycolide)
PGA-TMC   poly(glycolide-*co*-trimethylene carbonate)
LPLG   poly(L-lactide-*co*-glycolide)
PCL   poly(ε-caprolactone)

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The general criteria for selecting a polymer for use as a biomaterial is to match the mechanical properties and the time of degradation to the needs of the application. The ideal polymer for an application would have the following properties:

- does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect,
- is metabolized in the body after fulfilling its purpose leaving no trace,
- is easily processed into the final product form,
- has acceptable shelf life,
- is easily sterilized.

The mechanical properties match the application so that sufficient strength remains until the surrounding tissue has healed

2. Synthesis

As expected, biodegradable polymers can be either natural or synthetic. Here we will cover uses and properties of synthetic biodegradable polymers. These synthetic polymers in general offer greater advantages over natural materials in that they can be tailored to give a wider range of properties and have more predictable lot-to-lot uniformity than materials from natural sources. Also a more reliable source of raw materials is obtained with synthetic polymers that are free of concerns of immunogenicity [2].

The factors that affect the mechanical performance of biodegradable polymers are those that are well known to the polymer scientist. These factors are monomer selection, initiator selection, process conditions, and the presence of additives. These factors in turn influence the polymer's hydrophilicity, crystallinity, melt and glass transition temperatures, molecular weight, molecular weight distribution, end groups, sequence distribution (random versus blocky), and the presence of residual monomer or additives [10]. In addition, the polymer scientist working with biodegradable polymers must also

evaluate each of these variables for its effect on biodegradation. Examples will be given throughout the text illustrating how some of these variables affect performance.

Biodegradation has been accomplished by synthesizing polymers that have hydrolytically unstable linkages in the backbone. These most common chemical functional groups are esters, anhydrides, orthoesters, and amides.

The following is an overview of the synthetic-biodegradable polymers that are currently being used or investigated for use as wound closure (sutures, staples), and orthopedic fixation devices (pins, rods, screws, tacks, ligaments). Most of the commercially available biodegradable devices are polyesters composed of homopolymers or copolymers of glycolide and lactide. There are also products made from copolymers of trimethylene carbonate, ε-caprolactone, and polydioxanone.

2.1. Notation

A polymer is generally named based on the monomer it is synthesized from. For example, ethylene is used to produce poly(ethylene). For both glycolic acid and lactic acid, an intermediate cyclic dimer is prepared and purified, prior to polymerization. These dimers are called glycolide and lactide, respectively. Although most references in the literature refer to poly(glycolide) or poly(lactide), you will also find references to poly(glycolic acid) and poly(lactic acid). Poly(lactide) exists in two stereo forms, signified by a D or L for dexorotary or levorotary, or by DL for the racemic mix.

Poly(glycolide) (PGA) Poly(glycolide) is the simplest linear aliphatic polyester. PGA was used to develop the first totally synthetic absorbable suture that has been marketed as DEXON® since the 1960s by Davis and Geck [5,6]. Glycolide monomer is synthesized from the dimerization of glycolic acid. The ring opening polymerization of glycolide yields high-molecular-weight materials with about 1–3% residual monomer present (Fig. 1). PGA is highly crystalline (45–55%) with a high melting point (220–225°C) and a glass transition temperature of 35–40°C [6]. Because of its high degree of crystallization, it is not soluble in most organic solvents; the
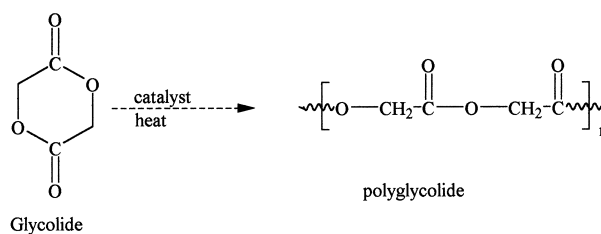

Fig. 1. Synthesis of poly(glycolide) (PGA).

Table 1
List of commercial biodegradable devices [13]

Application	Trade name	Composition	Manufacturer
Fracture fixation	SmartPins	SR-LPLA	Bionx Implants
Fracture fixation	SmartPins	SR-PGA	Bionx Implants
Fracture fixation	SmartScrew	SR-LPLA	Bionx Implants
Fracture fixation	SmartTack	SR-LPLA	Bionx Implants
Fracture fixation	Phantom SofThread Soft Tissue Fixation Screw	LPLA	DePuy
Fracture fixation	Orthosorb Pin	PDO	J & J Orthopedics
Interference screws	Full Thread Bio–Interference Screw	LPLA	Arthrex
Interference screws	Sheathed Bio–Interference Screw	LPLA	Arthrex
Interference screws	Phantom Interference Screw	LPLA	DuPuy
Interference screws	Biologically Quiet Interference Screw	85/15 DLPLG	Instrument Makar
Interference screws	BioScrew	LPLA	Linvatec
Interference screws	Sysorb	LLPLA	Sulzer Orthopedics
Interference screws	Endo–Fix Screw	PGA–TMC	Smith and Nephew
Suture anchors	Bankart Tack	SR-LPLA	Bionx Implants
Suture anchors	SmartAnchor-D	SR-LPLA	Bionx Implants
Suture anchors	SmartAnchor-L	SR-LPLA	Bionx Implants
Suture anchors	Phantom Suture Anchor	LPLA	DuPuy
Suture anchors	BioROC EZ 2.8 mm	LPLA	Innovasive Devices
Suture anchors	BioROC EZ 3.5 mm	LPLA	Innovasive Devices
Suture anchors	Biologically Quiet Biosphere	85/15 DLPLG	Instrument Makar
Suture anchors	Biologically Quiet Mini-Screw	85/15 DLPLG	Instrument Makar
Suture anchors	Bio-Anchor	LPLA	Linvatec
Suture anchors	GLS	LPLA	Mitek Products
Suture anchors	Panalok	LPLA	Mitek Products
Suture anchors	Panalok RC	LPLA	Mitek Products
Suture anchors	Suretak 6.0	PGA–TMC	Smith and Nephew
Suture anchors	Suretak 8.0	PGA–TMC	Smith and Nephew
Suture anchors	Suretak II w spikes	PGA–TMC	Smith and Nephew
Suture anchors	TAG 3.7 mm Wedge	PGA–TMC	Smith and Nephew
Suture anchors	TAG Rod II	PGA–TMC	Smith and Nephew
Suture anchors	SD sorb 2 mm	82/18 LPLG	Surgical Dynamics
Suture anchors	SD sorb 3mm	82/18 LPLG	Surgical Dynamics
Suture anchors	SD sorb E–Z TAC	82/18 LPLG	Surgical Dynamics
Suture anchors	Bio–Statak	LPLA	Zimmer
Craniomaxillofacial fixation	LactoSorb Screws and Plates	82/18 LPLG	Biomet
Meniscus repair	Menicus Arrow	SR–LPLA	Bionx Implants
Meniscus repair	Clearfix Meniscal Dart	LPLA	Innovasive Devices
Meniscus repair	Clearfix Meniscal Screw	LPLA	Innovasive Devices
ACL reconstruction	Biologically Quiet Staple	85/15 DLPLG	Instrument Makar
Meniscus repair	Meniscal Stinger	LPLA	Linvatec
Meniscus repair	SD sorb Meniscal Staple	82/18 LPLG	Surgical Dynamics

exceptions are highly fluorinated organic solvents such as hexafluoroisopropanol. Fibers from PGA exhibit high strength and modulus and are too stiff to be used as sutures except as braided material. Sutures of PGA lose about 50% of their strength after two weeks and 100% at four weeks and are completely absorbed in 4–6 months [6]. Glycolide has been copolymerized with other monomers to reduce the stiffness of the resulting fibers [11,12]. Barber [13] has reviewed the commercially available orthopedic devices and only one device was made of PGA (Table 1).

Poly(lactide) (PLA) Lactide is the cyclic dimer of lactic acid, which exists as two optical isomers, D and L. L-lactide, is the naturally occurring isomer, and DL-lactide is the synthetic blend of D-lactide and L-lactide. The
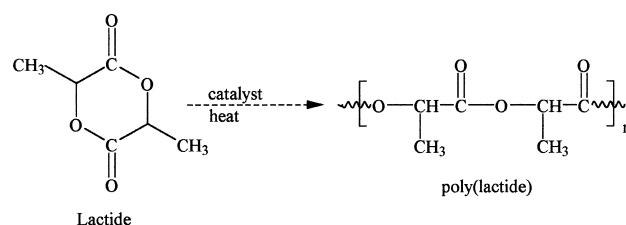

Fig. 2. Synthesis of poly(lactide) (PLA).

polymerization of lactide is similar to that of glycolide (Fig. 2). The homopolymer of L-lactide (LPLA) is a semi-crystalline polymer. PGA and LPLA exhibit high tensile strength and low elongation and consequently have

a high modulus that makes them more applicable than the amorphous polymers for load-bearing applications such as in orthopedic fixation and sutures. Poly(DL-lactide) (DLPLA) is an amorphous polymer having a random distribution of both isomeric forms of lactic acid and accordingly is unable to arrange into a crystalline organized structure. This material has lower tensile strength and higher elongation and much more rapid degradation time making it more attractive as a drug delivery system. Poly(L-lactide) is about 37% crystalline with a melting point of 175–178°C and a glass transition temperature of 60–65°C [14,15]. The degradation time of LPLA is much slower than that of DLPLA requiring greater than 2 years to be completely absorbed [16]. Copolymers of L-lactide with glycolide or DL-lactide have been prepared to disrupt the L-lactide crystallinity accelerating the degradation process [1,6]. Barber's review of 40 commercial orthopedic devices listed 22 of the devices as being composed of LPLA [13] (Table 1).

Poly(ε-caprolactone) (PCL): The ring opening polymerization of ε-caprolactone (Fig. 3) yields a semicrystalline polymer with a melting point of 59–64°C and a glass-transition temperature of −60°C. The homopolymer has a degradation time of the order of two years. Copolymers of ε-caprolactone with DL-lactide have been synthesized to yield materials with more rapid
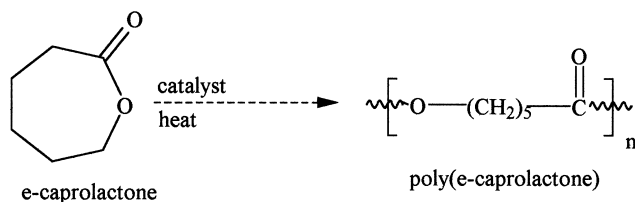
degradation rates [17]. A block copolymer of ε-caprolactone with glycolide that has reduced stiffness compared to pure PGA is being sold as a monofilament suture under the trade name MONOCRYL® by Ethicon [5,11,12], but no commercial medical devices are listed by Barber as made of PCL [13].

Poly(dioxanone) (a polyether-ester): The ring opening polymerization of *p*-dioxanone resulted in the first clinically tested monofilament synthetic suture that is known as PDS® marketed by Ethicon (Fig. 4). This material has about 55% crystallinity with a glass-transition temperature of −10 to 0°C. Poly(dioxanone) demonstrated no acute or toxic effects on implantation [6]. Johnson and Johnson Orthopedics has an absorbable pin for fracture fixation composed of poly(dioxanone) on the market [13].

Poly(lactide-co-glycolide) (PLG): Using the polyglycolide and poly(L-lactide) properties as base materials, it is possible to copolymerize the two monomers to extend the range of homopolymer properties (Fig. 5). Copolymers of glycolide with both L-lactide and DL-lactide have been developed for both device and drug-delivery applications. It is important to note that there is not a linear relationship between the copolymer composition and the mechanical and degradation properties of the materials. For example, a copolymer of 50% glycolide and 50% DL-lactide degrades faster than either homopolymer (Fig. 6) [18]. Copolymers of L-lactide with

Fig. 3. Synthesis of poly(ε-caprolactone) (PCL).

Fig. 4. Synthesis of poly(dioxanone) (PDS).

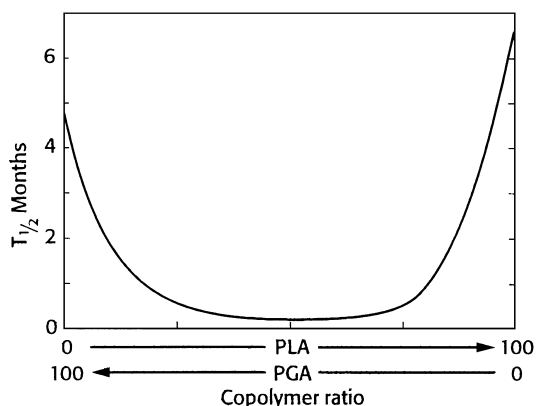Fig. 6. Half-life of PLA and PGA homopolymers and copolymers implanted in rat tissue [11].

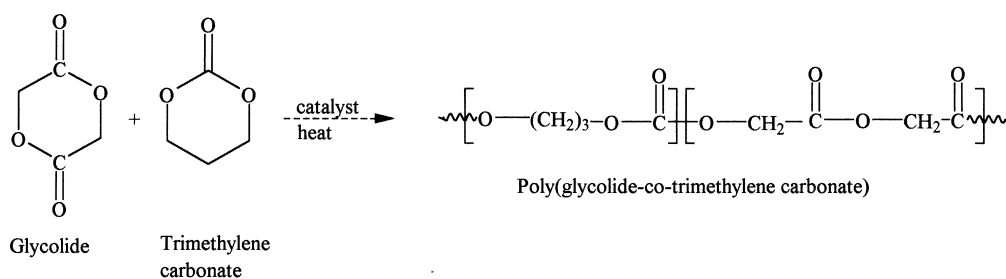Fig. 5. Synthesis of poly(lactide-*co*-glycolide) (PLG).

Fig. 7. Synthesis of poly(glycolide-co-trimethylene carbonate) (PGA–TMC).

25–70% glycolide are amorphous due to the disruption of the regularity of the polymer chain by the other monomer [1]. The Biologically Quiet™ line of products by Instrument Makar are composed of an 85/15 poly(DL-lactide-co-glycolide). Surgical Dynamics and Biomet have chosen an 82/18 poly(L-lactide-co-glycolide) copolymer for use as suture anchors and as screws and plates for craniomaxillofacial repair respectively [13, 19].

Copolymers of glycolide with trimethylene carbonate (TMC) called polyglyconate have been prepared as both sutures (MAXON®, Davis and Geck) [12] and as tacks and screws (Smith and Nephew Endoscopy) [13]. Typically these are prepared as A–B–A block copolymers in a 2 : 1 glycolide : TMC ratio with a glycolide-TMC center block (B) and pure glycolide end blocks (A) (Fig. 7). These materials have better flexibility than pure PGA and are absorbed in about seven months [6]. Glycolide has also been polymerized with TMC and *p*-dioxanone (BIO-SYN® by US Surgical) to form a terpolymer suture with reduced stiffness compared to pure PGA fibers, with absorption within 3–4 months [13].

Currently, only resorbable fixation devices made from homopolymers or copolymers of glycolide, lactide, caprolactone, *p*-dioxanone and trimethylene carbonate have been commercialized [13]. There are other polymers, however, that are being investigated for use as materials for biodegradable devices that merit mentioning.

Poly(amino acids): The use of synthetic poly(amino acids) as polymers for biomedical devices would seem a logical choice because of their wide occurrence in nature. However, in practice, pure insoluble poly(amino acids) have found little utility due to their high crystallinity which makes them difficult to process and gives relatively slow degradation. Also, the antigenicity of polymers with more than three amino acids in the chain also makes them inappropriate for use in vivo [20]. To circumvent these problems, modified "pseudo" poly(amino acids) have been synthesized using a tyrosine derivative. Tyrosine-derived polycarbonates are high strength materials that may be useful as orthopedic implants [5,20].

The search for new candidate polymers for drug delivery may offer potential for medical device applications as
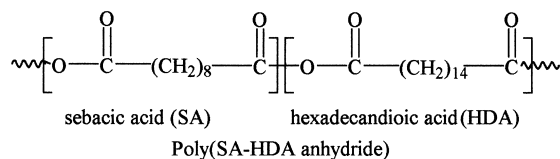

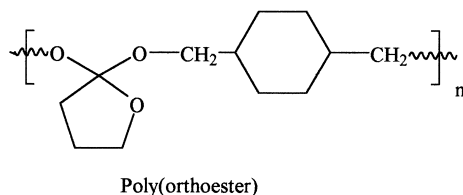Fig. 8. Molecular structure of a polyanhydride.

Fig. 9. Molecular structure of a polyorthoester.

well. In drug delivery the formulation scientist is concerned not only with shelf life stability of the drug but also with stability after implantation, where the drug may reside in the implant for 1–6 months or more. For drugs that are hydrolytically unstable, a polymer that absorbs water may be counter-indicated, so researchers began evaluating more hydrophobic polymers that degrade by surface erosion rather than bulk hydrolytic degradation. Two classes of these polymers are the polyanhydrides and the polyorthoesters.

Polyanhydrides: Polyanhydrides have been synthesized by the dehydration of diacid molecules by melt polycondensation (Fig. 8). Degradation times may be adjusted from days to years by degree of hydrophobicity of monomer selection. They degrade primarily by surface erosion and possess excellent in vivo compatibility. So far they have been only approved as a drug delivery system. The Gliadel® product designed for delivery of BCNU in the brain was approved by the FDA in 1996 and is being produced by Guilford [3,5].

Polyorthoesters: Polyorthoesters were first investigated in the 1970s by the Alza Corporation and SRI International in search of a new synthetic biodegradable polymer for drug-delivery applications (Fig. 9). These

materials have gone through several generations of synthetic improvements to yield materials that can be polymerized at room temperature without production of condensation by-products. These materials are hydrophobic with hydrolytic linkages that are acid-sensitive, but stable to base. They degrade by surface erosion and degradation rates may be controlled by incorporation of acidic or basic excipients [2,4,5].

3. Physical properties

The selection of a material for an orthopedic implant depends on the mechanical properties needed for the application and the degradation time desired. Polymers may be either semicrystalline or amorphous. Semicrystalline polymers have regular repeating units that allow the chains to fold into dense regions called crystallites. These act as crosslinks giving the polymer higher tensile strengths and higher modulus (stiffness) as compared to an amorphous analog. No polymer can completely organize into a fully crystalline material so there are still amorphous areas in semicrystalline polymers. When a semicrystalline polymer is raised above its melting point (T_m) it may be shaped into rods or molded parts. Amorphous polymers and the amorphous regions of semicrystalline polymers exhibit a glass transition temperature or T_g. At temperatures above T_g, a polymer acts more like a rubber and at temperatures below T_g, a polymer acts more like a glass. A polymer that has a T_g around body temperature may be much more ductile when implanted than it appears to be at room temperature. These properties can affect both the mechanical properties as well as the degradation time of the implant [10,21]. For the polyesters, the presence of water can act as a plasticizer and lower the T_g and affect degradation

and mechanical properties. Koelling et al. [22] evaluated the mechanical properties of 90/10 poly(L-lactide-co-DL-lactide) under both wet and dry conditions. They saw the mechanical properties were lower for the polymers tested in the wet condition.

A good example of the differences between a semicrystalline and amorphous polymer is illustrated by the differences between poly(L-lactide) and poly(DL-lactide) discussed earlier under the synthesis section. The semicrystalline poly(L-lactide) has a modulus about 25% higher than poly(DL-lactide) and a degradation time on the order of 3 to 5 years. The amorphous poly(DL-lactide) has a degradation time of 12 to 16 months [21,23,24].

A common way of affecting crystallinity is by the use of comonomers in the synthesis. Unlike monomers do not typically co-crystallize and crystallinity can be disrupted by copolymerization, with the effect being more pronounced at higher comonomer levels. For example, both glycolide and L-lactide homopolymers are semicrystalline, and copolymers of L-lactide and glycolide exhibit some crystallinity when either monomer is present over 70 mol% [1]. Copolymers of DL-lactide and glycolide are amorphous when DL-lactide is the major component [23]. For applications where an implant will be under substantial load the family of semicrystalline biodegradable polymers would typically be chosen. Daniels et al. [14] have reviewed the mechanical properties for both reinforced and unreinforced biodegradable polymers. Table 2 shows some of the physical properties and degradation times for selected biodegradable polymers.

4. Processing

Biodegradable polymers may be processed similar to any engineering thermoplastic in that they can be melted

Table 2
Physical, mechanical, and degradation properties of selected biodegradable polymers; bone and steel included as reference materials [20,21,23]

Polymer	Melting point (°C)	Glass transition temperature (°C)	Modulus[a] (Gpa)	Elongation (%)	Degradation time[b] (months)
PGA	225–230	35–40	7.0	15–20	6 to 12
LPLA	173–178	60–65	2.7	5–10	> 24
DLPLA	Amorphous	55–60	1.9	3–10	12 to 16
PCl	58–63	− 65– − 60	0.4	300–500	> 24
PDO	N/A	− 10–0	1.5	N/A	6 to 12
PGA–TMC	N/A	N/A	2.4	N/A	6 to 12
85/15 DLPLG	Amorphous	50–55	2.0	3–10	5 to 6
75/25 DLPLG	Amorphous	50–55	2.0	3–10	4 to 5
65/35 DLPLG	Amorphous	45–50	2.0	3–10	3 to 4
50/50 DLPLG	Amorphous	45–50	2.0	3–10	1 to 2
Bone			10–20		
Steel			210		

[a] Tensile or flexural modulus.
[b] Time to complete resorption.

and formed into fibers, rods and molded parts. Final parts can be extruded, injection molded, compression molded, or solvent spun or cast. In some circumstances the primary processing may be followed by subsequent machining into final parts.

The additional complication during processing is the potential for molecular weight decrease due to the hydrolytic sensitivity of the polymer bonds. The presence of moisture during processing can reduce the molecular weight and alter the final polymer properties. To avoid hydrolytic degradation during processing, extra precautions need to be taken to dry the polymer before thermally processing and preventing moisture from contacting the polymer during processing. Michaeli and von Oepen [25,26] have studied the influence of several processing factors on degradation during processing. Drying a polymer 24 h at 80°C prior to processing reduced degradation by approximately 30% when processing above 200°C. Drying may be accomplished by vacuum drying or drying in a resorption circulating air dryer. Von Oepen reported drying semicrystalline polymers at 140°C resulted in moisture contents of less than 0.02% without incurring degradation during drying. They recommend moisture content not to exceed 0.02% to avoid excessive degradation during processing [25]. Michaeli and von Oepen reported that most of the moisture is removed after 4 h drying [26]. Middleton et al. [27] reported the effects of drying on the melt viscosity of PGA when processed at 250°C. Here the polymer was vacuum dried 24 h at room temperature followed by vacuum drying 24 h at 100°C. This drying cycle reduced the moisture from 0.02 to 0.003%. PGA processed at 250°C with 0.02% moisture resulted in over 50% degradation as indicated by a decrease in melt viscosity, whereas drying to 0.003% did not. Care must be exercised when drying polymers above room temperature. For example, amorphous polymer pellets may fuse when the drying temperature exceeds the glass transition temperature. Most of the amorphous polymers should only be dried at room temperature.

Other techniques may also be used to prevent moisture from entering the fabrication process. Packaging the polymers in small quantities is recommended so that the material is used up quickly during processing once the package is opened to prevent moisture absorption over time. Blanketing the material hopper or material inlet with nitrogen or dried air will also prevent moisture from entering the system.

Most synthetic, resorbable polymers have been synthesized by ring-opening polymerization and there exists a thermodynamic equilibrium between the polymerization reaction and the reverse reaction that will result in monomer formation. Excessively high processing temperatures can push the equilibrium to depolymerization resulting in monomer formation during the molding or extrusion process. The presence of excess monomer may

act as a plasticizer changing the mechanical properties and may catalyze the hydrolysis of the device resulting in altered degradation kinetics [6].

There are also strong interactions among temperature, moisture content, shear rate, and residence time in the machine. Residence time is defined as time at temperature the material is in the barrel of a molding machine. Michaeli and von Oepen [25,26] have studied the effect of these interactions on polymer degradation for LPLA. When the temperature was raised from 190 to 230°C all the other effects were inconsequential. Higher shear rates and longer residence times resulted in increasing polymer degradation even at lower temperatures. In general, processing at the mildest conditions possible and the rigorous exclusion of moisture are the recommended. In many cases this is difficult as the devices being extruded or molded are small fibers or parts from very high-molecular-weight polymer. High temperatures are often needed to reduce the melt viscosity or high pressures needed to enable the polymer to flow through small orifices to create fiber or fill a mold. Several iterations of molding or extrusion may be needed to get the final part properties necessary for the application.

5. Packaging and sterilization

Because these polymers are hydrolytically unstable, the presence of moisture can degrade them in storage, during processing (as already discussed), and after device fabrication. The solution for hydrolysis instability is simple in theory: eliminate the moisture and eliminate the degradation. Because the materials are naturally hygroscopic, eliminating water and keeping the polymer free of water are difficult. The as-synthesized polymers have relatively low water contents, as any residual water in the monomer is consumed in the polymerization reaction. The polymers are quickly packaged after manufacture and generally double bagged under an inert atmosphere or vacuum. The bag material may be polymeric or foil, but it must be very resistant to water permeability [23]. The polymers are typically stored in a freezer to minimize the effects of moisture present. The packaged polymer should always be at room temperature when opened to minimize condensation and should be handled as little as possible at ambient atmospheric conditions [5]. As expected, there is a relation between biodegradation rate, shelf stability and polymer properties. For example, the more hydrophilic glycolide polymers are much more sensitive to hydrolytic degradation than those prepared from the more hydrophobic lactide. Williams et al. [28] have studied six different storage conditions for biodegradable polymers and found that the polymers remain stable even at room temperature for over two years as indicated by molecular weight retention when packaged in desiccated moisture proof bags.

Final packaging consists of placing the suture or device in an airtight moisture-proof container. A desiccant can be added to reduce the effect of moisture. For example, sutures are wrapped around a specially dried paper holder that acts as a desiccant. In some cases the final device may be stored at sub-ambient temperature as an added precaution against degradation.

The final devices should not be sterilized by autoclaving or dry heat because this will degrade the device. Typically the device is sterilized by γ-radiation, ethylene oxide (EtO), or other less-known techniques such as plasma etching [5,7,25] or electron beam irradiation. Both γ radiation and EtO have disadvantages. Radiation, particularly at doses above 2 Mrad, can result in significant degradation of the polymer chain, resulting in reduced molecular weight and influencing final mechanical properties and degradation times [6,8,15]. Poly(glycolide), poly(lactide) and poly(dioxanone) are especially sensitive to γ-radiation, and these are usually sterilized for device applications by exposure to ethylene oxide. The use of highly toxic EtO presents a safety hazard, so great care is used to ensure that all the gas is removed from the device before final packaging [5]. This may result in extremely long vacuum aeration times. One researcher has recommended a period of over 2 weeks [29] to fully remove the residual EtO gas. The temperature and humidity conditions should also be considered when submitting devices for sterilization. Temperatures must be kept below the glass transition temperature of the polymer to prevent the part geometry from changing during sterilization. If necessary, parts can be kept at 0°C or lower during the irradiation process. Of the 40 commercial orthopedic devices listed in Barber's review 25 were sterilized by EtO and 15 by γ irradiation [13]. No other techniques were listed.

6. Degradation

Once implanted in the body, the biodegradable device should maintain mechanical properties until it is no longer needed and then be degraded, absorbed, and excreted by the body, leaving no trace. Simple chemical hydrolysis of the hydrolytically unstable backbone is the prevailing mechanism for the polymer degradation. For semicrystalline polymers this occurs in two phases. In the first phase, water penetrates the bulk of the device, preferentially attacking the chemical bonds in the amorphous phase and converting long polymer chains into shorter, ultimately water-soluble fragments. Because this occurs in the amorphous phase initially there is a reduction in molecular weight without a loss in physical properties as the device matrix is still held together by the crystalline regions. The reduction in molecular weight is soon followed by a reduction in physical properties as water begins to fragment the device. In the second phase, enzy-
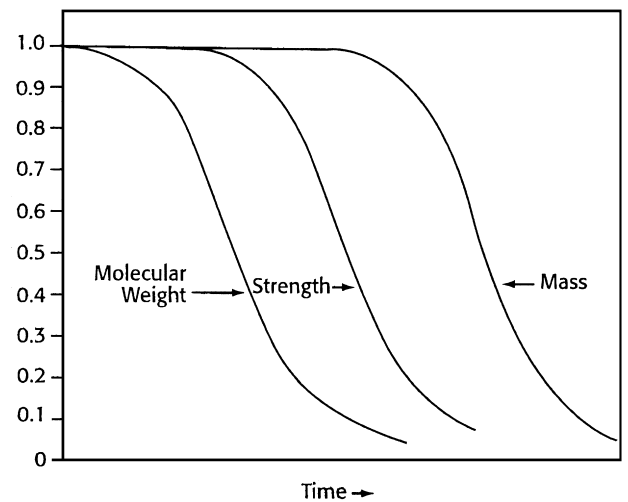

Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

matic attack of the fragments occurs. The metabolizing of the fragments results in a rapid loss of polymer mass (Fig. 10) [21].

Bulk erosion occurs when the rate at which water penetrates the device exceeds that at which the polymer is converted into water-soluble materials (resulting in erosion throughout the device). The lactide and glycolide commercially available devices and sutures degrade by bulk erosion [5]. This two-stage degradation mechanism has led one researcher to report that the degradation rate at the surface of large lactide–glycolide implants is slower that the degradation in the interior [30]. Initially, degradation does occur more rapidly at the surface due to the greater availability of water. The degradation products at the surface are rapidly dissolved in the surrounding fluid and removed from the bulk polymer. In the interior of the device the inability of large polymeric degradation products to diffuse away from the bulk device results in a local acidic environment in the interior of the implant. The increased acidic environment catalyses further degradation resulting in accelerated hydrolysis of the ester linkages in the interior. Athanasiou [31] has shown that low-porosity implants from 50/50 DLPLG degrade faster than high-porosity implants. He attributes this to the quick diffusion of low pH degradants from the interior of the high-porosity devices.

Polymer scientists have used this knowledge to tailor the degradation rates of biodegradable polymers. Tracy [32] reported the effects of replacing ester end groups with carboxylic acid end groups on DLPLG polymers (Figs. 11 and 12) accelerated both water uptake and degradation rate in vitro. The acid-end groups both add to the hydrophilicity of the polymer and catalyze degradation. Middleton et al. [33] conducted an in vitro degradation study in phosphate-buffered saline comparing
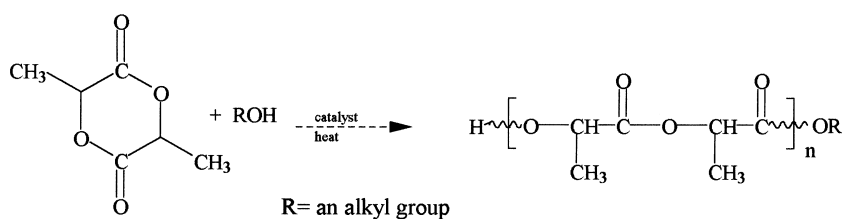
Fig. 11. Initiation of DL-lactide with an alcohol resulting in a polymer with one ester end group and one alcohol end group.
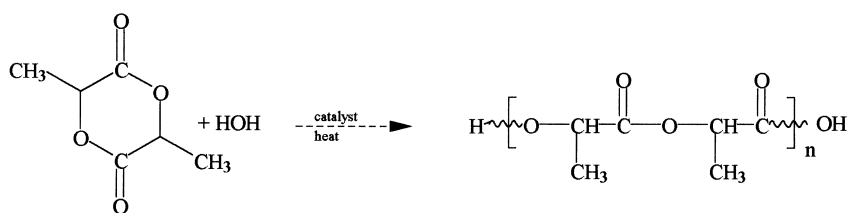

Fig. 12. Initiation of DL-lactide with water resulting in a polymer with one carboxylic-acid end group and one alcohol-end group.
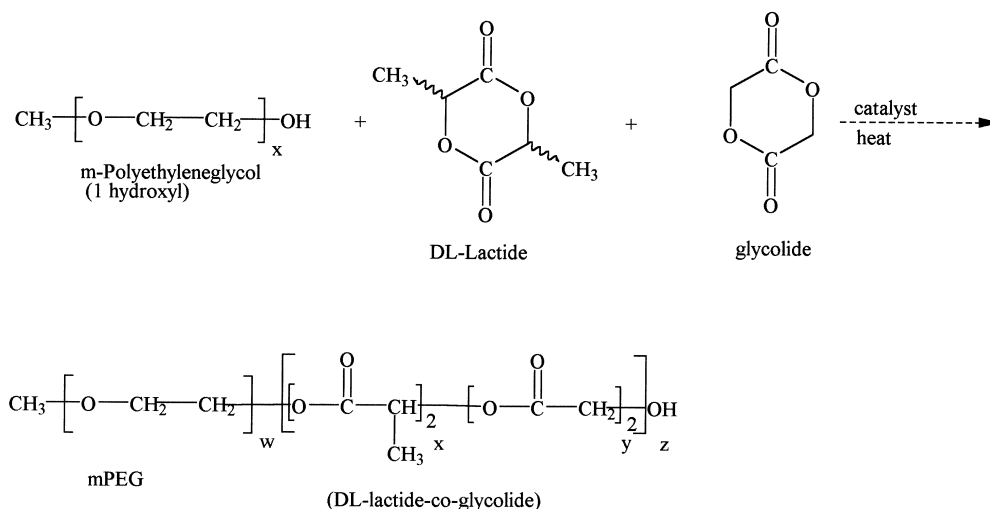

Fig. 13. Initiation of DL-lactide and glycolide with a monofunctional poly(ethyleneglycol) resulting a block copolymer consisting of a PEG block and a poly(DL-lactide-co-glycolide) block.

DLPLG rods where the ester end groups were replaced with covalently bound monofunctional poly(ethylene glycol) (mPEG) (Fig. 13). The mPEG-DLPLG demonstrated enhanced water uptake without accelerated degradation. It is believed the presence of the ethylene glycol units enhanced polymer hydrophilicity without lowering the pH of the local environment. By increasing the water uptake it may also have allowed the acidic degradants to more readily diffuse away from the interior of the rod.

There is a second type of biodegradation called surface erosion when the rate at which the polymer penetrates the device is slower than the rate of conversion of the polymer into water-soluble materials [5]. Surface erosion results in the device thinning over time while maintaining its bulk integrity. Polyanhydrides and polyorthoesters are examples of this type of erosion when the polymer is hydrophobic, but the chemical bonds are highly susceptible to hydrolysis. In general, this process is referred to in the literature as bioerosion rather than biodegradation.

The degradation-absorption mechanism is the result of many interrelated factors, including:

- the chemical stability of the polymer backbone,
- the presence of catalysts,
- additives,

- impurities or plasticizers,
- the geometry of the device,
- the location of the device.

The balancing of these factors to tailor an implant to slowly degrade and transfer stress to the surrounding tissue as it heals at the appropriate rate is one of the major challenges facing the researchers today.

The factors which accelerate polymer degradation are the following

- More hydrophilic monomer.
- More hydrophilic, acidic endgroups.
- More reactive hydrolytic group in the backbone.
- Less crystallinity.
- Smaller device size.

The location of the device can play an important role in the degradation rate of lactide–glycolide implants. Large devices implanted in areas with poor vascularization may degrade and overwhelm the body's ability to flush away degradants. This leads to a build up of acidic by-products. An acidic environment will catalyze the further degradation and cause further reduction in pH [7]. The local reduction in pH may also be responsible for adverse tissue reactions [34]. It has also been reported [35] that implants under stress degrade faster. It was proposed that the stressed implant may form microcracks increasing the surface area exposed to water [7].

7. Biocompatibility

Some of the requirements listed in the earlier section of this article stated that the ideal implant would not invoke an inflammatory or toxic response and that the degradants must be metabolized in the body after fulfilling its purpose leaving no trace. For example, poly(lactide) hydrolyzes to lactic acid that is a normal product of muscular contraction in animals. The lactic acid is then further metabolized through the tricarboxylic acid cycle and then excreted as carbon dioxide and water. Poly(glycolide) is degraded by hydrolysis and esterases to glycolic acid. Glycolic acid monomer may be excreted directly in urine or may react to form glycine. Glycine can be used to synthesize serine and subsequently transformed into pyruvic acid where it enters the tricarboxylic acid cycle [7].

There have been numerous studies on the biocompatibility of implants since the early 1960s mostly focusing on polymers of lactide and glycolide. The majority of results indicate that these polymers are sufficiently biocompatible, with a minority suggesting otherwise. The literature before 1993 has been summarized by Agrawal et al. [15].

Bergsma et al. [16] conducted a study on patients that have received PLLA implants for zygomatic fractures.

They removed and analyzed the remaining LPLA material after 3.3 to 5.7 years. Some highly crystalline LPLA particles remained after 5.7 years. The particles were not irritable and did not cause injury to the cell, but did induce a reaction in the form of detectable swelling. Barber [36] evaluated 85 patients in two groups that received either a metal or LPLA interference screw. No statistical differences were found between the two groups after two years.

As with the other areas we have explored, there are many factors that may influence the reaction of the body to the presence of a biodegradable implant. The response may be related to the size and composition of the implant as well as the implant site. The degradation rate of the polymer and the implant site's ability to eliminate the acidic degradants play an important role in the local tissue's reaction to the implant. If the surrounding tissue cannot eliminate the acid by-products of a rapidly degrading implant then an inflammatory or toxic response may result [34].

In summary, the results from studies in humans are mostly favorable with some negative reports. The complications arising from biodegradable orthopedic implants of polymers of lactide and glycolide typically occur at a rate of less than 10% [7]. Although initially significant, these problems resolve with time making the future of biodegradable implants bright.

8. Commercial biodegradable devices

The total US revenues from commercial products developed from absorbable polymers in 1995 was estimated to be over $300 million with over 95% of revenues generated from the sale of bioabsorbable sutures. The other 5% is attributed to orthopedic fixation devices in the forms of pins, rods and tacks, staples for wound closure, and dental applications [37]. In addition, research into biodegradable systems continues to increase, with 60 to 70 papers published each year in the late 1970s to over 400 each year in the early 1990s. The rate at which bioabsorbable fixation devices are cleared through the 510(k) process by the US Food and Drug Administration (FDA) is also increasing, with seven approved in 1995 [19].

The two routes for getting FDA approval to market and sell medical devices in the US are the 510(k) process and the premarket approval (PMA) process. The 510(k) process requires that the new device be shown to be equivalent to a device currently on the US market in terms of safety and efficacy. Clinical data may or may not be required for these devices. The PMA process always requires clinical data and is as stringent as the requirements for a new drug application.

Orthopedic fixation devices of synthetic biodegradable polymers have advantages over metal implants in that

they transfer stress over time to the damaged area, allowing healing of the tissues, and eliminate the need for a subsequent operation for implant removal. The current approved materials have not been commercialized as bone plates for long bone support such as the femur. They have found applications where lower-strength materials are sufficient, such as in the ankle, knee, and hand areas as interference screws, tacks and pins for ligament attachment and meniscal repair, suture anchors, and rods and pins for fracture fixation. Barber has recently compiled a review of the commercially available orthopedic devices [13]. He grouped the devices into four categories with the number of devices listed in each category in parentheses: fracture fixation (6), interference-fixation screws (6), suture anchors (21) and other devices (7). Other devices include screws and plates for maxillofacial repair, tacks for meniscal repair and an implant for ACL reconstruction. The list appears in Table 1.

In this article we have attempted to provide an overview of the orthopedic uses of biodegradable polymers. While sutures were the first commercial product and still account for 95% of all sales, a number of products are now approved for a wide range of applications. And it is expected that a number of additional products will be approved in the next decade.

What is it about these materials that makes them so attractive to the device industry? First, in this conservative field, where devices serve critical, perhaps life and death functions, the industry is slow to accept new materials or new designs. But polymers prepared from these materials, particularly lactide and glycolide, have a long history of safety including the approval of several products. Building on this solid history, researchers continue to evaluate these materials for other uses. The wide range of properties that can be obtained in polymers built with these few monomer units has allowed for a variety of products. We expect that in the future, even more than today, surgeons will have available a number of products using biodegradable products that will speed patient recovery and eliminate follow-up surgeries.

Acknowledgements

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