42.1 INTRODUCTION

The term biodegradation is loosely associated with materials that could be broken down by nature either through hydrolytic mechanisms without the help of enzymes and/or enzymatic mechanism. Other terms like absorbable, erodible, and resorbable have also been used in the literature to indicate biodegradation.

TABLE 42.1 Properties of Commercially Important Synthetic Absorbable Polymers

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Crystallinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>High</td>
</tr>
<tr>
<td>PLLA</td>
<td>High</td>
</tr>
<tr>
<td>PLA</td>
<td>None</td>
</tr>
<tr>
<td>Poly(lactide-910)%</td>
<td>High</td>
</tr>
<tr>
<td>Polysioxanone</td>
<td>High</td>
</tr>
<tr>
<td>Polyglycolate</td>
<td>High</td>
</tr>
<tr>
<td>Polyglycolone</td>
<td>High</td>
</tr>
<tr>
<td>Poliglycaprone25</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength</th>
<th>Modulus</th>
<th>Elongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPa</td>
<td>GPa</td>
<td>(%)</td>
</tr>
<tr>
<td>890</td>
<td>8.4</td>
<td>30</td>
</tr>
<tr>
<td>900</td>
<td>8.5</td>
<td>25</td>
</tr>
<tr>
<td>190</td>
<td>2.1</td>
<td>35</td>
</tr>
<tr>
<td>550</td>
<td>2.4</td>
<td>45</td>
</tr>
<tr>
<td>91,100</td>
<td>113,000</td>
<td>39</td>
</tr>
</tbody>
</table>

\( ^{d} \) Glycolide per lactide = 9/1.

\( ^{b} \) Glycolide per trimethylene carbonate = 9/1.

\( ^{c} \) Depending on the copolymer composition.

\( ^{d} \) 2/0 size Monocryl (glycolide-ε-caprolactone copolymer).

\( ^{e} \) PSI unit.

The interests in biodegradable polymeric biomaterials for biomedical engineering use have increased dramatically during the past decade. This is because this class of biomaterials has two major advantages that non-biodegradable biomaterials do not have. First, they do not elicit permanent chronic foreign-body reactions due to the fact that they are gradually absorbed by the human body and do not permanently leave traces of residual in the implantation sites. Second, some of them have recently been found to be able to regenerate tissues, so called tissue engineering, through the interaction of their biodegradation with immunologic cells like macrophages. Hence, surgical implants made from biodegradable biomaterials could be used as a temporary scaffold for tissue regeneration. This approach toward the reconstruction of injured, diseased, or aged tissues is one of the most promising fields in the next century.

Although the earliest and most commercially significant biodegradable polymeric biomaterials were originated from linear aliphatic polyesters like polyglycolide and polylactide from poly(ε-hydroxyacetic acids), recent introduction of several new synthetic and natural biodegradable polymeric biomaterials extends the domain beyond this family of simple polyesters. These new commercially significant biodegradable polymeric biomaterials include poly(orthoesters), polyanhydrides, polysaccharides, poly(ester-amides), tyrosine-based polyarylates or polyiminocarbonates or polycarbonates, poly(t,1-lactide-urethane), poly(β-hydroxybutyrate), poly(ε-
All the above biodegradable polymeric biomaterials could be generally divided into eight groups based on their chemical origin: (1) Biodegradable linear aliphatic polyesters (e.g., polyglycolide, polylactide, poly(caprolactone, poly(hydroxybutyrate) and their copolymers within the aliphatic polyester family like poly(glycolide-l-lactide) copolymer and poly(glycolide-ε-caprolactone) copolymer; (2) Biodegradable copolymers between linear aliphatic polyesters in (1) and monomers other than linear aliphatic polyesters like, poly(glycolide-trimethylene carbonate) copolymer, poly(l-lactic acid-l-lysine) copolymer, Tyrosine-based polarylates or polyiminocarbonates or polycarbonates, poly(D.L-lactide-urethane), and poly(ester-amine); (3) Poly-anhydrides (4) Poly(orthoesters); (5) Poly(ester-ethers) like poly-p dioxanone; (6) Biodegradable polysaccharides like hyaluronic acid, chitin, and chitson; (7) polyamino acids like poly-L-glutamic acid and poly-L-lysine (8) Inorganic biodegradable polymers like polyphosphazene and poly(bis(carboxylato(phenoxo)phosphazene) which have a nitrogen-phosphorus backbone instead of ester linkage. Recently, there is a new approach of making new biodegradable polymers through melt-blending of highly accepted biodegradable polymers like those of glycolide and lactide base [Shalaby, 1994].

The earliest, most successful, and frequent biomedical applications of biodegradable polymeric biomaterials have been in wound closure [Chu et al., 1996]. All biodegradable wound closure biomaterials are based upon the glycolide and lactide families. For example, polyglycolide [Dexon from American Cyanamid], poly(glycolide-l-lactide) random copolymer with 90 to 10 — ratio (Vicryl from Ethicon), poly(ester-ether) (PDS from Ethicon), poly(glycolide-trimethylene carbonate) random block copolymer (Maxon from American Cyanamid), and poly(glycolide-ε-caprolactone) copolymer (Monocryl from Ethicon). This class of biodegradable polymeric biomaterials is also the one most studied for their chemical, physical, mechanical, morphological, and biological properties and their changes with degradation time and environment. Some of the above materials like Vicryl have been commercially used as surgical meshes for repair of a hernia or the body wall.

The next largest biomedical application of biodegradable polymeric biomaterials that are commercially satisfactory is drug control/release devices. Some well-known examples in this application are poly(anhydrides and poly(ortho-ester). Biodegradable polymeric biomaterials, particularly totally resorbable composites, have also been experimentally used in the field of orthopedics, mainly as components for internal bone fracture fixation like PDS pins. However, their wide acceptance in other parts of orthopaedic implants may be limited due to their inherent mechanical properties and their biodegradation rate. Besides the commercial uses described above, biodegradable polymeric biomaterials have been experimented with as (1) vascular grafts (2) vascular stents, (3) vascular couplers for vessel anastomosis, (4) nerve growth conduits, (5) augmentation of defected bone, (6) ligament/tendon prostheses, (7) intramedullary plug during total hip replacement, (8) anastomosis ring for intestinal surgery, and (9) stents in ureteroureterostomies for accurate suture placement.

Due to space limitation, the emphasis of this chapter will be on the commercially most significant and successful biomedical biodegradable polymers based on (1) linear aliphatic polyesters, (2) some very recent research and development of important classes of synthetic biodegradable polymers, (3) a new theoretical approach to modeling the hydrolytic degradation of glycolide/lactide based biodegradable polymers, (4) the effects of some new extrinsic factors on the degradation of the most commercially significant biodegradable polymers, and (5) the new biomedical applications of this class of synthetic biodegradable polymers in tissue engineering and regeneration. The details of the applications of this family and other biodegradable polymeric biomaterials and their
chemical, physical, mechanical, biological, and biodegradation properties can be found in other recent reviews [Barrows, 1986; Vert et al., 1992; Kimura, 1993; Park et al., 1993; Shalaby, 1994; Hollinger, 1995; Chu et al., 1996].

42.2 GLYCOLIDE/LACTIDE BASED BIODEGRADABLE LINEAR ALIPHATIC POLYESTERS

This class of biodegradable polymers is the most successful, important, and commercially widely used biodegradable biomaterials in surgery. It is also the class of biodegradable biomaterials that were most extensively studied in terms of degradation mechanisms and structure—property relationships. Among them, polyglycolide or polyglycolic acid (PGA) is the most important one because most other biodegradable polymers are derived from PGA either through copolymerization, for example, poly(glycolide-L-lactide) copolymer or modified glycolide monomer, for example, poly-p-dioxanone.

42.2.1 Glycolide Based Biodegradable Homopolymers Polyesters

PGA can be polymerized either directly or indirectly from glycolic acid. The direct polycondensation produces a polymer of $M_n$ less than 10,000 because of the requirement of a very high degree of dehydration (99.28% up) and the absence of monofunctional impurities. For PGA of molecular weight higher than 10,000 it is necessary to proceed through the ring-opening polymerization of the cyclic dimers of glycolic acid. Numerous catalysis are available for this ring-opening polymerization. They include organometallic compounds and Lewis acids (Chujo et al., 1967; Wise et al., 1979). For biomedical applications, stannous chloride dihydrate or trialkyl aluminum are preferred. PGA was found to exhibit an orthorhombic unit cell with dimensions $a = 5.22$ Å, $b = 6.19$ Å, and $c$(fiber axis) = 7.02 Å. The planar zigzag-chain molecules form a sheet structure parallel to the ac plane and do not have the polyethylene type arrangement [Chatani et al., 1968]. The molecules between two adjacent sheets orient in opposite directions. The tight molecular packing and the close approach of the ester groups might stabilize the crystal lattice and contribute to the high melting point, $T_m$, of PGA (224 to 230°C). The glass transition temperature, $T_g$, ranges from 36 to 40°C. The specific gravities of PCA are 1.707 for a perfect crystal and 1.50 in a completely amorphous state [Chujo et al., 1967a]. The heat of fusion of 100% crystallized PCA is

![FIGURE 42.1 FTIR spectra of polyglycolic acid disks as a function of in vitro hydrolysis time in phosphate buffer of pH 7.44 at 37°C. (a) 0 day; (b) 55 h; (c) 7 days; (d) 21 days.](image)
reported to be 12 kJ/mol (45.7 cal/g) [Brandrup et al., 1975]. A recent study of injection molded PCA disks reveals their IR spectroscopic characteristics [Chu et al., 1995]. As shown in Figure 42.1, the four bands at 850, 753, 713, and 560 cm$^{-1}$ are associated with the amorphous regions of the PGA disks and could be used to assess the extent of hydrolysis. Peaks associated with the crystalline phase included those at 972, 901, 806.6, and 590 cm$^{-1}$. Two broad, intense peaks at 1142 and 1077 cm$^{-1}$ can be assigned to C—O stretching modes in the ester and oxymethylene groups, respectively. These two peaks are associated mainly with ester and oxymethylene groups originating in the amorphous domains. Hydrolysis could cause both of these C—O stretching modes to substantially decrease in intensity.

42.2.2 Glycolide-Based Biodegradable Copolyesters Having Aliphatic Polyester Based Co-Monomers

Other commercially successful glycolide-based biodegradable polymeric biomaterials are the copolymers of glycolide with other monomers within linear aliphatic polyesters like lactides, carbonates, and ε-caprolactone. The glycolide-lactide random copolymers are the most studied and have a wide range of properties and applications, depending on the composition ratio of glycolide to lactide. Figure 42.2 illustrates the dependence of biodegradation rate on the composition of glycolide to lactide in the copolymer. For wound closure purposes, a high concentration of glycolide monomer is required for achieving proper mechanical and degradation properties. Vicryl sutures, sometime called polyglactin 910,


contain a 90/10 molar ratio of glycolic to L-lactide and this molar ratio is important for the Vicryl suture to retain crystalline characteristics. For biomedical use. Lewis acid catalysts are preferred for the copolymers Wise et al., 1979. If D,L-instead of L-lactide is used as the co-monomer. the U-shape relationship between the level of crystallinity and glycolide composition disappears. This is because poly(lactide from 100% D,L-lactide composition is totally amorphous. IR bands associated with Vicryl molecules in the amorphous domains are 560, 710, 850, and 888 cm$^{-1}$, while 590, 626, 808, 900, and 972 cm$^{-1}$ are associated with the crystalline domains [Frederick et al., 1984]. Like PCA, these IR bands could be used to assess the extent of hydrolysis.

A relatively new block copolymer of glycolide and carbonates, such as trimethylene carbonate, has been commercialized. Maxon is made from a black copolymer of
glycolide and 1,3-dioxan-2-one (trimethylene carbonate or GTMC) and consists of 32.5% by weight (or 36 mol%) of trimethylene carbonate [Casey et al., 1984; Katz et al., 1985]. Maxon is a poly(ester-carbonate). The polymerization process of Maxon is divided into two stages. The first stage is the formation of a middle block which is a random copolymer of glycolide and 1,3-dioxan-2-one. Diethylene glycol is used as an initiator and stannous chloride dehydrate (SnCl$_2$.2H$_2$O) serves as the catalyst. The polymerization is conducted at about 180°C. The weight ratio of glycolide to trimethylene carbonate in the middle block is 15:85. After the synthesis of the middle block, the temperature of the reactive bath is raised to about 220°C to prevent the crystallization of the copolymer and additional glycolide monomers as the end blocks are added into the reaction bath to form the final triblock copolymer.

The latest glycolide-based copolymer that has become commercially successful is Monocryl suture. It is a segmented block copolymer consisting of both soft and hard segments. The purpose of having soft segments in the copolymer is to provide good handling properties like pliability, while the hard segments are used to provide adequate strength. The generic copolymerization process between glycolic acid and ε-caprolactone was recently reported by Fukuzaki et al. in Japan (1989, 1991). The resulting copolymers are low molecular weight biodegradable copolymers of glycolic acid and various lactones for potential drug delivery purposes. The composition of lactone ranged from as low as 15 to as high as 50 mol% and the weight average for molecular weight ranged from 4,510 to 16,500. The glass transition temperature ranged from 8°C to −43°C, depending on the copolymer composition and molecular weight.

Monocryl is made from two stages of the polymerization process (Bezwada et al., 1995). In the first stage, soft segments of prepolymer of glycolide and ε-caprolactone are made. This soft segmented prepolymer is further polymerized with glycolides to provide hard segments of polyglycolide. Monocryl has a composition of 75% glycolide and 25% ε-caprolactone and should have a higher molecular weight than those glycolide/ε-caprolactone copolymers reported by Fukuzaki et al., for adequate mechanical properties required by sutures. The most unique aspect of Monocryl monofilament suture is its pliability as claimed by Ethicon (Bezwada et al., 1995). The force required to bend a 2/0 suture is only about $2.8 \times 10^6$ lb-in$^2$ for Monocryl, while the same size PDSII and Maxon monofilament sutures require about 3.9 and $1.6 \times 10^4$ lb-in$^2$ force, respectively. This inherent pliability of Monocryl is due to the presence of soft segments and $T_g$ resulting from the ε-caprolactone co-monomer unit. Its $T_g$ is expected to be between 15 and −36°C.

42.2.3 Glycolide-Based Biodegradable Copolyesters with Non-Aliphatic

Polyester-Based Co-Monomers: In this category, the most important one is the glycolide copolymer consisting of poly(ethylene1,4phenylene-bis-oxyacetate) (PEPBO) [Jamiokowski and Shalaby, 1991]. The development of this type of glycolide-based copolymer was initiated because of the adverse effect of γ irradiation on the mechanical properties of glycolide-based synthetic absorbable sutures. There is a great desire to develop γ-irradiation sterilizable, synthetic absorbable polymers to take advantage of the highly convenient and reliable method of sterilization. Shalaby et al. recently reported that the incorporation of about 10 mol% of a polymeric radiostabilier like PEPBO into PGA backbone chains would make the copolymer sterilizable by γ irradiation without a significant accelerated loss of mechanical properties upon hydrolysis when compared with the unirradiated copolymer control (MPG) [Jamiokowski et al., 1991]. The changes in tensile breaking force of both MPG and PGA sutures implanted intramuscularly and subcutaneously in rats for various periods show the great advantage of such copolymer. MPG fibers γ-irradiated at 2.89 Mrads did not show any loss in tensile breaking force during the first 14 days postimplantation when compared with unimplanted samples. On the contrary, PGA sutures γ-irradiated at 2.75 Mrads lost 62% of the tensile breaking
Lecture Note

force of their unimplanted samples. There was no tensile breaking force remaining for the irradiated PGA at the end of 21 days, while both 2.89 and 5 Mrads irradiated MPG retained 72 and 55% of their corresponding 0 day controls, respectively. The inherent more hydrolytic resistance of MPG must be attributed to the presence of an aromatic group in the backbone chains. This aromatic polyester component is also responsible for the observed γ-irradiation stability, it is not known at this time whether the new γ-irradiation-resistant MPG is biocompatible with biologic tissues due to the lack of published histologic data.

42.2.4 Glycolide-Derived Biodegradable Polymers Having Ether Linkage

Poly-p-dioxanone (PDS) is derived from the glycolide family with better flexibility. It is polymerized from ether-containing lactones, 1,4-dioxane-2.5-dione (i.e., p-dioxanone) monomers with a hydroxyl initiator and tin catalyst [Shalaby, 1994]. The resulting polymer is semi-crystalline with $T_m$ about 106—115°C and $T_g$ -10 - 0°C. The improved flexibility of PDS relative to PGA as evidenced in its lower $T_g$ is due to the incorporation of an ether segment in the repeating unit which reduces the density of ester linkages for intermolecular hydrogen bonds. Because of the less dense ester linkages in PDS when compared with PCA or glycolide-L-lactide copolymers. PDS is expected and has been shown to degrade at a slower rate in vitro and in vivo. PDS having an inherent viscosity of 2.0 dl/g in hexafluoroisopropanol is adequate for making monofilament sutures. Recently, an advanced version of PDS, PDSII, was introduced. PDSII was achieved by subjecting the melt-spun fibers to a high temperature (128°C) for a short period of time. This additional treatment partially melts the outermost surface layer of PDS fibers and leads to a distinctive skin-core morphology. The heat employed also results in larger crystallites in the core of the fiber than the untreated PDS fiber. The tensile strength-loss profile of PDSII sutures is better than that of PDS sutures.

A variety of copolymers having high molar ratios of PDS compared to other monomers within the same linear aliphatic polyester family have been reported for the purpose of improving the mechanical and biodegradation properties [Shalaby, 1994]. For example, copolymer of PDS (80%) and PGA (up to 20%) has an absorption profile similar to Dexon and Vicryl sutures but it has compliance similar to PDS. Copolymer of PDS (85%) and PLIA (up to 15%) results in a more compliant (low modulus) suture than homopolymer PDS but with absorption profiles similar to PDS [Bezwada et al., 1990].

Copolymer fibers made from POS and monomers other than linear aliphatic polyester like morpholine-2,5-dione (MD) exhibit rather interesting biodegradation properties. This copolymer liberation was absorbed 10 to 25% earlier than POS. The copolymer, however, retained a tensile breaking strength profile similar to PDS with a slightly faster strength loss during the earlier stage, that is, the first 14 days [Shalaby, 1994]. This ability to break the inherent fiber structure—property relationship through copolymerization is a major improvement in biodegradation properties of absorbable sutures. It is interesting to recognize that a small % (3%) of MD in the copolymer suture is sufficient to result in a faster mass loss profile without the expense of its tensile strength-loss profile. The ability to achieve this ideal biodegradation property might be attributed to both an increasing hydrophilicity of the copolymer and the disruption of crystalline domains due to MD moiety. As described later, the loss of suture mass is mainly due to the destruction of crystalline domains, while the loss of tensile breaking strength is chiefly due to the scission of tie-chain segments located in the amorphous domains. The question is why MD—PDS copolymeric suture retains its strength-loss similar to POS. The possible explanation is that the amide functional groups in MD could form stronger intermolecular hydrogen bonds than ester functional groups. This stronger hydrogen bond contributes to the strength retention of the copolymer of PDS and MD during in vivo biodegradation. The incorporation of MD moiety into PL)S also lowers the unknot and knot strength of unhydrolyzed specimens, but increases elongation.
at break. This suggests that the copolymer of PDS and MD should have a lower level of crystallinity than POS which is consistent with its observed faster mass loss in vivo.

To improve γ-irradiation stability of PDS, radiostabilizers like PEPlO have been copolymerized with PDS to form segmented copolymers the same way as PEPBO with glycolide described above (Koelmel et al., 1991; Shalaby, 1994). The incorporation of 5 to 10% of such stabilizer in PDS has been shown not only to improve γ-irradiation resistance considerably but to also increase the compliance of the material. For example, PEPBO-PDS copolymer retained 79, 72, and 57% of its original tensile breaking strength at 2, 3, and 4 weeks in in vivo implantation, while PDS homopolymer retained only 43, 30, and 25% at the corresponding periods. It appears that an increasing (CH2) group between the two ester functional groups of the radiation stabilizers improves the copolymer resistance toward γ-irradiation.

42.2.5 Lactide Biodegradable Homopolymers and Copolymers

Polylactides, particularly poly-L-lactide (PLLA), and copolymers having >50% L- or DL-lactide have been explored for medical use without much success mainly due to their much slower absorption and difficulty in melt processing. PLEAs are prepared in solid state through ring-opening polymerization due to their thermal instability and should be melt-processed at the lowest possible temperature (Shalaby, 1994). Other methods like solution spinning, particularly for high molecular weight, and suspension polymerization have been reported as better alternatives. PLEA is a semi-crystalline polymer with \( T_m = 170^\circ\text{C} \) and \( T_g = 56^\circ\text{C} \). This high \( T_g \) is mainly responsible for the extremely slow biodegradation rate reported in the literature. The molecular weight of lactide-based biodegradable polymers suitable for medical use ranges from 1.5 to 5.0 dl/g inherent viscosity in chloroform. Ultra high molecular weight of polylactides have been reported [Tunc, 1983; Leenslag et al., 1984]. For example, an intrinsic viscosity as high as 13 dl/g was reported by Leenslag et al. High strength PLEA fibers from this ultra high molecular weight polylactide was made by hot-drawing fibers from solutions of good solvents. The resulting fibers had tensile breaking strength close to 1.2 GPa (Gogolewski et al., 1983). Due to a dissymmetric nature of lactic acid, the polymer made from the optically inactive racemic mixture of D and L enantiomers, poly-DL-lactide, however, is an amorphous polymer.

Lactide-based copolymers having a high percentage of lactide have recently been reported, particularly those copolymerized with aliphatic polycarbonates Like trimethylene carbonate (TMC) or 3,3-dimethyltrienylene carbonate (DMTMC) [Shieh et al., 1990]. The major advantage of incorporating TMC or DMTMC units into lactide is that the degradation products from TMC or DMTMC are largely neutral pH and hence are considered to be advantageous. Both in vitro toxicity and in vivo non-specific foreign body reactions like sterile sinuses have been reported in orthopaedic implants made from PCA and/or PLIA [Eitenmuller et al., 1989; Flostman et al., 1990; Daniels et al., 1992; Hofmann, 1992; Winet et al., 1993]. Several investigators indicated that the glycolic or lactic-acid rich-degradation products have the potential to significantly lower the local pH in a closed and less body-fluid buffered regions surrounded by bone [Sugnuma et al., 1992]. This is particularly true if the degradation process proceeds with a burst mode (i.e., a sudden and rapid release of degradation products). This acidity tends to cause abnormal bone resorption and/or demineralization. The resulting environment may be cytotoxic [Daniels e al., 1992]. Indeed, inflammatory foreign body reactions with a discharging sinus and osteolytic foci visible on x-ray have been encountered in clinical studies [Eitenmuller et al, 1989]. Hollinger et al. recently confirmed the problem associated with PCA and/or PLIA orthopaedic implants [Winet et al., 1993]. A rapid degradation of a 50:50 ratio of glycolide-lactide copolymer in bone chambers of rabbit tibias has been found to inhibit bone regeneration. However, emphasis has been placed on the fact that extrapolation of in vitro toxicity to in vivo biocompatibility must consider
microcirculatory capacity. The increase in the local acidity due to a faster accumulation of the highly acidic degradation products is also known to lead to an accelerated acid-catalyzed hydrolysis in the immediate vicinity of the biodegradable device. This acceleration in hydrolysis could lead to a faster loss of mechanical property of the device than we expect. This finding suggests the need to use components in totally biodegradable composites so that degradation products with less acidity would be released into the surrounding area. A controlled slow release rather than a burst release of degradation products at a level that the surrounding tissue could timely metabolize them would also be helpful in dealing with the acidity problem. Copolymers of composition ratio of 10DMTMC/90LLA or 10TMC/90LLA appear to be a promising absorbable orthopaedic device. Other applications of this type of copolymers include nerve growth conduits, tendon prostheses, and coating materials for biodegradable devices.

Another unique example of lactide copolymer is the copolymer of lactide and 3-(S)[(alkyloxycarbonyl) methyl]-1,4-dioxane-2,5-dione, a cyclic diester [Kimura, 1993]. The most unique aspect of this new biodegradable copolymer is the carboxyl acid pendant group which obviously would make the new polymer not only more hydrophilic and hence faster biodegradation but also more reactive toward future chemical modification through the pendant carboxyl group. The availability of these carboxyl reactive pendant sites could be used to chemically bond antimicrobial agents or other biochemicals like growth factors for making future wound closure biomaterials having new and important biological functions. Unfortunately, there are no reported data to evaluate the performance of this new absorbable polymer for biomedical engineering use up to the present time.

Block copolymers of PLLA with poly(amino acids) have also been reported as a potential controlled drug delivery system Nathan et al., 19941. This new class of copolymers consists of both ester and amide linkages in the backbone molecules and is sometimes referred as poly depsipeptides or poly(esters-amides). Poly(depsipeptides) could also be synthesized from ring-opening polymerization of morpholine-2,5-dione and its derivatives [Helder et al., 1986]. Barrows has also made a series of poly(ester-amides) from polyesterification of diols that contain preformed amide linkages, such as amidodiols [Barrows, 1994]. Katsarava and Chu et al. just reported the synthesis of high-molecular-weight poly(ester-amides) of M from 24,000 to 167,000 with narrow polydispersity (M/Mn = 1.20—1.81) via solution polycondensation of di-p-toluenesulfonic acid salts of bis-(α-amino acid) α,ω-alkylene diesters and di-p-nitrophenyl esters of diacids [Katsarava et al., In press]. These poly(ester-amides) consisted of naturally occurring and non-toxic building blocks and had excellent film forming properties. These polymers were mostly amorphous materials with Tg from 11 to 59°C. The rationale for making poly(ester-amides) is to combine the well-known absorbability and biocompatibility of linear aliphatic polyesters with the high performance and the flexibility of potential chemical reactive sites of amide of polyamides. Poly(ester-amides) could be degraded either by enzyme and/or nonenzymatic mechanisms. There is no commercial use of this class of copolymers at the present time.

The introduction of poly(ethylene oxide) (PEO) into PLLA in order to modulate the hydrophilicity and degradability of PLLA for drug control/release biomaterials has been reported and an example is the triblock copolymer of PLA/PEO/PLA [Li et al., 1998a]. Biomaterials having an appropriate PLLA and PEO block length were found to have a hydrogel property that could deliver hydrophilic drugs as well as hydrophobic ones like steroids and hormones. Another unique biodegradable biomaterial consisting of a star-block copolymer of PLLA, PGA, and PEO was also reported for protein drug delivery devices [Li et al., 1998b]. This star-shaped copolymer has 4 or 8 arms made of PEO, PLLA, and PGA. The glass transition temperature and the crystallinity of this star-
shaped block copolymer were significantly lower than the corresponding linear PLLA and PGA.

Because of the characteristic of very slow biodegradation rate of PLLA and the copolymers having a high composition ratio of PLLA, their biomedical applications have been mainly limited to (1) orthopaedic surgery, (2) drug control/release devices, (3) coating materials for suture, (4) vascular grafts, and (5) surgical meshes to facilitate wound healing after dental extraction.

42.3 NON-GLYCOLIDE/LACTIDE BASED LINEAR ALIPHATIC POLYESTERS

All glycolide/lactide based linear aliphatic polyesters are based on poly(α-hydroxy acids). Recently, there are two unique groups of linear aliphatic polyesters based on poly(ω-hydroxy acids) and the most famous ones are poly(ε-caprolactone) [Kimura, 1993], poly(β-hydroxybutyrate) (PHB), poly(β-hydroxyvalerate) (PHV) and the copolymers of PHB/PHV [Gross, 1994]. Poly(ε-caprolactone) has been used as a comonomer with a variety of glycolide/lactide based linear aliphatic polyesters described earlier. PHB and PHV belong to the family of poly(hydroxyalkanoates) and are mainly produced by prokaryotic types of microorganisms like *Pseudornonas oleovorans* or *Akaligenes eutrophus* through biotechnology. PHB and PHV are the principal energy and carbon storage compounds for these microorganisms and are produced when there are excessive nutrients in the environment. These naturally produced PHH and PHV are stereochemically pure and are isotactic. They could also be synthesized in labs, but the characteristics of stereoregularity is lost.

This family of biodegradable polyesters is considered to be environmentally friendly because they are produced from propionic acid and glucose and could be completely degraded to water, biogas, biomass, and hurnic materials [Gross, 1994]. Their biodegradation requires enzymes. Hence, PHB, PHV, and their copolymers are probably the most important biodegradable polymers for environmental use. However, the biodegradability of this class of linear aliphatic polyesters in human or animal tissues has been questionable. For example, high molecular weight PHB or PHB/PHV fibers do not degrade in tissues or simulated environments over periods of up to six months [Williams, 1990]. The degradability of PHB could be accelerated by γ-irradiation or copolymerization with PHV.

An interesting derivative of PHB, poly((β-malic acid) (PMA), has been synthesized from β-benzyl malolactoriate followed by catalytic hydrogenolysis. PMA differs from PHB in that the β-(CH₃) substituent is replaced by —COOH [Kimura, 1993]. The introduction of pendant carboxylic acid group would make PMA more hydrophilic and easier to be absorbed.

42.4 NON-ALIPHATIC POLYESTERS TYPE BIODEGRADABLE POLYMERS

42.4.1 Aliphatic and Aromatic Polycarbonates

The most significant aliphatic polycarbonates are based upon DMTMC and TMC. They are made by the same ring-opening polymerization as glycolide-based biodegradable polyesters. The homopolymers are biocompatible with a controllable rate of biodegradation. Pellets of poly(ethylene carbonate) were absorbed completely in two weeks in the peritoneal cavity of rats. A slight variation of this polycarbonate, that is, poly(propylene carbonate), however, did not show any sign of absorption after two months [Barrows, 1986]. Copolymers of DMTMC/ε-caprolactone and DMTMC/TMC have been reported to have adequate properties for wound closure, tendon prostheses, and vascular grafts. The most important advantage of aliphatic polycarbonates is the neutral pH of the degradation products.
Poly(BPA-carbonates) made from bisphenol A (BPA) and phosgene is non-biodegradable, but an analog of poly(BPA-carbonate) like poly(aminocarbonates) have been shown to degrade in about 200 days [Barrows, 1986]. In general, this class of aromatic polycarbonates takes an undesirably long period to degrade, presumably due to the presence of an aromatic ring which could protect adjacent ester bonds to be hydrolyzed by water or enzymes. Different types of degradation products of this polymer under different pH environments are produced. At pH >7.0, the degradation products of this polymer are BPA, and ammonia and CO$_2$, while insoluble poly(BPA-carbonate) oligomers were produced with pH <7.0 [Barrows, 1986]. The polymer had good mechanical properties and acceptable tissue biocompatibility. Unfortunately, there is currently no commercial use of this class of polymer in surgery.

42.4.2 Poly(alkylene oxalates) and Copolymers

This class of high crystalline biodegradable polymers was initially developed (Shalaby, 1994) for absorbable sutures and their coating. They consist of [―ROOC–COO―]$_n$ repeating unit where R is (CH$_2$)$_x$, with $x$ ranging from 4 to 12. R could also be cyclic (1,4-trans-cyclohexanediol) or aromatic (1,4-benzene, 1,3-benzene dimethanol) for achieving higher melting temperature. The biodegradation properties depend on the number of (CH$_2$) group, $x$, and the type of R group (i.e., acyclic vs. cyclic or aromatic). In general, a higher number of methylene group and/or the incorporation of cyclic or aromatic R group would retard the biodegradation rate and hence make the polymer absorbed slower. For example, there was no mass of the polymer with $x = 4$ remaining in vivo (rats) after 28 days, while the polymer with $x = 6$ retained 80% of its mass after 42 days in vivo. An isomorphic copolyoxalate consisting of 80% cyclic R group like 1,4-trans-cyclohexanediol and 20% with acyclic R group like 1,6-hexanediol retained 56% of its original mass after 180 days in vivo. By varying the ratio of cyclic to acyclic monomers, copolymers with a wide range of melting temperatures could be made, for example, copolymer of 95/5 ratio of cyclic (i.e., 1,4-trans-cyclohexanediol)/acyclic (i.e., 1,6-hexanediol) monomers had a $T_m = 210^\circ$C, while the copolymer with 5/95 ratio had a $T_m = 69^\circ$C. Poly(alkylenoxalates) with $x = 3$ or 6 had been experimented with as drug control/release devices. The tissue reaction to this class of biodegradable polymers has been minimal.

42.5 BIODEGRADATION PROPERTIES OF SYNTHETIC BIODEGRADABLE POLYMERS

The reported biodegradation studies of a variety of biodegradable polymeric biomaterials have mainly focused on their tissue biocompatibility, the rate of drug release, or loss of strength and mass. Recently, the degradation mechanisms and the effects of intrinsic and extrinsic factors, such as pH [Chu, 1981, 1982], enzymes [Williams et al., 1977, 1984; Williams, 1979; Chu et al., 1983], γ-irradiation [Campbell et al., 1981; Chu et al., 1982, 1983; Williams et al., 1984; Zhang et al., 1993], electrolytes [Pratt et al., 1993a], cell medium [Chu et al., 1992], annealing treatment [Chu et al., 1988], plasma surface treatment [Loh et al., 1992], external stress [Miller et al, 1984; Chu, 1985a], and polymer morphology [Chu et al., 1989] and on a chemical means to examine the degradation of PGA fibers [Chu et al, 1985] have been systematically examined and the subject has been recently reviewed [Chu, 1985b, 1991, 1995a; Hollinger, 1995; Chu et al., 1996]. Table 42.2 is an illustration of structural factors of polymers that could control their degradation [Kirmura, 1993]. Besides these series of experimental studies of a variety of factors that could affect the degradation of biodegradable polymeric biomaterials, there are two new areas that broaden the above traditional study of biodegradation properties of biodegradable polymers into the frontier of science. They are: theoretical modeling and the role of free radicals.
TABLE 42.2 Structural Factors to Control the Polymer Degradability

<table>
<thead>
<tr>
<th>Factors</th>
<th>Methods of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure of main chain and side</td>
<td>Selection of chemical bonds and functional groups</td>
</tr>
<tr>
<td>groups</td>
<td>Processing, copolymerization</td>
</tr>
<tr>
<td>Aggregation state</td>
<td>Polymer blend</td>
</tr>
<tr>
<td>Crystalline state</td>
<td>Copolymerization, introduction of functional groups</td>
</tr>
<tr>
<td>Hydrophilic/hydrophobic balance</td>
<td>Micropores</td>
</tr>
<tr>
<td>Surface area</td>
<td>Fiber, film, composite</td>
</tr>
<tr>
<td>Shape and morphology</td>
<td></td>
</tr>
</tbody>
</table>


42.5.1 Theoretical Modeling of Degradation Properties

The most systematic theoretical modeling study of degradation properties of biodegradable biomaterials was reported by Pratt and Chu who used computational chemistry to theoretically model the effects of a variety of substituents which could exert either steric effect and/or inductive effect on the degradation properties of glycolide/lactide based biodegradable polymers [Pratt et al., 1993a, 1994a,b]. This new approach could provide scientists with a better understanding of the relationship between the chemical structure of biodegradable polymers and their degradation behavior at a molecular level. It also could help the future research and development of this class of polymers through the intelligent prediction of structure–property relationships. In those studies, Pratt and Chu examined the affect of various derivatives of linear aliphatic polyester (PGA) and a naturally occurring linear polysaccharide (hyaluronic acid) on their hydrolytic degradation phenomena and mechanisms.

The data showed a decrease in the rate of hydrolysis by about a factor of 10^6 with isopropyl α-substituents, but nearly a six-fold increase with t-butyl a-substituents [Pratt et al., 1993b]. The role of electron donating and electron withdrawing groups on the rate of hydrolytic degradation of linear aliphatic polyesters was also theoretically modeled by Pratt and Chu [Pratt et al., 1994a]. Electron withdrawing substituents α to the carbonyl group would be expected to stabilize the tetrahedral intermediate resulting from hydroxide attack, that is. favoring hydroxide attack but disfavoring alkoxide elimination. Electron releasing groups would be expected to show the opposite effect. Similarly, electron negative substituents on the alkyl portion of the ester would stabilize the forming alkoxide ion and favor the elimination step. Pratt and Chu found that the rate of ester hydrolysis is greatly affected by halogen substituents due primarily to charge delocalization. The data suggest that the magnitude of the inductive effect on the hydrolysis of glycolic esters decreases significantly as the location of the substituent is moved further away from the a-carbon because the inductive effect is very distance-sensitive. In all three locations of substitutions (α, β, and γ), Cl and Br substituents exhibited the largest inductive effect compared to other halogen elements.

Therefore, Pratt and Chu concluded that the rate of ester hydrolysis is greatly affected by both alkyl and halogen substituents due primarily to either steric hindrance or charge delocalization. In the steric effect, alkyl substituents on the glycolic esters cause an increase in activation enthalpies, and a corresponding decrease in reaction rate, up to about three carbon sizes, while bulkier alkyl substituents other than isopropyl make the rate-determining elimination step more facile. It appears that aliphatic polyesters containing a isopropyl groups, or slightly larger linear alkyl groups, such as n-butyl, n-pentyl, etc., would be expected to show a longer strength retention, given the same fiber morphology. In the inductive effect, α-substituents on the acyl portion of the ester favor the formation of the tetrahedral intermediate through charge delocalization, with the largest effect seen with Cl substitution, but retard the rate-determining alkoxide
elimination step by stabilizing the tetrahedral intermediate. The largest degree of stabilization is caused by the very electronegative $F$ substituent.

**42.5.2 The Role of Free Radicals in Degradation Properties**

Salihouse et al. had demonstrated that the biodegradation of synthetic absorbable sutures is closely related to macrophage activity through the dose adhesion of macrophage onto the surface of the absorbable sutures [Matlaga et al., 1980]. It is also known that inflammatory cells, particularly leukocytes and macrophages are able to produce highly reactive oxygen species like superoxide (O$_2^-$) and hydrogen peroxide during inflammatory reactions toward foreign materials [Badwey et al., 1980; Devereux et al., 1991]. These highly reactive oxygen species participate in the biochemical reaction, frequently referred to as a respiratory burst, which is characterized by the one electron reduction of O$_2$ into superoxide via either NADPH or NADH oxidase as shown below. The reduction of O$_2$ results in an increase in O$_2$ uptake and the consumption of glucose.

\[
2\text{O}_2 + \text{NADPH} \xrightarrow{\text{(NADPH Oxidase)}} 2\text{`O}_2^- + \text{NADP}^+ + \text{H}^+ \quad (42.1)
\]

The resulting superoxide radicals are then neutralized to H$_2$O$_2$ via cytoplasmic enzyme superoxide dismutase (SOD).

\[
2\text{`O}_2^- + 2\text{H}^+ \xrightarrow{\text{(SOD)}} \text{H}_2\text{O}_2 + \text{O}_2 \quad (42.2)
\]

Very recently, Williams et al. suggested that these reactive oxygen species may be harmful to polymeric implant surfaces through their production of highly reactive, potent, and harmful hydroxyl radicals OH in the presence of metals like iron as shown in the following series of redox reactions [Williams et al., 1991; Ali et al., 1993; Zhong et al., 1994].

\[
\text{O}_2^- + \text{M}^{+n} \rightarrow \text{O}_2 + \text{M}^{+(n-1)} \quad (42.3)
\]

\[
\text{H}_2\text{O}_2 + \text{M}^{+(n-1)} \rightarrow \text{`OH} + \text{HO}^- + \text{M}^{+n} \quad (42.4)
\]

The net reaction will be:

\[
\text{`OH} + \text{H}_2\text{O}_2 \rightarrow \text{`OH} + \text{HO}^- + \text{O}_2 \quad (42.5)
\]

and is often referred to as the metal-catalyzed Haber--Weiss reaction [Haber et al., 1934].

Although the role of free radicals in the hydrolytic degradation of synthetic biodegradable polymers is largely unknown, a very recent study using absorbable sutures like Vicryl in the presence of an aqueous free radical solution prepared from H$_2$O$_2$ and ferrous sulfate, FeSO$_4$, raised the possibility of the role of free radicals in the biodegradation of synthetic absorbable sutures [Williams et al., 1997; Zhong et al., 1994]. As shown below, both `OH radicals and OH$^-$ are formed in the process of oxidation of Fe$^{2+}$ by H$_2$O$_2$ and could exert some influence on the subsequent hydrolytic degradation of Vicryl sutures.

\[
\text{Fe}^{+2} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{+3} + \text{`OH} + \text{OH}^-
\]

SEM results indicated that Vicryl sutures in the presence of free radical solutions exhibited many irregular surface cracks at both 7 and 14 days *in vitro*, while the same sutures in the two controls (H$_2$O$_2$ or FeSO$_4$ solutions) did not have these surface cracks. Surprisingly, the presence of surface cracks of Vicryl sutures treated in the free radical solutions did not accelerate the tensile breaking strength-loss as would be expected.
Thermal properties of Vicryl sutures under the free radical and 3% \( \text{H}_2\text{O}_2 \) media showed the classical well-known maximum pattern of the change of the level of crystallinity with hydrolysis time. The level of crystallinity of Vicryl sutures peaked at 7 days in both media (free radical and 3% \( \text{H}_2\text{O}_2 \)). The time for peak appearance in these two media was considerably earlier than Vicryl sutures in conventional physiological buffer media. Based on the Chu’s suggestion of using the time of the appearance of the crystallinity peak as an indicator of degradation rate, it appears that these two media accelerated the degradation of Vicryl sutures when compared with regular physiological buffer solution. Based on their findings, Williams et al. proposed the possible routes of the role of \(^{\prime}\text{OH}\) radicals in the hydrolytic degradation of Vicryl sutures [Zhong et al., 1994]. Unfortunately, the possible role of \(^{-}\text{OH}\), one of the byproducts of Fenton reagents (\( \text{H}_2\text{O}_2/\text{FeSO}_4 \)), was not considered in the interpretation of their findings. \(^{-}\text{OH}\) species could be more potent than \(^{\prime}\text{OH}\) toward hydrolytic degradation of synthetic absorbable sutures. This is because hydroxyl anions are the sole species which attack carbonyl carbon of the ester linkages during alkaline hydrolysis. Since an equal amount of \(^{\prime}\text{OH}\) and \(^{-}\text{OH}\) are generated in Fenton reagents, the observed changes in morphological, mechanical, and thermal properties could be partially attributed to \(^{-}\text{OH}\) ions as well as \(^{\prime}\text{OH}\) radicals.

Besides hydroxyl radicals, the production of superoxide ions and singlet oxygen during phagocytosis has been well documented [Babior et al., 1973]. Although the role of superoxide in simple organic ester hydrolysis has been known since the 1970s [Forrester et al., 1984, 1987; Johnson, 1976; Mango et al., 1976; San Fillipo et al., 1976], its role in the hydrolytic degradation of synthetic biodegradable polyester-based biomaterials has remained largely unknown. Such an understanding of the superoxide ion role during the biodegradation of foreign materials has become increasing desirable because of the advanced understanding of how the human immune system reacts to foreign materials and the increasing use of synthetic biomaterials for human body repair.

Lee and Chu very recently examined the reactivity of the superoxide ion towards biodegradable biomaterial having an aliphatic polyester structure at different reaction conditions such as temperature, time, and superoxide ion concentration [Lee et al., 1996a]. Due to the extreme reactivity of the superoxide ion, it has been observed that (he effect of superoxide ion-induced hydrolytic degradation of PDLLA and PLLA was significant in terms of changes in molecular weights and thermal properties. The superoxide ion-induced fragmentation of PDLLA would result in a mixture of various species with different chain lengths. A combined GPC method with a chemical tagging method revealed that the structure of oligomer species formed during the superoxide-induced degradation of PDLLA and PLLA was linear. The significant reduction in molecular weight of PDLLA by superoxide ion was also evident in the change of thermal properties like \( T_g \). The linear low molecular species (oligomer, trimers, and dimers) in the reaction mixture could act as an internal plasticizer to provide the synergetic effects of lowering \( T_g \) by increasing free volume. The effect of the superoxide ion-induced hydrolytic degradation on molecular weight of PLLA was similar to PDLLA but with a much smaller magnitude. The mechanism of simple hydrolysis of ester by superoxide ion proposed by Forrester et al. was subsequently modified to interpret the data obtained from the synthetic biodegradable polymers.

In addition to the PDLLA and PLLA, superoxide ions also have a significant adverse effect on the hydrolytic degradation of synthetic absorbable sutures [Lee et al., 1996c]. A significant reduction in molecular weight has been found along with mechanical and thermal properties of these sutures over a wide range of superoxide ion concentrations, particularly during the first few hours of contact with superoxide ions. For example, the PGA suture lost almost all of its mass at the end of 24 h contact with superoxide ions at 25°C, while the same suture would take at least 50 days in an in vitro buffer for a complete mass loss. The surface morphology of these sutures was also altered.
drastically. The exact mechanism, however, is not fully known yet: Lee et al. suggested the possibility of simultaneous occurrence of several main-chain scissions by three different nucleophilic species.

Lee and Chu also reported that the addition of Fenton agent or hydrogen peroxide to the degradation medium would retard the well-known adverse effect of the conventional γ-irradiation sterilization of synthetic absorbable sutures [Lee et al., 1996a]. They found that these γ-irradiated sutures retained better tensile breaking strength in the Fenton medium than in the regular buffer media. Chu et al. postulated that the γ-irradiation induced α-carbon radicals in these sutures react with the hydroxyl radicals from the Fenton agent medium and hence neutralize the adverse effect of α-carbon radicals on the backbone chain scission. This mechanism is supported by the observed gradual loss of ESR signal of the sutures in the presence of the Fenton agent in the medium.

Instead of the adverse effect of free radicals on the degradation properties of synthetic biodegradable polyesters, Lee and Chu described an innovative approach of covalent bonding nitroxyl radicals onto these biodegradable polymers so that the nitroxyl radical attached polymers would have biological functions similar to nitric oxide (Lee et al., 1996b, 1998). A preliminary in vitro cell culture study of these new biologically active biodegradable polymers indicated that they could retard the proliferation of human smooth muscle cells as native nitric oxide. The full potential of this new class of biologically active biodegradable polymers is currently under investigation by Chu for a variety of therapeutic applications.

42.6 THE ROLE OF LINEAR ALIPHATIC BIODEGRADABLE POLYESTERS IN TISSUE ENGINEERING AND REGENERATION

The use of biodegradable polymers as the temporary scaffolds either to grow cells/tissues in vitro for tissue engineering applications or to regenerate tissues in vivo has very recently become a highly important aspect of research and development that broadens this class of biodegradable polymers beyond their traditional use in wound closure and drug control/release biomaterials. The scaffolds used in either tissue engineering or regeneration are to provide support for cellular attachment and subsequent controlled proliferation into a predefined shape or form. Obviously, a biodegradable scaffold would be preferred because of the elimination of chronic foreign body reaction and the generation of additional volume for regenerated tissues.

Although many other biodegradable polymers of natural origin like alginate [Mala et al., 1994], hyaluronate [Henedetti et al., 1993; Larsen et al., 1993], collagen [Hirai et al., 1995] and laminin [Dixit, 1994] have been experimented with for such a purpose, synthetic biodegradable polymers of linear aliphatic polyesters like PGA, PLA, and their copolymers [Bwald et al, 1979, 1980; Greisler, 1982; Greisler et al., 1985, 1987a, b, 1988a, b, c, 1991a; Freed et al., 1993; Mikos et al., 1993; Yu et al., 1993, 1994; Mooney et al, 1994, 1995, 1996a, b, c; Kim et al., 1998a,b] have received more attention because of their consistent sources, reproducible properties, means to tailor their properties, and versatility in manufacturing processes.

Biodegradable polymers must be fabricated into stable textile structures before they can be used as the scaffold for tissue engineering or regeneration. The stability of the scaffold structure is important during tissue engineering and regeneration in order to maintain its proper size, shape, or form upon the shear force imposed by the circulating culture media in a bioreactor, the contractile force imposed by the growing cells on the scaffold surface, and other forces like the compression from surrounding tissues.

Kim et al. reported that, although ordinary non-woven PGA matrices have very good porosity (to facilitate diffusion of nutrients) with a high surface to volume ratio (to promote cell attachment and proliferation) and have been used to engineer dental pulp
Lecture Note

and smooth muscle tissues having comparable biological contents as the native tissues [Kim et al. 1998b; Mooney et al., 1996c], these non-woven PGA matrices could not maintain their original structure during tissue engineering due to the relatively weak non-woven textile structure and stronger contractile force exerted by the attached and proliferated cells/tissues [Kim et al., 1998a]. This led to deformed engineered tissues that may have undesirable properties; for example, the smooth muscle engineered on collagen gels exhibited significant contraction over time [Zeigler et al., 1994; Hirai et al., 1995].

Because of this shortcoming of the existing non-woven PGA matrices, Kim et al very recently reported the use of PLLA to stabilize the PGA matrices (Kim et al., 1998a). A 5% w/v PLLA solution in chloroform was sprayed onto PGA non-woven matrices (made of 12 µm diameter PGA fibers) of 97% porosity and either 3 mm or 0.5 mm thickness. The PLLA impregnated PGA non-wovens could be subjected to additional heat treatment at 195°C to enhance their structural stability further. Figure 42.3 shows the morphology of such a heat annealed PLLA-impregnated PGA non-woven matrix [Kim et al., 1998]. The PLLA was deposited mainly on the crosspoints of PGA fibers and hence interlocked the possible sliding of PGA fibers upon external force. Depending on the amount of PLLA used and subsequent heat treatment, the resulting PLLA-impregnated PGA non-woven matrices had an increase in compressive modulus of 10 to 35-fold when compared with the original PGA non-woven. The PLLA-impregnated PGA non-woven matrices also retained their initial volume (101 ± 4%) and about same shape as the original during the seven weeks in culture, while the untreated PGA non-woven exhibited severe distortion in shape and contracted about 5% of its original volume. Since PLLA is well-known to degrade at a much slower rate than PGA, its presence on the PGA fibers surface would be expected to make the treated PGA non-woven matrices degrade at a much slower rate than the untreated PGA non-woven. For example, the PLLA treated PGA non-woven retained about 80% of its initial mass, while the untreated PGA control had only 10% at the end of the seven week culture.

Linear aliphatic polyesters like PGA, its lactide copolymer, and poly-p-dioxanone have also been fabricated into both woven and knitted forms for the in vivo
regeneration of blood vessels in animals [Bowald et al., 1979, 1980; Greisler, 1982; Greisler et al., 1985, 1987a, 1988c, 1991b; Yu et al., 1993, 1994]. The published results from a variety of animals like dogs and rabbits indicate that full-wall healing with pseudo-endothelial lining was observed. This class of synthetic biodegradable polymers are promising candidates for the regeneration of vascular tissue.

These encouraging findings were believed to be associated with the intense macrophage/biomaterial interactions. [Greisler, 1988a; Greisler et al, 1989]. This interaction leads to a differential activation of the macrophage which, in turn, yields different macrophage products being released into the microenvironment [Greisler et al, 1991b]. Greisler et al. [1988b] have documented active stimulatory or inhibitory effects of various bioresorbable and non-resorbable materials on myofibroblast, vascular smooth muscle cell, and endothelial cell regeneration, and has shown a transinterstitial migration to be their source when lactide/glycolide copolymeric prostheses are used. The rate of tissue ingrowth parallels the kinetics of macrophage mediated prosthetic resorption in all lactide/glycolides studied [Greisler, 1982; Greisler et al., 1985, 1987a, 1988a]. Macrophage phagocytosis of the prosthetic material is observed histologically as early as one week following implantation of a rapidly resorbed material, such as PGA or polyglactin 910 (PG91O), and is followed by an extensive increase in the myofibroblast population and neovascularization of the inner capsules (Greisler, 1982; Greisler et al., 1985, 1986). Autoradiographic analyses using tritiated thymidine demonstrated a significantly increased mitotic index within these inner capsular cells, that mitotic index paralleling the course of prosthetic resorption [Greisler et al., 1991a]. Polyglactin 910, for example, resulted in a mitotic index of 20.1 ± 16.6% three weeks following implantation, progressively decreasing to 1.2 ± 1.3% after 12 weeks. The more slowly resorbed polydioxanone prostheses demonstrated a persistently elevated mitotic index 7.1 ± 3.8%, 12 weeks after implantation, a time in which the prosthetic material was still being resorbed. By contrast Dacron never yielded greater than a 1.2 ± 1.3% mitotic index [Greisler et al, 1991a]. These mitotic indices correlated closely with the slopes of the inner capsule thickening curves suggesting that myofibroblast proliferation contributed heavily to this tissue deposition.

Therefore, the degradation property of synthetic biodegradable polymers somehow relates to macrophage activation which subsequently leads to the macrophage production of the required growth factors that initiate tissue regeneration. Different degradation properties of synthetic biodegradable polymers would thus be expected to result in different levels of macrophage activation, i.e., different degrees of tissue regeneration.

DEFINING TERMS

**Biodegradation**: Materials that could be broken down by nature either through hydrolytic mechanisms without the help of enzymes and/or enzymatic mechanism. It is loosely associated with absorbable, erodable, resorbable.

**Tissue Engineering**: The ability to regenerate tissue through the help of artificial materials and devices.