Fabrication and Characterization of PLA–PGA Orthopedic Implants

C. MAULI AGRAWAL, Ph.D., P.E., GABRIELE G. NIEDERAUER, Ph.D., and KYRIACOS A. ATHANASIOU, Ph.D., P.E.

ABSTRACT

Fabrication methods and property characterization of polyglycolic acid (PGA), polylactic acid (PLA), and their copolymers are reviewed. Both of these aliphatic polyesters belong to the α-hydroxy group and biodegrade in a physiological environment to monomeric acids, which are readily processed and excreted from the body. The physical and mechanical characteristics discussed include molecular weight, crystallinity, stress–strain behavior, permeability, and melting/glass transition temperatures. The most common methods of fabricating PLA–PGA materials into medical devices are described.

INTRODUCTION

The use of biodegradable materials for the fabrication of orthopedic implants has seen unprecedented growth in recent years. Out of the relatively small group of materials that are both biocompatible and biodegradable, the family of polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers has certainly been the most studied. In the field of orthopedics these materials have been used to develop sutures, controlled release systems for drugs and other bioactive agents, scaffolds for regenerating both cartilage and bone, fracture fixation plates and screws for bone, as well as devices for ligament and tendon healing. To accurately match the properties of these devices with the specific requirements of each application, the fabrication process as well as the starting material have to be carefully chosen. The properties of the starting material often influence the fabrication parameters and the properties of the final device. At the same time the fabrication process can significantly alter the starting material properties. Thus, it is important to understand the interplay between the molecular structure, material properties, and fabrication processes.

STRUCTURE

Polylactic acid (PLA) and polyglycolic acid (PGA) are both aliphatic polyesters and belong to the α-hydroxy group. PLA can exist in two stereoisomeric forms: d and l. L-PLA crystallizes in pseudoorthorhombic or hexagonal forms and has a typical crystallinity of about 37%. Also, L-PLA can have two crystalline modifications, α and β; α is a helix conformation and β is an extended helix conformation. PGA has a simple linear structure and typically exhibits a crystallinity of approximately 50%. Unlike PLA, PGA does not have a methyl group, and this fact contributes to differences in their degradation kinetics. When sub-
jected to high temperatures under vacuum, PLA, PGA, and their copolymers thermally degrade to form lactides and glycolides.\textsuperscript{2}

To synthesize high-molecular-weight PLA and PGA, ring opening polymerization of the cyclic diesters glycolide or lactide is most commonly used.\textsuperscript{1,2} Often catalysts such as antimony, zinc, lead, or antimony are utilized for the polymerization process.\textsuperscript{1,2} However, low-molecular-weight homo- and copolyesters of lactic acid and glycolic acid have also been synthesized by direct polycondensation in the presence of water without using catalysts.\textsuperscript{3,4} Typically, polymerization of PLA and PGA requires 2–6 h at temperatures of approximately 175°C.\textsuperscript{5} The purity of the starting materials and processing humidity are critical parameters in obtaining quality polymers.\textsuperscript{5}

**DEGRADATION**

PLA and PGA biodegrade mainly by nonspecific hydrolytic scission, where the polymer chains are essentially cleaved by simple hydrolysis of the ester linkages.\textsuperscript{5,6} For example, PLA undergoes hydrolytic scission to its monomeric form, lactic acid, which is eliminated from the body by incorporation into the tricarboxylic acid cycle. The lactic acid is finally excreted by the lungs as CO\textsubscript{2} and in urine, with its principal elimination path being respiration.\textsuperscript{7} PLA implants labeled with radioactive carbon (\textsuperscript{14}C) and placed subcutaneously in rats for 3 months resulted in no significant radioactivity in feces or urine, confirming that the polymer is degraded and probably eliminated through CO\textsubscript{2} during respiration.\textsuperscript{8} PGA can be broken down in two ways, by hydrolysis and by nonspecific esterases and carboxypeptidases.\textsuperscript{9} Like lactic acid, the glycolic acid monomer is either excreted in urine or enters the tricarboxylic acid cycle.

The degradation rate of PLA, PGA, and their copolymers depends on numerous factors such as molar ratio of the constituents,\textsuperscript{3,6,10} blood supply at implant site,\textsuperscript{11} crystallinity of the polymers,\textsuperscript{3,10,12} thermal history,\textsuperscript{12} inherent viscosity (average molecular weight),\textsuperscript{12} geometry and available surface area/porosity for interaction with tissue,\textsuperscript{11–13} uptake of water, and wettability of the polymer.\textsuperscript{3,14} Table 1 gives the range of degradation rates for PLA, PGA, and their copolymers. An examination of these rates shows that the half-life of these polymers in terms of molecular weight can be varied by altering the PLA to PGA ratios. The broad range of degradation times for each copolymer can be attributed to differences in the shape/size, processing, and sterilization procedures used for the specimens, as well as the molecular weight and distribution of the starting material.

Polymer hydrolysis usually starts in the amorphous portion of the specimen as water can intrude easily into these regions. Therefore, a partly crystalline polymer will be preferentially degraded in the amorphous portion, leaving the crystalline regions temporarily intact. This leads to an overall increase of the crystallinity during degradation.\textsuperscript{15,16}

Researchers have also shown that enzymes play a definite role in the breakdown of lactide/glycolide materials.\textsuperscript{9,17,18} After testing the effects of 15 different enzymes on the in vitro hydrolysis of PGA, it was shown that the degradation of PGA in aqueous media is significantly influenced by enzymes with esterase activity.\textsuperscript{17} In addition, degradation has been shown to vary as a function of location in the implant. For example, degradation of high-molecular-weight PLA was found to proceed more rapidly in the center of the

<table>
<thead>
<tr>
<th>Composition</th>
<th>Degradation time</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polylactide (PLA)</td>
<td>6 months–over 4 years</td>
<td>5, 6, 10, 12, 13, 60</td>
</tr>
<tr>
<td>Poly-DL-lactide (DL-PLA)</td>
<td>24 weeks–18 months</td>
<td>5, 10, 12</td>
</tr>
<tr>
<td>Polyglycolide (PGA)</td>
<td>2–5 months</td>
<td>5, 6, 10, 12, 27</td>
</tr>
<tr>
<td>50 PLA:50 PGA</td>
<td>7–60 days</td>
<td>5, 6, 36, 61, 62</td>
</tr>
<tr>
<td>70 PLA:30 PGA</td>
<td>30 weeks</td>
<td>4</td>
</tr>
<tr>
<td>85 PLA:15 PGA</td>
<td>90–240 days</td>
<td>3, 5, 10, 12</td>
</tr>
<tr>
<td>90 PLA:10 PGA</td>
<td>2 months</td>
<td>5, 10, 12</td>
</tr>
</tbody>
</table>

242
implant than at the surface. Furthermore, the change in molecular weight of L-PLA ultrahigh strength rods tested in rabbits was found to depend on implantation site and environment. Molecular weight was reduced most in the medullary cavity, followed by the subcutis, and \textit{in vitro} degradation in phosphate-buffered saline at 37°C. By 8 weeks the molecular weight had decreased 75% from 220 to approximately 50 kDa.

The biodegradation process of aliphatic polyesters is initially manifested by a decrease in molecular weight due to random hydrolytic cleavage of the ester linkage, followed by a decrease in mass and mechanical strength. As mentioned earlier, crystallinity also appears to increase upon degradation as shown in a study of initially amorphous PLA, where percent crystallinity changed from 0 to 49% over a 90-week period.

Methods for characterizing the degradation of these polymers have been developed both \textit{in vivo} and \textit{in vitro}. \textit{In vitro} degradation assessment usually involves exposing polymer specimens to a physiological environment, such as saline or aqueous buffer solution at 37°C. After various exposure times, samples are usually vacuum dried and molecular weight or mass changes, mechanical properties, intrinsic viscosity, crystallinity, and other properties may be determined. For intrinsic viscosity measurements, a 0.5% polymer solution in chloroform at 25°C (ASTM Standard D445-88) can be used. Molecular weight measurements are routinely performed using gel permeation chromatography or by terminal-carboxyl-group analysis. An accelerated \textit{in vitro} hydrolysis test at 80°C has been suggested as a tool for preliminary analysis to compare the degradability of various polymers. Using this procedure, L-PLA and D-PLA were compared, and L-PLA was found to have higher viscosity over time, thus, indicating least molecular weight loss. \textit{In vivo} degradation has been quantified by measuring the temporal changes in molecular weight or intrinsic viscosity of PLA-PGA materials by excising implants that have been placed in animals for various times. Comparison of \textit{in vitro} and \textit{in vivo} degradation has shown that the results are comparable.

As expected, the implant’s functional environment affects its \textit{in situ} degradation characteristics. For example, the \textit{in vivo} degradation response of L-PLA plates has been shown to be affected by mechanical loading such that the tensile strength of bone plates subjected to mechanical stresses decreased in comparison to those not loaded. Interestingly, no corresponding significant changes were detected in the molecular weight.

To decrease the degradation rate of PLA-PGA devices, coatings have been used to act as barriers to hydrolysis by Vasenius et al. However, they reported that even though the coatings of slowly absorbing polymers assisted in strength retention \textit{in vitro}, no significant effects were observed \textit{in vivo}.

**PHYSICAL AND MECHANICAL CHARACTERISTICS**

Orthopedic biodegradable materials, such as PLA-PGA, are often intended to act in lieu of metallic implants for internal fixation. Obviously, the mechanical properties of such devices play a significant role in the support of healing bone, such that gross motion at the repair site promoted by insufficient stiffness results in inadequate healing, or that complete elimination of micromotion results in stress-shielding. In many instances, PLA-PGA materials are used as porous scaffolds for tissue ingrowth, and, therefore, the stress fields and fluid flow patterns created in the scaffolds, as a result of the functional environment, may be detrimental to existing or migrating cells due to a mismatch in mechanical properties with surrounding tissues. It is thus necessary to critically evaluate the mechanical characteristics of these devices—such as stiffness, strength, Poisson’s ratio, toughness, permeability—immediately prior to implantation. An additional difficulty is created by the fact that these properties are significantly altered with biodegradation, which implies that rates at which mechanical properties change \textit{in situ} must be determined a priori. The mechanical properties of PLA-PGA polymers are usually a function of their molecular weight, crystallinity, molecular orientation, porosity, pore size, and pore interconnectivity.

**Molecular Weight**

One of the most important physical properties of PLA, PGA, and their copolymers is molecular weight, since it greatly influences these materials’ mechanical and degradation characteristics. The entire functional response of medical PLA-PGA devices hinges significantly upon the initial value of molecular weight,
which is also affected by the production or manufacturing methodology, and in vivo temporal variations due to the in situ mechanical and physiological environments.

Initial molecular weights of various biodegradable polymers either commercially available or measured by gel permeation chromatography have been reported to vary widely.\textsuperscript{26} For L-PLA, values of weight-average molecular weight ($M_w$) have been reported to range from 50 to 756 kDa. For DL-PLA, $M_w$ ranges from 21 to 550 kDa.\textsuperscript{26} PLA–PGA polymers of various molecular weights (ranging from 20 to 550 kDa for PLA and 20 to 145 kDa for PGA) can be purchased from numerous suppliers. Number-average molecular weight values reported in the literature range from 19.6 to 150 kDa for L-PLA and 13.4 to 163 kDa for DL-PLA. Another measure of the average size of molecular chains in a polymer is its intrinsic viscosity, which has also been shown to vary widely from 0.6 to 8.2 dl/g for L-PLA and from 0.25 to 2.01 dl/g for DL-PLA.\textsuperscript{126} Owing to its insolubility in common organic solvents, such as chloroform or methylene chloride, molecular weight measurements for PGA are relatively uncommon. PGA used for fiber extrusion is soluble in hexafluoroisopropanol and has an intrinsic viscosity of 0.6–1.6 dl/g at 0.5% solution, which corresponds to an $M_w$ range of 20–145 kDa.\textsuperscript{27}

During fabrication of PLA–PGA implants or other medical devices, the materials are often exposed to significant mechanical stresses or fluctuations in temperature and pressure, with sometimes detrimental results as far as molecular weight is concerned. As an example, an almost 50% reduction in initial viscosity-average molecular weight occurs for L-PLA following extrusion and drawing.\textsuperscript{19} Obviously if the potential for significant alterations in molecular weight is expected during production, it is essential that appropriate design measures be implemented so as to account for such reductions in the final product’s molecular weight.

**Crystallinity**

Adjacent sections of polymeric molecular chains can sometimes pack into a stable crystalline arrangement, which represents an ordered structure. Most polymers display low crystallinity, never reaching 100%, and are thus either amorphous or semicrystalline. As a general rule, the greater the crystallinity of a polymer the greater are its stiffness and density. A measure of crystallinity can be obtained from density measurements. The density of PGA has been reported as 1.5–1.64 g/cm$^3$,\textsuperscript{27} while densities of 1.29 and 1.25 g/cm$^3$ have been reported for the crystalline and amorphous phases of L-PLA, respectively.\textsuperscript{1} There is no linear proportionality between the glycolic acid/lactic acid ratio and the crystallinity of the corresponding copolymer. PGA is highly crystalline, but crystallinity rapidly decreases in PLA–PGA copolymers. The degree of crystallinity depends upon the molecular chemistry and chain structure, temperature, and the rate of cooling during solidification from a melt. Molecular structure is important because side branches and cross-linking hinder the mobility of chains. Molecular chemistry plays a significant role in determining crystallinity because monomer units containing large or complex chemical species render crystalline order very difficult. Elevated temperatures and a slow rate of cooling enable the chains to be mobile and realign themselves in a more ordered solid structure. Thus, the crystallinity of PLA–PGA polymers can be altered as a result of fabrication processes where heat is used. For instance, a 74% crystallinity has been reported for L-PLA screws fabricated from a 65% crystalline batch of L-PLA.\textsuperscript{28} The percent crystallinity of a polymer sample can be estimated by X-ray diffraction, by infrared spectroscopy, or by measuring its heat of fusion using a differential scanning calorimeter and relating this measured value to the heat of fusion for a known degree of crystallinity. PGA sutures typically are 46–52% crystalline,\textsuperscript{2} while the crystallinity of L-PLA has been reported to range from 15 to 74%.\textsuperscript{2,26,28} DL-PLA is predominantly amorphous. Copolymers of L-PLA and PGA are usually amorphous when the PGA content is in the range of 25–70%. The same is true for DL-PLA and PGA copolymers when PGA content is 0–70%.\textsuperscript{2}

**Stress–Strain Properties**

The two physical characteristics discussed above, i.e., polymer molecular weight and crystallinity, are directly responsible for rendering PLA–PGA polymers strong and functionally capable. Usually as molecular weight and crystallinity increase so does the implant’s strength. It should be noted that mechanical strength does not follow a linear relationship with an increasing ratio of glycolic acid to lactic acid. The mechanical properties (tensile strength and modulus) of DL-PLA are dramatically improved with increas-
ing molecular weight.\textsuperscript{26} Tensile strength of L-PLA can also be improved with increasing crystallinity.\textsuperscript{1} It has been suggested that L-PLA or DL-PLA should possess a molecular weight of at least 100 kDa to achieve "good mechanical properties" necessary for orthopedic applications such as nails.\textsuperscript{26} In the same study, the relative brittleness of L-PLA compared to DL-PLA was also presented.\textsuperscript{26} Ductility, like most other mechanical properties, can be manipulated by altering fabrication techniques or starting with different molecular weights. For example, hot drawn melt-spun and solution-spun fibers have shown 12–26\% elongations at break,\textsuperscript{1} while braided melt-spun L-PLA fibers have been reported to exhibit initial elongations of approximately 15–35\%.\textsuperscript{29}

In a review paper covering studies performed on various biodegradable polymers and composites between 1980 and 1988 it was reported that PLA (including L-PLA and DL-PLA) has been shown to exhibit tensile and flexural strengths of 11.4–72 and 45–145 MPa, respectively, with tensile and flexural moduli of 0.6–4 and 2.4–10 GPa.\textsuperscript{30} Fiber reinforcement of PLA employed by a number of researchers was reported to result in significant increases in tensile and flexural characteristics; tensile and flexural strengths increased up to 200 and 412 MPa, respectively, with tensile and flexural moduli increasing up to 29.9 and 124.4 GPa, respectively.\textsuperscript{30} Percent elongations at yield and break for L-PLA have been reported to be between 1.8 and 3.7 and 2.0 and 6.0\%, respectively.\textsuperscript{26} Unreinforced PGA has tensile strength of 57 MPa and tensile modulus of 6.5 GPa, but is exceedingly brittle, failing at only 0.7\% elongation.\textsuperscript{31} Self-reinforced PGA rods were reported to have significantly increased flexural strength (370 MPa) and shear strength (250 MPa), but by 5 weeks in distilled water the flexural strength dropped to only 5\% of its original value.\textsuperscript{32} Using a sintering technique to achieve self-reinforcement\textsuperscript{33} or a drawing technique,\textsuperscript{27} it has been shown that PGA can attain elongations of 7–8 or 15–35\%, respectively.

Strength and stiffness characteristics of PLA–PGA copolymers, which are expected to depend on their glycolic acid to lactic acid ratio, are generally lower than their homopolymers and have been reported to vary significantly. For example, a 90\% PGA–10\% PLA copolymer had tensile and flexural strengths of 45 and 150 MPa, respectively, which were reduced to 4 and 7\% of these initial values after 4 weeks in distilled water.\textsuperscript{34} Reinforcement of this copolymer increased the initial tensile and flexural strengths; for example 7\% volume of carbon fiber bundles increased the tensile and flexural strengths to 90 and 190 MPa, respectively.\textsuperscript{34} Self-reinforced PLA–PGA rods were reported to exhibit ductile behavior, while melt molded PLA–PGA rods exhibited brittle characteristics.\textsuperscript{34}

\textit{Permeability}

Permeability is a significant mechanical characteristic of biodegradable, porous structures, which is often overlooked. By definition, permeability is the ability of an object to be traversed by another substance. In orthopedic applications, where PLA–PGA scaffolds are used to encourage repair of musculoskeletal tissues, permeability denotes the ease or difficulty of body fluids (e.g., vascular supplies, synovial fluid) to move through the pores of the biomaterial. Obviously, this property can have profound effects in modulating the repair process, since it regulates the volume and flow rate of nutrient-carrying fluids, which are necessary for initiating or maintaining cellular activities in and near the repair site. A large permeability can also be essential in aiding degradation through rapid evacuation of byproducts. It can additionally assist in providing a buffering action to maintain the pH, which can be severely affected by the acidic byproducts of degradation, especially in the vicinity of PLA–PGA implants. The degree of permeability can also affect the release of bioactive agents carried by the implant. A suitable means to measure this mechanical property is by applying Darcy's Law, which can be conveniently expressed by

\[
k = \frac{QL}{hAt}
\]

where \( k \) is the permeability constant, \( Q \) is the quantity of discharge, \( L \) is the length of the sample in the direction of flow, \( A \) is the cross-sectional area of the sample, \( h \) is the hydraulic head, and \( t \) is the time. This mechanical property can be expected to be related to the material's porosity, pore size, and pore interconnectivity.
To overcome the inherent difficulty of water entering the usually air-filled pores of PLA-PGA foams, a two-step immersion in ethanol and water was recently reported. For L-PLA porous discs, void volume filled by water was reported to have increased from 23 to 79% after 1 h prewetting in ethanol. For PLA-PGA copolymers the increase was from 59 to 97%. Of course, porous materials such as the ones used by Mikos et al. or Athanasiou and co-workers are expected to exhibit significant values of hydraulic permeability. Such values can easily be measured using a direct permeation experiment and applying Darcy's Law.

Melting and Glass Transition Points

Glass transition temperature and melting temperature, obtained from a specific volume versus temperature plot, represent properties of the amorphous and crystalline phases of the polymer, respectively. For L-PLA, glass transition and melting temperatures have been reported to be in the range of 54–59 and 159–178°C, respectively. Glass transition temperature for the amorphous DL-PLA is in the range of 50–53°C. For L-PLA and DL-PLA, there is a slight tendency for glass transition temperature to increase with molecular weight; no such relationships are shown between molecular weight and melting point, or degree of crystallinity. PGA exhibits a glass transition temperature of 36°C, while its melting temperature ranges from 210 to 226°C. PLA-PGA copolymers have glass transition temperatures of 37–55°C.

FABRICATION

PLA, PGA, and their copolymers are thermoplastic in nature, which implies that upon heating they soften and melt. In addition, they are usually soluble in several organic solvents. As a result, these polymers are highly conducive to being formed into intricate final shapes using a variety of techniques. The choice of a particular technique is often dictated by the physical and thermal properties of the specific material being processed as well as the desired form and properties of the final product.

Fiber Fabrication

One of the most widely used forms of PLA-PGA polymers are fibers, which are used extensively to fabricate sutures and also to reinforce composites. Fibers can be produced by solution-spinning, melting followed by extrusion or dry spinning, or a combination of these processes. Eling et al. compared melt spun and solution spun L-PLA fibers. Solution spun fibers were fabricated by extruding an L-PLA solution in toluene at 110°C while melt spun fibers were made by melt extrusion at 185°C. Above this temperature it was not possible to melt spin because of the low viscosity of the melt. The authors determined that in general solution-spun fibers show improved tensile properties compared to those melt-spun. For example, solution-spun and melt-spun L-PLA fibers exhibited tensile strengths of 1.0 and 0.5 GPa, respectively. This difference was attributed to a lower number of entanglements in the solution-spun fibers. Hyon et al. determined that melt-spun acetylated L-PLA fibers have tensile properties comparable to those of conventional crystalline polymers. Dauner et al. reported that the surface of melt-spun fibers is smoother compared to those solution-spun.

The molecular weight of a polymer plays an important role in determining the parameters for fiber fabrication. As the molecular weight increases the viscosity of the melt or solution for spinning increases correspondingly, thereby influencing the fabrication process. In a study on L-PLA, Suuronen noted that while polymers with a molecular weight of 180 kDa can be melt spun, suitable molecular weights for solution-spinning are in the range of 250 to 530 kDa.

The tensile properties of fibers can be significantly improved by hot drawing the fibers after spinning. Recently, Andriano et al. published an extensive study on the processing and characterization of PLA fibers. They examined DL-PLA polymers with different D/L ratios and determined that the tensile strength, elastic modulus, and birefringence increased up to a draw ratio of 6.7 and declined thereafter. These properties are a strong function of both the draw ratio as well as the drawing temperature. The drawing process results in improved alignment of the molecular chains leading to enhanced mechanical properties in the longitudinal direction. In addition, the hot drawing process can also cause an increase in crystallinity.
Once produced, fibers can be used as sutures in the form of monofilaments or can be braided to form multifilament sutures. Frazza et al.\textsuperscript{27} presented an overview of PGA sutures with regard to their fabrication, characterization, and \textit{in vivo} evaluation. Sutures and fibers of PLA–PGA can also be used to reinforce biodegradable composites, weave fabrics, or meshes, and fabricate three-dimensional scaffolds for tissue engineering.

\textit{Hot Molding and Machining}

PLA–PGA plates, rods, and screws used in orthopedics are often fabricated using injection molding techniques.\textsuperscript{41} The physical and mechanical properties of the final product are in part determined by the molding parameters. These properties include molecular weight, percent crystallinity, chain orientation, and stiffness. Leenslag et al.\textsuperscript{42} have described the use of 200°C and 18,000 kg “pressure” for fabrication of L-PLA implants. Plates and screws can also be machined from larger blocks of material. For cases where the use of heat and solvents has to be restricted for a variety of reasons, PLA–PGA can be compression molded under high pressure with no heat application.\textsuperscript{43} In such cases the low-molecular-weight fractions in the polymer plastically deform and fuse or coalesce together to yield the final molded product.

\textit{Microparticle Formation}

The use of microparticles for the delivery of drugs and proteins is steadily expanding. Although they are not currently used much for orthopedic applications the recent growth in the field of tissue engineering of bone and cartilage is likely to foster the increased use of microparticles in this area. Microparticles of PLA and PGA polymers can be readily formed because the polymers are soluble in organic solvents. Three different techniques are commonly used for microparticle fabrication:\textsuperscript{5} phase separation, solvent evaporation, and fluidized bed coating.

Phase separation is useful for microencapsulating water soluble compounds in PLA–PGA polymers. This process involves dissolving the polymer in an organic solvent followed by coacervating it with the use of a nonsolvent such as silicone oil.

Solvent evaporation is perhaps the technique most commonly used for microsphere formation and works best for encapsulating water-insoluble compounds. The polymer is first dissolved in an organic solvent and the compound is added to this solution under agitation. The solution is then emulsified in a solution of polyvinyl alcohol or another surfactant in water under continuous stirring. The resulting microspheres are extracted by filtration or by removal of the volatile solvent under vacuum.

Grandfils et al.\textsuperscript{44} described the use of solvent evaporation for fabrication of DL-PLA microspheres for embolic material. They examined the use of different tensioactive agents (polyvinyl alcohol, gelatin, and methylcellulose), stirring speed, and dispersed phase viscosity on the size of the microspheres. It was determined that the viscosity of the dispersed phase was the best parameter to alter to manipulate the size of the particles. In another recent study, Hafeli et al.\textsuperscript{45} used a solvent evaporation technique to encapsulate Fe\textsubscript{3}O\textsubscript{4} particles in PLA to produce magnetic microspheres that could be guided to a specific location \textit{in vivo} with the aid of an external magnetic field.

As in the two techniques described above, the fluidized bed technique uses a solution of the polymer in an organic solvent. This solution is then processed through an air suspension coating system to produce microspheres.\textsuperscript{44}

\textit{Gel Casting}

Coombes and Heckman\textsuperscript{46,47} described a gel casting technique to produce microporous implants of PLA–PGA polymers. This process involves first dissolving the polymer in a solvent such as acetone. The solution is then poured into a mold and allowed to stand at room temperature until it forms a gel. The gel is extracted and processed through several stages of solvent exchange in mixtures of acetone, ethanol, and water to yield a microporous solid implant. Bioactive factors may be incorporated in these implants by adding them to the starting solution.\textsuperscript{48,49} In one embodiment of this type of implant, Agrawal et al.\textsuperscript{49} used a 50:50 PLA–PGA copolymer to fabricate implants with bone morphogenetic protein and soybean trypsin inhibitor. Studies examining protein release kinetics determined that a high percentage of the proteins in-
corporated in these devices were released in the first 48 h even though the release continued thereafter for more than 70 days. The advantage of this technique is that it uses low heat (<45°C), so the probability of denaturing bioactive agents is low. In addition, implants of complicated shapes can be fabricated.

**Solution Casting**

PLA–PGA polymers can be dissolved in appropriate organic solvents and molded into different shapes by extracting the solvent using either evaporation or the addition of a nonsolvent such as ethanol, whereupon the polymer precipitates. Schmitz and Hollinger\textsuperscript{11} have described such a technique. They solubilized a 50:50 copolymer of PLA–PGA in chloroform, precipitated it with the addition of methanol, and combined it with demineralized freeze-dried bone. The doughy composite was then forced in molds and subjected to temperatures of 45–48°C for up to 24 h. The resulting implants were surgically placed in the calvaria of rabbits.

Heckman et al.\textsuperscript{50} have reported the solution casting of PLA implants with bone morphogenetic protein to treat fracture nonunions in a canine model. In a series of reports published by Athanasiou et al.\textsuperscript{36,51,52} the fabrication and use of solution cast implants for treating cartilage defects have been described. These implants were fabricated from a 50:50 copolymer of PLA–PGA, which was dissolved in acetone and precipitated in ethanol. The resulting “gummy” precipitate was packed into Teflon® molds, placed in a vacuum, and subjected to a specific temperature regime. The resulting microporous structure is shown in Figure 1.

**Solvent-Casting Particulate Leaching**

Several studies have recently reported the fabrication of biodegradable foams or scaffolds using a particulate leaching technique.\textsuperscript{53,54} Mikos et al.\textsuperscript{53} described a process wherein different copolymers of PLA–PGA are dissolved in chloroform. Sieved particles of sodium chloride were added to these solutions, which were then vortexed and allowed to dry by evaporation. The salt to polymer ratio was 9:1. The residual solvent was extracted by vacuum treatment. The sodium chloride crystals were leached out by immersion in deionized water at 25°C for 48 h to yield porous membranes. Three dimensional scaffolds were

![FIG. 1. Scanning electron micrograph of microporous PLA–PGA polymer implant showing an average pore size of 150 μm and a porosity of 60% by volume (magnification 80×).](image-url)
formed by laminating these membranes. The growth of cells on these scaffolds has been investigated in vitro.53,54

Fiber Bonding

A unique technique for forming three-dimensional scaffolds has been developed by Mikos et al.55 L-PLA polymer was dissolved in chloroform and added to a Petri dish containing a nonwoven mesh of PGA fibers. After the solvent was removed by evaporation, the resulting PLA–PGA composite was subjected to a temperature of at least 195°C for 90 min. The composite was removed from the oven and immersed in liquid nitrogen followed by air drying and vacuum treatment. Next the L-PLA matrix of the composite was removed by dissolution in methylene chloride utilizing the fact that PGA is insoluble in this solvent. This process yielded a scaffold of PGA fibers bonded together by the heat treatment. The seeding and proliferation of cells isolated from rats on these scaffolds have been investigated by the researchers.55

Composites

The mechanical properties of PLA–PGA materials are usually inferior to those of bone and hence the use of these polymers in bulk form may not be adequate for fracture fixation. To address this problem researchers have attempted to increase the mechanical strength of such biodegradable devices using fiber reinforcement. As mentioned previously, Daniels et al.30 compiled an extensive review of such implants. The reinforcing components include PLA, PGA fibers, carbon fibers, and ceramics. Several studies have reported the use of self-reinforced PLA–PGA and PGA rods.32,56–58 Self-reinforced PGA rods were fabricated by Törmälä et al.33 by sintering together bundles of PGA sutures (Dexon®) at temperatures of 205–232°C for time periods of 3 to 7 min under high pressure. In another study by the same group of researchers melt molded, self-reinforced, and carbon fiber-reinforced PLA–PGA composites were compared.34 It was determined that self-reinforcement significantly improved the flexural strength of the rods, while the carbon-reinforced rods exhibited high tensile strengths. In all cases, reinforced materials were determined to be superior to the melt-molded devices.

Suuronen et al.28 reported on the use of melt extruded L-PLA plates. The molecular orientation in these devices was further increased by die-drawing at 150°C to a draw ratio of 4. The enhanced orientation of the molecular chains in the draw direction results in self-reinforcement of the plates. A technique for reinforcing PLA matrices using a PGA fabric has also been described.59 Such a configuration results in enhancing the properties of the resulting devices in more than one direction.

In summary it is important to note that the properties of PLA–PGA devices are a strong function of both the starting material and the fabrication process. Although, PLA–PGA polymers offer the convenience of being formed into devices using a variety of techniques, these techniques have the potential of significantly altering the properties of the starting material. Thus, it is imperative to bear this point in mind while choosing a particular fabrication technique. In addition, the properties of the device should be carefully evaluated after fabrication and prior to use.

REFERENCES


Address reprint requests to:
Dr. C. Mauli Agrawal
Department of Orthopedics
The University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, TX 78284-7774

252