Degradation Rates of Oral Resorbable Implants (Polylactates and Polyglycolates): Rate Modification with Changes in PLA/PGA Copolymer Ratios

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Summary

This study determined the difference in rate of degradation between pure polymers of lactic acid (PLA), glycolic acid (PGA), and various ratios of copolymers of these two substances. Fast-cured and slow-cured polyglycolide was compared with copolymers of glycolide/lactide intermixed in ratios of 75:25, 50:50, and 25:75, as well as pure polylactide. A total of 420 rats were implanted with carbon-14 and tritium-labeled polymers in bone and soft tissue. At intervals of 1, 2, 3, 5, 7, 9, and 11 months, groups of five animals with the implants in bone and five with the implants in the abdominal wall were sacrificed. The implant area as well as tissue from the liver, spleen, kidney, lung and some muscle tissue was analyzed for radioactivity along with the urine and feces collected throughout the experiment. Half-lives of the different polymers and copolymers were calculated from the radioactivity present in the implant area for each time interval. Half-life of the polymers and copolymers decreased from 5 months for 100% PGA to 1 week with 50:50 PGA:PLA copolymer and rapidly increased to 6.1 months for 100% PLA. Fast-cured PGA had a half-life in tissue of 0.85 months. No significant radioactivity was detected in urine, feces, or tissue samples. From this study, it is concluded that control of degradation rate of the implant could best be attained by varying the composition of PLA and PGA between 75% and 100% PLA along with a corresponding 25% to 0% PGA. This would provide a half-life range of the implant of from 2 weeks to 6 months.

In the search for an ideal implant material, certain flexibility in design is required in order to satisfy the variable needs of a healing wound site. Although requirements of a biologic application such
as rigidity, nonallergenicity, and minimum inflammatory potential may be universally demanded, requirements such as size, shape, and duration of the implant in the tissue may need adaptability. Previous investigations have demonstrated the suitability of poly(lactic acids) and poly(glycolic acids) as implant material as determined by lack of inflammatory response and satisfactory healing of the implant site.\textsuperscript{1-6} Polylactate degradation rate was found to be relatively inflexible, with a half-life in the implant site of 168 days. This is satisfactory for utilization in bone fracture repair but may be of too long duration for use in healing of soft tissues. In addition, a recent application of resorbable lactate as a vehicle for pharmacologic agents such as vitamins may require a variable degradation rate.\textsuperscript{7} Histologic evaluation of degradation rates of polymers and copolymers of poly(lactic acids) and poly(glycolic acids) suggested a difference in implant degradation rate when different copolymer ratios were used.\textsuperscript{6} With the availability of radio-labeled polymers and copolymers of poly(lactic acids) and poly(glycolic acids), it was decided to measure the degradation rate of these materials when used in a variety of concentration ratios in soft tissue and bone.

**METHODS AND MATERIALS**

Carbon-14 and tritium-labeled polymer and copolymer pellets of poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) (Battelle Columbus Laboratories, Columbus, Ohio) were implanted in Sprague-Dawley rats. The polymers and copolymers were prepared from glycolic acid \([\text{1-}^{14}\text{C}]\) and \(\text{L-}(+)-\text{lactic acid}\) \([\text{2-}^{3}\text{H}(\text{N})]\). The composition, approximate activity, molecular size, and crystallinity are given in Table I as supplied by the manufacturer. The 100\% PGA material was fabricated by both slow and fast polymerization while the remaining polymers and copolymers were fabricated by slow polymerization.

The pellet weights ranged from 5 to 6 mg. A total of 420 rats, divided into six groups of 70 rats per sample, were implanted with the radioactive polymers, maintained on a normal diet, and sacrificed at 1, 2, 3, 5, 7, 9, and 11 months. Five animals that had the pellet implanted in the tibia and five animals that had the pellet implanted in the abdominal wall were used for each material at the time of sacrifice.
<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Glycolide/lactide</th>
<th>Composition (slow) (fast)</th>
<th>dpm/pellet of C-14</th>
<th>dpm/pellet of H-3</th>
<th>Molecular size (gel-permeation chromatography)</th>
<th>Crystallinity (differential thermal analysis)</th>
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<tr>
<td>1a</td>
<td>100/0</td>
<td>6.35 × 10^4</td>
<td>4.76 × 10^4</td>
<td>5.17 × 10^5</td>
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<tr>
<td>1b</td>
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<td>6.35 × 10^4</td>
<td>4.76 × 10^4</td>
<td>5.17 × 10^5</td>
<td>4.6 × 10^4</td>
<td>High</td>
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<tr>
<td>2</td>
<td>75/25</td>
<td>6.35 × 10^4</td>
<td>4.76 × 10^4</td>
<td>5.17 × 10^5</td>
<td>4.6 × 10^4</td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>50/50</td>
<td>6.35 × 10^4</td>
<td>4.76 × 10^4</td>
<td>5.17 × 10^5</td>
<td>4.6 × 10^4</td>
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</tr>
<tr>
<td>4</td>
<td>25/75</td>
<td>2.59 × 10^4</td>
<td>1.59 × 10^4</td>
<td>1.55 × 10^4</td>
<td>4.6 × 10^4</td>
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</tr>
<tr>
<td>5</td>
<td>0/100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4.6 × 10^4</td>
<td>Low to Moderate</td>
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After implantation the animals were housed in separate groups according to the material implanted and the sacrifice time. Urine and feces samples were collected and stored for analysis.

At the time of sacrifice, the implantation sites were excised from each animal along with the liver, spleen, kidney, lung, and a portion of the muscle tissue. Tissue and feces samples were weighed wet and burned on the Model 305 Automatic Sample Oxidizer (Packard Instrument Co., Downer's Grove, Ill.) The tritium and carbon-14 samples were collected from the oxidizer and diluted with Oxifluor (New England Nuclear, Boston, Mass.) Urine samples were diluted directly with Oxifluor. The samples were measured for radioactivity on the Model 3380 Liquid Scintillation Spectrophotometer in conjunction with the Model 544 Absolute Activity Analyzer.

RESULTS

The percentage of radioactivity remaining at the implant site of the 100% PLA group is shown in Figure 1. The degradation has

![Figure 1](image-url)
been plotted both linearly and exponentially. At 1 month, 87.4% of the implanted radioactivity remained. The activity decreased to 38% at 11 months. The degradation has a somewhat better correlation coefficient to the least-squares equation (exponential fit) than to the linear regression equation for the time period the animals were studied. The half-life of the 100% PLA was 6.6 months.

Both the fast- and slow-cured 100% PGA degradation rates are shown in Figure 2. The slow-cured polymer had 85% of the implanted activity remaining at 1 month and 29.5% at 9 months. The fast-cured PGA decreased rapidly from 30.8% of the implanted activity remaining at 1 month to 2.7% remaining at 5 months. The half-life of the slow-cured polymer was 5 months, compared to a half-life of 0.85 months for the fast-cured polymer. Use of different curing rates, therefore, varied the half-life from 1 to 5 months.

The degradation in activity of both the 75% PLA and the 75% PGA copolymers are shown in Figure 3. The half-life of the 75% PLA:25% PGA copolymer (0.6 months) is almost equal to the half-life of the 75% PGA:25% PLA (0.55 months). The percentage of

![Graph showing percent radioactivity remaining of slow- and fast-cured polyglycolate at implant sites from 1 to 9 months.](image)

Fig. 2. Percent radioactivity remaining of slow- and fast-cured polyglycolate at implant sites from 1 to 9 months.
Fig. 3. Percent radioactivity remaining of 75% PGA:25% PLA copolymer implants from 1 to 4 months.

Fig. 4. Half-life (in months) of various ratios of PLA and PGA as copolymers implanted in rat tissue.
the 75% PGA polymers activity remaining after 2 months was 10.2%, compared to 11.3% of the activity remaining in the 75% PLA implants.

The 50% PGA:50% PLA degraded very rapidly, with only 5.6% of the original activity remaining after 1 month. The half-life was approximately 0.24 months or 1 week.

Figure 4 summarizes the half-life periods of the polymers and copolymers studied. It represents graphically the approximate copolymer ratios required for any given half-life between 1 week and 6.1 months. Half-life of the polymers decreased rapidly from 5 months for 100% PGA to 1 week with the 50:50 PGA:PLA copolymer and then rapidly increased to 6.1 months for 100% PLA. The fast-cured PGA is not shown on this graph because all the copolymers were prepared from the slow-cured polymer.

Of all the polymers and copolymers studied, no significant difference in activity was observed between the implantation in soft tissue or that in the osseous tissue. The activities of both tritium and carbon-14 in the copolymer studies decreased at equal rates, indicating that the copolymer degraded as a copolymer rather than as a mixture of two polymers degrading at different rates.

The distribution of the radioactivity in the tissues was negligible, with no significant tritium or carbon-14 activity observed in any of the tissues analyzed. In all the groups of animals studied, no activity was found in the feces samples, and less than 7% of implanted radioactivity was found in the urine of the 50:50 PLA:PGA copolymer samples during the first 2 weeks after implantation.

**DISCUSSION**

The differences in rate of loss of radioactivity between the PLA and PGA polymers could be due to their breakdown by different metabolic pathways, namely, lactic dehydrogenase (PLA) and glycolate oxidase (PGA), although this was not investigated in this study.

An earlier study in this laboratory of DL poly(lactic acid) implants indicated that at 5.5 months 63% of the radioactivity was still present, and there was a linear rate of degradation.\(^1\) In this study, the poly(lactic acid) polymer had 55.8% of its radioactivity remaining at 5 months, which was similar to the previous study even though the implant site was 1/10 of the size of that in the previous study.
The degradation curve was found to be exponential when the duration of the experiment was lengthened.

The slow-cured poly(glycolic acid) polymer had a slightly lower half-life than the poly(lactic acid). One advantage of using the poly(glycolic acid) is that the degradation time can be varied by changing the curing time. It appears that the degradation rate is proportional to curing time. This is in disagreement with a previous study with PGA implants where the degradation of the implant was measured by means of a micrometer, and no significant difference in rate of degradation was seen between the fast- and slow-cured implants. The difference we have observed could be the result of C-14 labeled glycolic acid molecules being trapped and loosely contained within the fast-cured polymer, or it could indicate a more extensive tissue infiltration into the fast-cured pellet than into the slow-cured pellet while the outer dimensions remained approximately the same.

Another method of regulating the rate of degradation is varying the ratio of PLA to PGA. Using PLA as a substrate while varying the concentrations of PGA would give a greater range of degradation rates since the PLA had the longer half-life. The 50:50 copolymer would be of little value because of the short half-life of approximately 1 week. Increasing the ratio to 75% PLA:25% PGA increases the resorption rate to a half-life of 2 weeks (0.6 month). Varying the ratios between 75–100% PLA:25–0% PGA would give the most optimum half-life range: from 2 weeks to 6 months. While further studies are required on other proportions of the copolymers in this ratio range to obtain the exact ratio required, the current study gives the approximate PLA–PGA ratio for a given half-life.

References

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