TISSUE ENGINEERING
Volume 3, Number 4, 1997
Mary Ann Liebert, Inc.

Elevated Temperature Degradation of a 50:50 Copolymer of PLA-PGA

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ABSTRACT

***In vitro* degradation studies of devices fabricated from polylactic acid (PLA) and polyglycolic acid (PGA) are usually performed at the physiologic 37°C and often take long periods of time to complete. The objective of the present study was to examine the degradation of a 50:50 PLA-PGA copolymer over a wide temperature range (25°C to 80°C) and compare the degradation characteristics at temperatures below and above the polymer's glass transition temperature (T_g). Samples were fabricated using a solvent-casting technique and subjected to degradation in phosphate-buffered saline at the different test temperatures (T) for different periods of time. At the end of each test period, the samples were examined for changes in mass and molecular weight. The pH of the degradation media was also measured. Using the Arrhenius equation, activation energies were calculated for the degradation reaction. The results indicated that the rates of change of mass and molecular weight increased with increasing test temperatures. Activation energies for the degradation reaction at temperatures below and above the T_g were distinctly different. Thus, it is recommended that tests performed at $T > T_g$ should not be used to predict degradation behavior at $T < T_g$.**

INTRODUCTION

THE USE OF POLYLACTIC ACID (PLA) and polyglycolic acid (PGA) and their family of copolymers is steadily increasing in the field of orthopedics and tissue engineering.[1–3] These polymers are popular for several reasons: they have been used extensively for fabricating implantable devices and have been found to be fairly biocompatible;[4] their structure-property relationships have been examined in detail and have proven to be adequate for numerous implant applications;[5–7] additionally, their biodegradation characteristics have been studied extensively.[8–23] To determine the useful life of devices fabricated from these materials, *in vitro* tests are often performed prior to *in vivo* implantation. In general, most *in vitro* degradation experiments are conducted at the physiologically relevant temperature of 37°C. As pointed out by Bergsma et al.,[24] the need for studies encompassing complete material degradation has become even more critical because of reports of *in vivo* aseptic sinus formation or bone resorption at sites of implantation of

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This paper was presented at the inaugural meeting of the Tissue Engineering Society, Orlando, FL, December 13–15, 1996.

these materials.[25–27] Such adverse reactions have generally been associated with the degradation products of PLA-PGA materials.[27] Thus, comprehensive *in vitro* studies monitoring the degradation characteristics of PLA-PGA implants have become essential as screening tests that help to decrease the number of *in vivo* studies. However, the degradation of most commonly used PLA-PGA materials is relatively slow at 37°C, and studies may take several weeks or even years to complete. Consequently, there is a need to establish techniques to decrease the time period of these studies while ensuring that the results remain relevant and valid.

In the past, several studies have examined the effects of elevated temperatures on the degradation of PLA-PGA materials, which are poly-α-esters and degrade primarily by hydrolysis.[24,28–30] Makino et al.[29] investigated the degradation of L-PLA and D,L-PLA microcapsules at temperatures of 21°C, 37°C, and 45°C and used the weight-average molecular weight as an indicator of degradation. Using Arrhenius plots, they determined activation energy values of 19.9 Kcal/mole and 20.0 Kcal/mole for D,L-PLA and L-PLA microcapsules, respectively.

Buchholz[28] examined the effects of temperature on the degradation of D,L-PLA using two temperatures: 37°C and 80°C. Based on the measurement of intrinsic viscosity as a function of temperature and using the Arrhenius law, he estimated the activation energy for the degradation reaction to be 27.5 Kcal/mole. It is noteworthy that his calculations were based on only two temperature points, which spanned the glass transition temperature (57°C) of D,L-PLA. Bergsma et al.[24] investigated the degradation of L-PLA and D,L-PLA (96%L, 4%D) at 90°C. They concluded that, although the test temperature significantly exceeded the glass transition temperature (T_g) for the polymer, there was a good correlation between *in vitro* and physiologically degraded materials. However, they cautioned that calculations made for temperatures above T_g may not be able to predict degradation characteristics below this temperature. Reed and Gilding[30] studied the degradation of PGA sutures (T_g = 36°C) at the following temperatures: 25°C, 30°C, 35°C, 40°C, 45°C, and 50°C. They determined, that in general, an increase in temperature caused a corresponding increase in the degradation rate of the polymer; particularly, exceeding the glass transition temperature caused a significant rise in the rates of loss of mass and tensile properties.

Amorphous polymers change from a glassy to a rubbery state if their temperature exceeds the glass transition temperature. As is clear from a review of the above studies, T_g may have a significant effect on the degradation characteristics of these polymers. However, these studies have not examined the degradation behavior of PLA-PGA polymers at temperatures significantly higher than the T_g and compared it to degradation characteristics at temperatures below the T_g. The goal of the present study was to investigate the degradation of a 50:50 PLA-PGA copolymer over a wide temperature range and determine if degradation studies performed at temperatures above the T_g can be used to predict the degradation at physiologic temperatures and thereby reduce the amount of time required for performing *in vitro* degradation studies.

MATERIALS AND METHODS

A total of 144 cylindrical specimens (7-mm diameter × 3-mm thickness) were fabricated from a 50:50 PLA-PGA copolymer (inherent viscosity = 0.58 dL/g, T_g = 49.3°C) obtained from Birmingham Polymers, Inc., Birmingham, AL. The polymer was dissolved in acetone, precipitated in ethanol, packed in molds, and subjected to a regimen of temperature and vacuum.[12] The resulting microporous implants were divided into six groups corresponding to test temperatures of 25°C, 37°C, 44°C, 54°C, 65°C, and 80°C. Each group was further subdivided into four equal subgroups corresponding to different degradation periods ranging from 3 h to 70 days as outlined in Table 1. These degradation time periods were determined on the basis of preliminary studies. The specimens were each weighed and then immersed in 10 ml of phosphate buffered saline (pH 7.4) in individual vials at the appropriate test temperatures. At the completion of each test period, six specimens from each subgroup were removed, dried in a vacuum for 72 h, and analyzed for changes in mass and molecular weight (M_w). The mass was measured using an electronic balance with an accuracy of 1 μg, and the weight-average molecular weight was determined using gel permeation chromatography with polystyrene standards and chloroform at 32°C as the mobile phase. The pH of the degradation media was also measured at each time point.

TABLE 1. DEGRADATION TIMES USED FOR THE DIFFERENT TEST TEMPERATURES

	Degradation times			
Temperature	*1*	*2*	*3*	*4*
25°C	18 days	35 days	53 days	70 days
37°C	11 days	21 days	32 days	42 days
44°C	4 days	8 days	12 days	16 days
54°C	1.5 days	3 days	4.5 days	7 days
65°C	6 h	12 h	18 h	24 h
80°C	3 h	6 h	9 h	12 h

Statistics

All data were compiled as mean ± standard deviation and analyzed using analysis of variance as needed.

RESULTS

The pH of the degradation media decreased with degradation time as shown in Figure 1 where time is plotted on a logarithmic scale. The rate of pH change increased with increasing temperature, and this rate was the lowest for samples evaluated at 25°C. The samples tested at temperatures in the range of 25 to 54°C exhibited significant decreases in the pH after the second time point in each case. Although the pH of the degradation media for the samples tested at 65°C and 80°C did display changes, these decreases were not as dramatic.

For all test temperatures, the molecular weight of the polymer exhibited a steady decrease as a function of time (Fig. 2). An increase in the test temperature resulted in accelerated degradation. At 25°C, the degradation was noticeably slower, and at 70 days the specimens underwent only a 19% loss in their molecular weight compared to samples tested at the next higher temperature (37°C), which had lost almost 27.7% of its molecular weight in just 11 days.

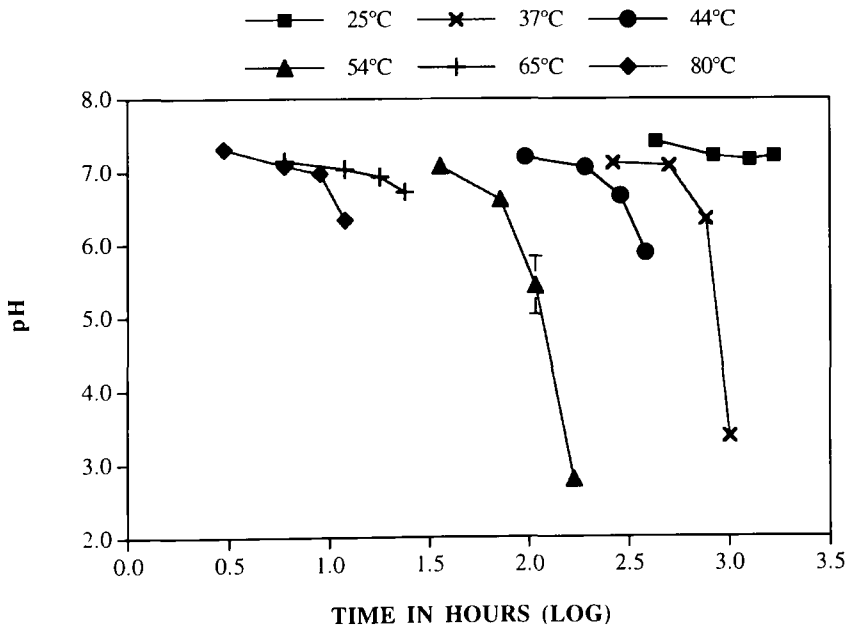

FIG. 1. Variations in pH of the degradation media as a function of time (mean ± standard deviation). The rate of change in pH increases with increasing temperature.

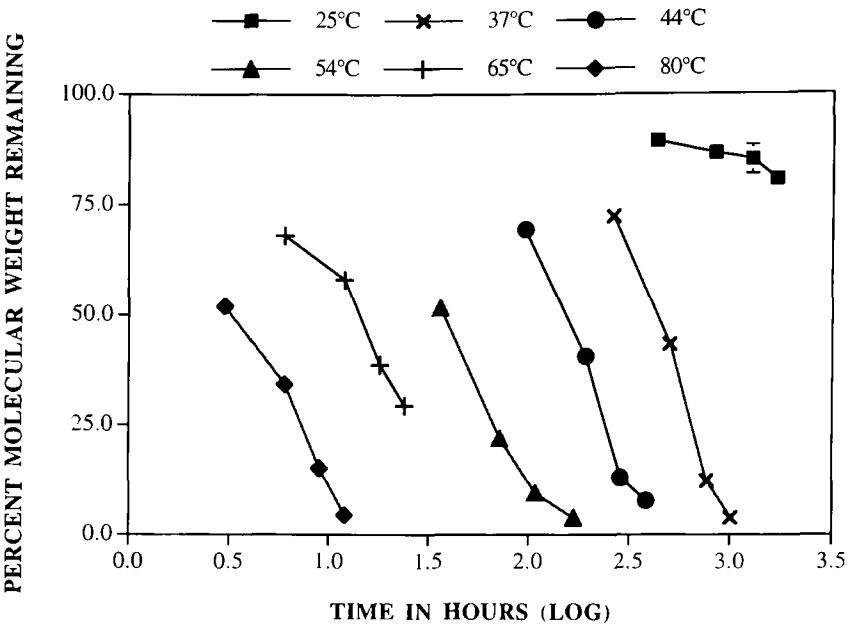

FIG. 2. Changes in the weight-average molecular weight of the 50:50 PLA-PGA copolymer as a function of time (mean ± standard deviation). The rate of decrease of molecular weight is a strong function of the test temperature.

The loss in mass (Fig. 3) was not as rapid as the decrease in molecular weight. For test temperatures in the range of 25 to 54°C, the decrease in mass as a function of time was initially low but showed dramatic changes at higher time points. The samples from test temperatures of 65°C and 80°C transformed into a gel-like material and visually appeared different from the samples tested at other temperatures. These samples also did not exhibit consistent changes in mass and sometimes showed an increase in mass that might be due to retention of fluid.

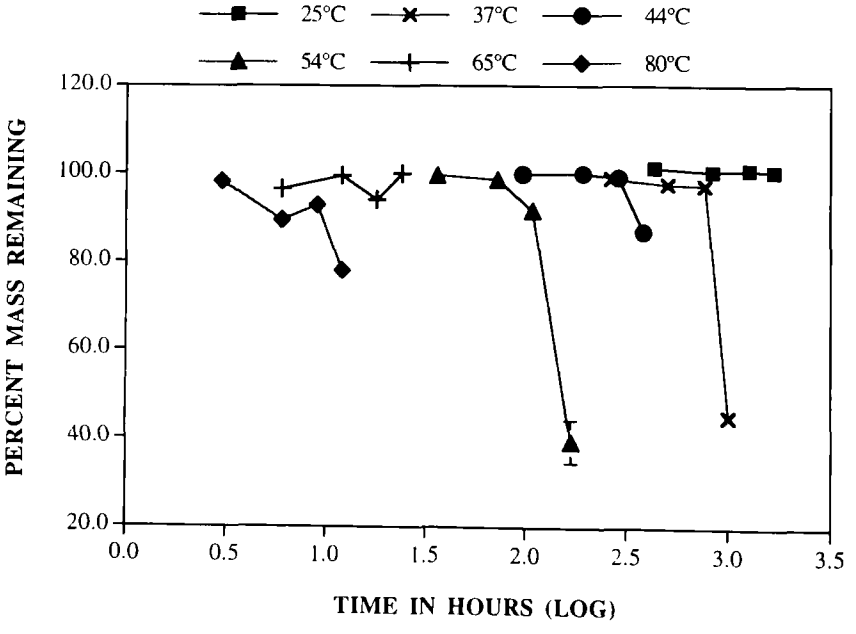

FIG. 3. Loss of mass of the PLA-PGA specimens as a function of time and test temperature (mean ± standard deviation). The specimens tested at 65°C and 80°C transformed into a gel-like form and provided inconsistent mass loss data.

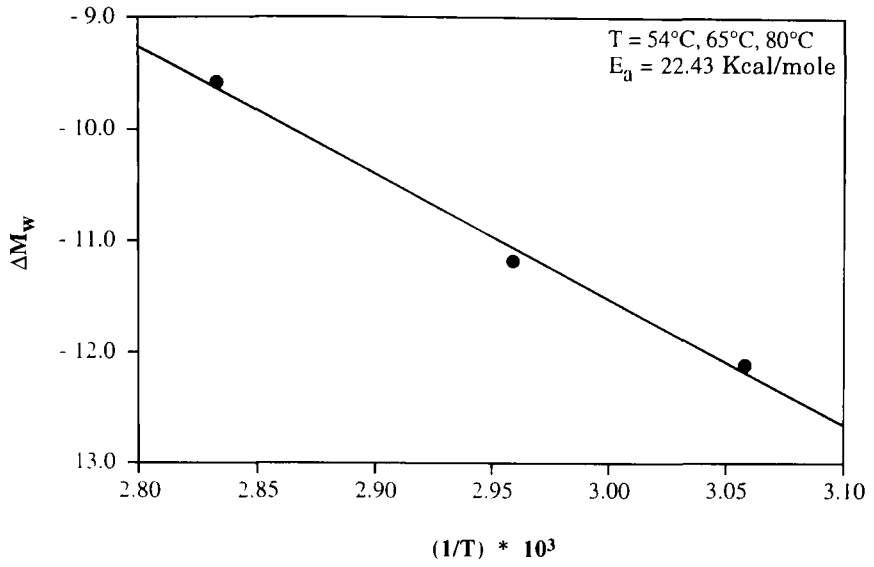

FIG. 4. Arrhenius plot for the rate of molecular weight loss (ΔM_w) as a function of time for temperatures greater than the glass transition temperature. The slope of this line can be used to calculate the activation energy E_a.

Arrhenius Equation

The temperature dependency of a reaction can be modeled using the Arrhenius equation (Eq. 1), which is a relationship between the activation energy E_a, absolute temperature T, and the specific rate constant of the reaction, k, at that temperature.

$$k = A \cdot \exp(-E_a/RT), \tag{1}$$

where A is a constant and R is the universal gas constant. This equation can be expressed as a logarithmic relationship:

$$\ln k = \ln A - E_a/RT, \tag{2}$$

which provides a linear relationship between the logarithm of k and the inverse of the test temperature ($1/T$). The slope of this line yields the activation energy. In the present study, activation energies were calculated for the chain scission degradation reaction assuming that (a) hydrolysis is the primary degradation mechanism for the test polymer, and (b) the temperature dependency of the hydrolysis rate follows Arrhenius' law. Changes in weight-average molecular weight were used as the basis for the calculations; hence, its rate of change, ΔM_w, was substituted for k in the above equations. First, the molecular weight was plotted as a function of degradation time for each test temperature to yield ΔM_w. Next the logarithm of ΔM_w was graphed as a function of $1/T$, and a linear curve was fitted to the data. The activation energy for the reaction was then calculated from the gradient of this curve. Such a plot for temperatures greater than T_g is shown in Fig. 4. The results for temperatures below and above the T_g were first analyzed as separate groups and then together. Table 2 shows the values for E_a for each case.

TABLE 2. ACTIVATION ENERGY AS A FUNCTION OF TEMPERATURE RANGE

Temperature range	*Activation energy,* E_a
25°C–44°C (below T_g)	40.9 Kcal/mole
54°C–80°C (above T_g)	22.4 Kcal/mole
25°C–80°C (test range)	27.2 Kcal/mole

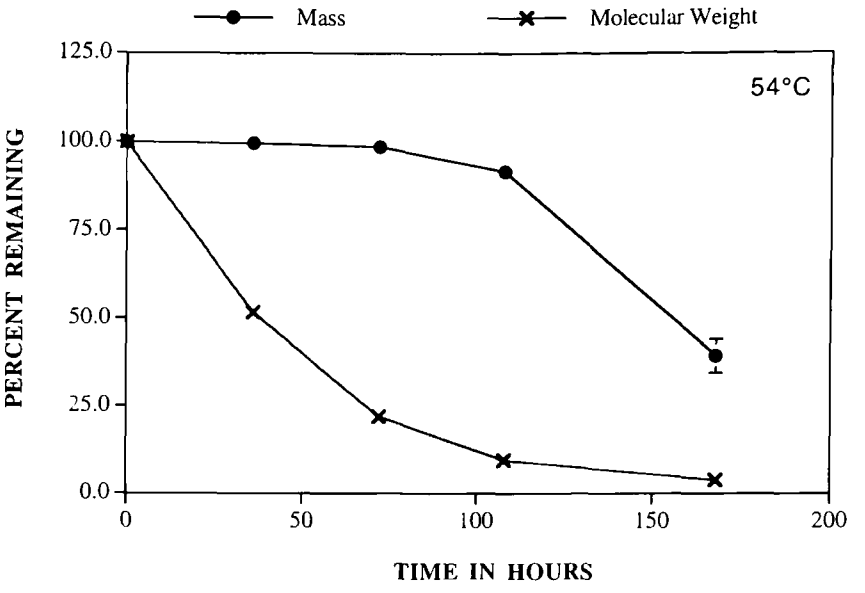

FIG. 5. Differences in the rate of change of mass and molecular weight for specimens tested at 54°C (mean ± standard deviation).

DISCUSSION

In general, the molecular weight of the samples degraded at a rate higher than changes in their mass. For example, at 37°C, the M_w had lost approximately 56.7% of its initial value at 21 days compared to only a 2.3% decrease in mass. Similar differences in the rates of change of mass and molecular weight at 54°C are shown in Fig. 5. This mismatch between the changes in mass and molecular weight is characteristic of PLA-PGA polymers and has been reported previously.[9] These polymers undergo bulk degradation wherein hydrolytic scission of the molecular chains commences immediately upon contact with water and is manifested as a decrease in molecular weight. However, the still bulky molecular chains are unable to diffuse out of the polymer implant until their size is sufficiently reduced. Thus, changes in mass are initially small. In the present study, the rate of change of mass increased with the test temperature, with higher temperatures yielding significantly faster rates of degradation because of the higher energy available for the chain scission reaction and enhanced chain mobility.

The mass loss for the samples tested at 65°C and 80°C showed inconsistencies because at some time points the samples exhibited an increase in mass (Fig. 3). Under gross examination, these samples appeared to be soft and gel-like in nature. It is possible that the increase in mass was due to retention of fluid. However, attempts to remove fluids from these specimens using a vacuum proved unsuccessful. Thus, the mass loss data for these test temperatures were ignored.

Samples at all temperatures exhibited a steady decrease in molecular weight as a function of time. However, the rate of decrease was a function of the test temperature, and the samples exhibited significantly higher rates of degradation with increasing temperatures. Changes in molecular weight showed the same overall trends for temperatures below or above the T_g. Although the samples tested at 65°C and 80°C showed anomalies in changes in mass, the molecular weight of these samples showed a steady decrease.

The pH of the degradation media surrounding the samples mirrored the changes in their mass. PLA and PGA degrade to lactic acid and glycolic acid, respectively. As these acidic by-products are released into the surrounding environment, they can alter its pH. The effect of the degradation process on the pH is important because it can adversely influence not only the response of the adjacent tissue *in vivo*, but it can also alter the degradation rate since the hydrolysis reaction is catalyzed by an acidic environment. As described above, upon commencement of the degradation process, the molecular weight of the polymer starts to decrease immediately, albeit the decrease in mass is only minimal initially. The pH of the media would

change only upon the release of the degradation by-products. Thus, decreases in the pH would be expected to mirror more closely changes in the mass than those in molecular weight. Upon comparison of Figures 1–3, it is clear that the results of the present study support this reasoning. It is noteworthy that, although the samples tested at 65°C and 80°C exhibited some increases in mass, the pH did not reflect these discrepancies. However, the smaller decrease in pH for these two temperatures when compared to tests performed at 37°C, 44°C, and 55°C implies that, although these samples underwent chain scission, the degradation products were substantially retained within the polymer matrix.

The polymer undergoes a thermal transition at its T_g, and the molecular chains gain segmental mobility. Such a state of higher energy would render them more susceptible to increased chain scission and a faster rate of degradation. This state is reflected in the lower activation energy measured for temperatures greater than T_g. The value of E_a estimated for the full temperature range investigated was 27.2 Kcal/mole, which compared well with the value of 27.5 Kcal/mole reported by Buchholz[28] for D,L-PLA using temperatures of 37°C and 80°C. Buccholz[28] noted that his value for E_a agreed well with values calculated by others using lower temperatures (below T_g). However, he expressed the need for detailed studies to explore if discontinuities in the rate of degradation exist at the T_g. In the present study, the activation energy estimated for the degradation reaction at temperatures below T_g was significantly different from that for temperatures exceeding T_g (Table 2). This difference brings into question the validity of performing tests at temperatures greater than T_g and using the data to predict degradation at more physiologic temperatures. Additionally, the transformation of the samples into a more gel-like state at elevated temperatures further augments the argument against using such extrapolations. Bergsma et al.[24] raised similar concerns, although they determined that tests performed at temperatures significantly higher than the T_g compared well with *in vivo* tests. If the T_g of the biodegradable implant material under consideration is higher than the physiologic 37°C, then, based on the results of the present study, it is recommended that elevated temperature studies should be performed only at temperatures below T_g. Although this study was performed for a 50:50 PLA-PGA copolymer, it is expected that similar concepts would hold true for other amorphous PLA-PGA copolymers as well.

With proper precautions, elevated temperature degradation studies can be of great value. For example, for the polymer used in this study, a 36-day study at 37°C can be completed in approximately 16 days at 44°C, resulting in immense savings of time and research funds.

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