

Predictors of Glass Transition in the Biodegradable Poly-lactide and Poly-lactide-co-glycolide Polymers

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ABSTRACT: The biodegradable polylactide (PLA) and poly(lactide-co-glycolide)s (PLGAs) are being widely investigated for use as scaffolds in bone and ligament reconstruction. The glass transition temperatures (T_g) for these polymers are generally greater than 37°C, causing PLA and PLGA devices to possess brittle characteristics in physiological conditions. To evaluate the possibility of obtaining PLGA polymers with T_g values below 37°C, we evaluated the determinants of T_g in PLA and PLGA copolymers. The T_g , changes in specific heat capacity (ΔC_p), and enthalpic relaxation (ΔH_g) in two consecutive heating cycles were correlated with lactide/glycolide content and intrinsic viscosity $[\eta]$ for PLA, PLGAs 90:10, 75:25, 65:35, and 50:50. A linear correlation was observed between T_g and intrinsic

viscosity, with 0.1 dL/g increase in viscosity resulting in an increase in T_g by about 3.55°C. The selection of PLA and PLGA copolymers with $[\eta]$ values <0.19 dL/g, corresponding to a viscosity average molecular weight of <70 kDa, will obtain PLA/PLGA polymers with T_g values below 37°C. The lowest attainable T_g values were found to be 28–30°C. Intrinsic viscosity also correlated with ΔC_p differences between aged and rapidly cooled polymers, and is therefore important in predicting free volume changes within these polymers upon aging. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 100: 1983–1987, 2006

Key words: glass transition; biodegradable; PLGA; intrinsic velocity; thermal analysis

INTRODUCTION

Flexible devices with plastic or rubbery consistency have numerous applications in drug delivery and tissue engineering. Current biomaterials used for fabricating flexible devices include hydroxyapatite cement,^{1–3} silicone,^{4,5} collagen,^{6–8} gelatin sponges,^{9–11} and their combinations with synthetic or natural polymers such as elastin,^{12,13} chitosan,^{14,15} and polytetrafluoroethylene.^{16,17}

The polylactide (PLA) and poly(lactide-co-glycolide) (PLGA) group of polyesters are biocompatible, biodegradable polymers being used extensively for numerous biomedical applications including bone regeneration and repair.^{18–20} An additional methyl group renders lactic acid more hydrophobic than glycolic acid, and varying the lactide to glycolide ratios in PLGAs causes them to possess a wide range of hydrophilicity and degradation profiles. Despite extensive use and wide applicability for PLA and PLGA, the fabrication of flexible devices using these polymers has been limited because of their high glass transition temperatures (T_g). General ranges for T_g include: L-PLA, 60–65°C; DL-PLA, 55–60°C; PLGA 85/15 and 75/25, 50–

55°C; PLGA 65/35 and 50/50, 45–50°C.²¹ Although T_g appears to decrease with increasing glycolic acid ratio, the value for all PLA and PLGA polymers is greater than the physiological temperature of 37°C. Devices fabricated using these polymers therefore tend to be brittle and susceptible to fracture when subjected to tension- or load-bearing stresses during use in bone replacement and regeneration.

The overall goal of this research is to fabricate PLA and PLGA devices that exhibit flexible characteristics at or below 37°C. In this study, we propose that PLA and PLGA devices with $T_g < 37^\circ\text{C}$ may be obtained by selecting polymers with low intrinsic viscosities. We therefore examined correlations of T_g and lactide/glycolide ratio with the intrinsic viscosity $[\eta]$ for DL PLA, PLGA 90/10, 75/25, 65/35, and 50/50. To accurately determine the parameters of glass transition, values were determined and compared between two consecutive heating cycles. In addition, correlations were also examined between other parameters such as specific heat changes (ΔC_p) and enthalpic relaxation (ΔH_g) in the region of the glass transition.

EXPERIMENTAL

Methods

DL PLA100 (inherent viscosity 0.39 dL/g), PLGA copolymers 90/10, 75/25, 65/35, and 50/50, with inher-

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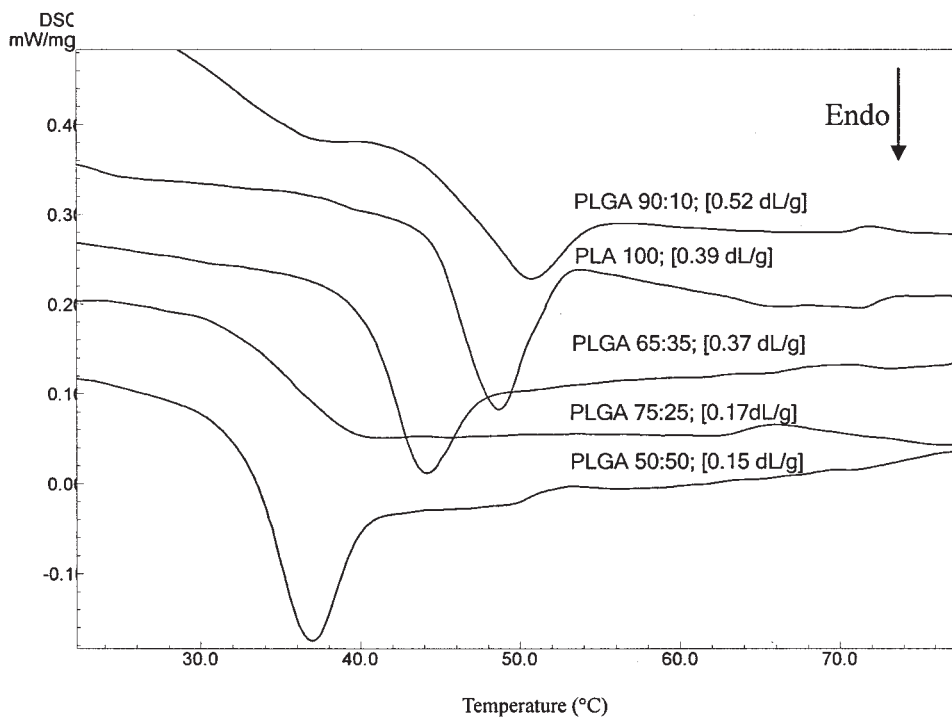


Figure 1 DSC thermograms obtained during the first heating cycle for PLA and PLGA copolymers. The thermograms are arranged in the order of their intrinsic viscosity (intrinsic viscosity is shown in square brackets).

ent viscosities 0.52, 0.17, 0.37, and 0.15 dL/g respectively, were obtained from Alkemers, OH. DSC thermograms were obtained using a Shimadzu, DSC-60, differential scanning calorimeter (DSC), fitted with a Shimadzu TA-60 data processor after calibration with an indium standard of melting point 156°C. The DSC contained a liquid-nitrogen-based cooling unit to achieve below-ambient temperatures. Thermograms were obtained by heating 3–8 mg samples in crimped aluminum pans at 10°C/min from –20 to 200°C in a nitrogen atmosphere (flow rate 20 mL/min). All samples were subjected to an initial heating cycle, cooled rapidly using the liquid-nitrogen accessory, and immediately subjected to a second heating cycle in the same temperature range. T_g , ΔC_p , and ΔH_g were measured using TA software. For all subsequent analyses, these parameters are denoted by the superscripts 1 and 2 to indicate the heating cycle in which they are obtained. Statistical correlations were examined using Minitab® Release 12.22 for windows, and linear (least squares) regression plots and coefficients were obtained using Microsoft® Office Excel 2003.

RESULTS

Figure 1 shows DSC thermograms obtained during the first heating cycle for PLA, PLGA 90/10, 65/30, 75/25, and 50/50. The thermograms were arranged vertically in the order of their $[\eta]$ (shown in square brackets) to enable comparison. From Figure 1, all

polymers showed a distinct glass transition with a mid-point (T_g^1) ranging from about 32 to 45°C (Table I). The transitions for all polymers except 75/25 were accompanied with an enthalpic relaxation, represented as an endothermic transition in the DSC thermograms.

Figure 2 shows DSC thermograms obtained during the second heating cycle for PLA, PLGA 90/10, 65/30, 75/25, and 50/50. The thermograms were arranged similar to those in Figure 1 to enable visual comparison. Figure 2 shows that the glass transition in all

TABLE I
Thermal Transitions in PLA and PLGA

Polymer	$[\eta]$ (dL/g)	Heating cycle	Glass transition		
			T_g (°C)	ΔC_p (mW/mg)	ΔH_g (J/g)
PLA 100	0.39	1	41.9	0.09	4.94
		2	45.3	0.13	2.64
PLGA 90:10	0.52	1	44.9	0.05	3.09
		2	48.7	0.11	2.22
PLGA 75:25	0.17	1	34.5	0.14	0
		2	36.5	0.13	2.40
PLGA 65:35	0.37	1	41.0	0.13	3.29
		2	42.8	0.14	2.55
PLGA 50:50	0.15	1	32.6	0.12	5.08
		2	35.7	0.10	3.82

$[\eta]$, intrinsic viscosity; T_g , glass transition temperature; ΔC_p , jump in specific heat; ΔH_g , enthalpic relaxation in the glass transition region.

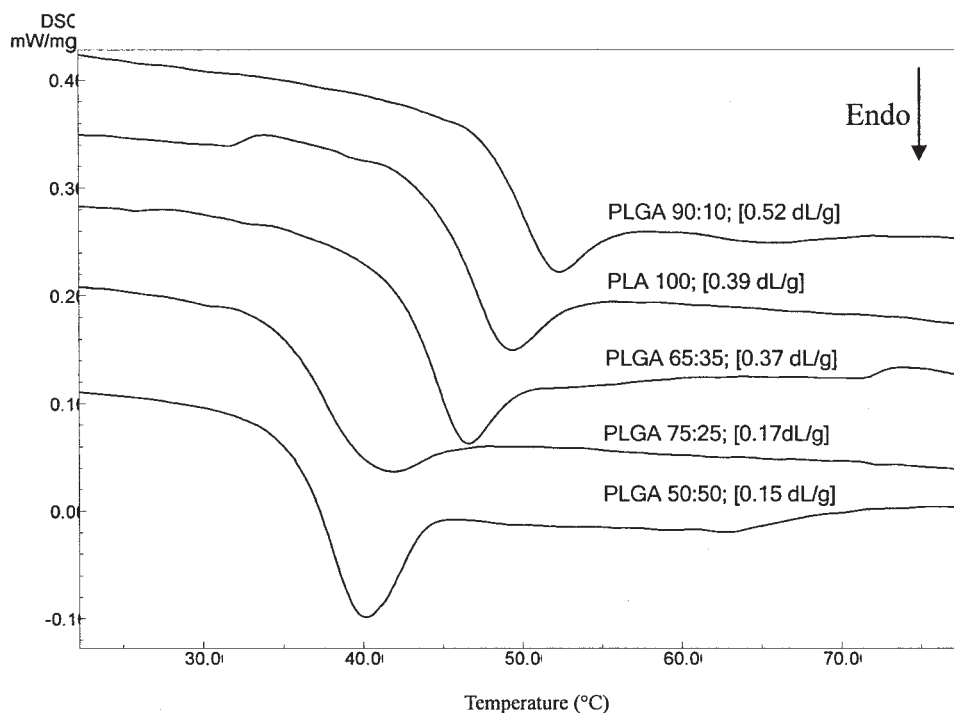


Figure 2 DSC thermograms obtained during the second heating cycle for PLA and PLGA copolymers. The thermograms are arranged in the order of their intrinsic viscosity (intrinsic viscosity is shown in square brackets).

polymers, including PLGA 75/25, was accompanied by endothermic relaxation. From Figures 1 and 2, a gradual decline in the glass transition with $[\eta]$ appears evident, with higher intrinsic viscosity polymers showing greater glass transition values.

These results are further evident in Table I. The glass transition temperatures obtained during the second heating cycles (T_g^2 values) were about 1–4°C higher than their corresponding T_g^1 values. A paired *t*-test examining differences between T_g^2 and T_g^1 returned a *P*-value of <0.001 for a hypothesized mean difference of 0, confirming that the differences were significant. Similarly, the enthalpic relaxation for all polymers except PLGA 75/25 was lower in the second heating cycle (i.e., $\Delta H_g^1 > \Delta H_g^2$) by about 0.5–2.5 J/g. These differences were also statistically significant at $P < 0.02$. No such correlations were observed between ΔC_p^1 and ΔC_p^2 .

Pearson's correlation coefficients were examined to detect if any relationships exist between the response variables (T_g , ΔC_p , and ΔH_g) and the predictors ($[\eta]$ and lactide/glycolide ratio). Significant correlations (significance level: $P < 0.001$) could only be obtained between T_g and $[\eta]$. Regression analysis resulted in a linear correlation of $[\eta]$ with both T_g^1 and T_g^2 as shown by eqs. (1) and (2) below:

$$T_g^1 = 28.5 + 32.9[\eta], R^2 = 0.98 \quad (1)$$

$$T_g^2 = 30.4 + 35.5[\eta], R^2 = 0.99 \quad (2)$$

The regression plots are shown in Figure 3. From the regression equations, a 0.1 dL/g increase in $[\eta]$ increases the glass transition by about 3.55°C for T_g^2 , and 3.29°C for T_g^1 . The regression equations also predict that: (1) polymers with T_g below physiological temperature of 37°C may be obtained when $[\eta]$ values are below 0.19–0.26 dL/g, and, (2) it is not possible to obtain PLA and PLGA polymers with T_g values below

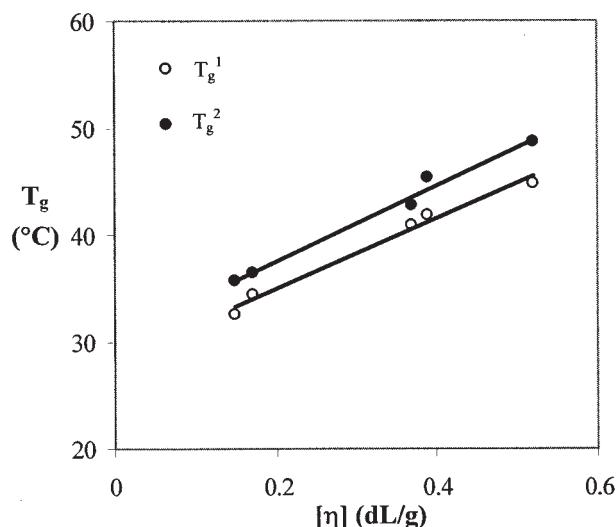


Figure 3 Correlation of intrinsic viscosity $[\eta]$ with the glass transition temperatures corresponding to the first heating cycle (T_g^1) and the second heating cycle (T_g^2).

28–30°C; plasticizing excipients will therefore be required to further lower the T_g below room temperature. This study therefore emphasizes the need for plasticizers to fabricate flexible biodegradable materials that exhibit plastic or elastic behavior at room temperature. No significant correlations were detected between the lactide/glycolide content and the glass transition temperatures.

DISCUSSION

DSC has been used extensively to characterize the thermal properties of PLA and PLGA-based devices.^{22,23} T_g values obtained from the first heating cycle are generally most frequently reported. This study emphasizes the need for measuring and comparing thermal transitions obtained during the first and second heating cycles during DSC. The first heating cycle represents thermal history and the effects of aging, whereas the second heating cycle represents more accurately the intrinsic properties of the polymer. Any transitions observed in the first heating may result from enthalpic relaxation during storage, plasticization due to moisture/residual solvent, or any other thermal history to which the polymers may have been subjected after synthesis. Following first heating, the previous thermal history is erased, and any volatile impurities, residual solvent, or adsorbed moisture are eliminated. Moreover, the increased mobility and lower viscosity resulting from the first heating may also be expected to improve thermal contact of the polymers with the aluminum pans, thereby decreasing thermal lag in the measurement of T_g .²

Intrinsic viscosity of polymers is a function of the viscosity average molecular weight (M_v), and may be determined using the Mark–Houwink's equation: $[\eta] = KM_v^\alpha$, where K and α are Mark–Houwink's constants.²⁴ The value for M_v lies between the number average (M_n) and weight-average molecular weight (M_w), and is closer to, and less than M_w by about 10–20%.²⁴ The significant linear correlation of T_g with $[\eta]$, and therefore M_v demonstrates the importance of rheology in predicting glass transition parameters in solid polymers. Using the Mark–Houwink's constants of $K = 5.45 \times 10^{-5}$ dL/g and $\alpha = 0.73$,²⁵ a viscosity of <0.19 dL/g corresponds to an M_v of about 70 kDa. The intrinsic viscosity, 0.19, used above was calculated from the regression equation for T_g ² only, which was considered to more accurately represent the true glass transition temperature of these polymers.

The systematic displacement of all glass transition temperatures to higher values during the second heating cycle may indicate the presence of a logical error such as thermal lag. However, if thermal lag was significant, the potential for improved thermal contact during the second heating cycle would result in T_g ²

being less than T_g ¹. The lower T_g ¹ values obtained in the first heating cycle were therefore attributed to factors other than thermal lag, such as plasticization by volatile impurities, residual solvent, or adsorbed moisture.

The term ΔC_p , or lowering in specific heat in the glass transition region has been attributed to a growth in the number of holes (free volume) and a change in the parameters of vibrational motion.²⁶ ΔC_p therefore represents the difference in free volume above and below the T_g . A low value for ΔC_p therefore suggests minimal growth in free volume when the amorphous polymer transitions from a glassy to rubbery state. Similarly, enthalpy relaxation in the region of the glass transition (ΔH_g) is known to occur when amorphous materials age below the T_g .²⁷ Under such conditions, amorphous polymers experience gradual loss of energy as certain polymeric fragments rearrange to more stable (crystalline) conformations.

As a polymer is rapidly cooled from a rubbery to a glassy state, the polymer molecules have limited opportunity to settle into more stable conformations. Rapid cooling therefore results in the polymeric molecules being frozen in their rubbery conformations, causing ΔC_p to assume low values. The ΔC_p ² values, which represent changes in free volume following rapid cooling, were therefore expected to be lower than ΔC_p ¹, causing ΔC_p ² – ΔC_p ¹ to be negative for all polymers. Interestingly, however, these values were negative only for PLGA 75/25, and PLGA50/50. For polymers with $[\eta]$ values 0.52, 0.39, 0.37, 0.17, and 0.15 dL/g, the corresponding ΔC_p ² – ΔC_p ¹ showed a gradual decline from 0.06, 0.04, 0.01, –0.01 to –0.02 mW/mg, respectively. Positive ΔC_p ² – ΔC_p ¹ for PLA, PLGA 90/10, and PLGA 65/35 suggest an increase in free volume in the glassy state after aging, which may result from enthalpic relaxation and formation of internal crystalline conformations without changes in total volume. In polymers with lower intrinsic viscosity, it is possible that the formation of more stable (crystalline) conformations are accompanied by a collapse of total volume as well, and are therefore not reflected as changes in ΔC_p . Additional studies involving mechanical and volume-expansion measurements will be necessary to validate this hypothesis.

For all polymers except PLGA 75/25, ΔH_g ¹ was greater than ΔH_g ² as expected, confirming significant effects of ageing on these polymers. The reason for the absence of endothermal relaxation in the aged, PLGA 75/25 sample remains unclear. No specific correlations could be obtained between ΔH_g ¹ – ΔH_g ² and $[\eta]$ or lactide/glycolide content.

CONCLUSIONS

This study examined the glass transition temperatures, changes in specific heat capacity, and enthalpic

relaxation for PLA and PLGA copolymers with varying lactide/glycolide ratios and intrinsic viscosity. Intrinsic viscosity rather than lactide/glycolide ratio appears to be the predominant factor in predicting glass transition temperatures for these polymers. Polymers with intrinsic viscosities below 0.19 dL/g or a viscosity average molecular weight of <70 kDa appear to have T_g values below physiological temperatures. Using the linear regression coefficients developed in this research, the lowest attainable T_g values were found to be around 28–30°C, thereby suggesting that T_g for PLA and PLGA cannot be reduced below room temperature without the use of plasticizing excipients. Intrinsic viscosity also correlated with ΔC_p differences between aged and rapidly cooled polymers, and is therefore important in predicting free volume changes within these polymers upon aging. Enthalpic relaxation in these polymers appears to be less dependent on intrinsic viscosity.

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