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Rapid cooling through the glass transition transiently increases ductility of PGA/PLLA copolymers: a proposed mechanism and implications for devices

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Abstract Heating bioabsorbable plates above T_g allows for temporary softening to facilitate adaptation to bone. This can, however, transiently alter the mechanical properties, a better understanding of which would provide further insight into the use of these polymers. Two types of unoriented L-lactide/glycolide copolymer wafer specimens (82:18 and 95:5 molar ratios) were heated to 90°C, cooled at various rates, and mechanically tested (three-point bend). Long cooling times (~8 h) did not change mechanical properties compared to unheated controls, whereas faster cooling rates resulted in increased ductility (50–200% increase in energy to break and peak deformation), however, there was gradual recovery. Under simulated physiological incubation conditions (pH 7.4 buffer, 37°C) partial recovery occurred within 48 h. These results fit well into the theoretical framework of free volume considerations. Following rapid cooling to below T_g, the polymer is not initially at equilibrium, containing excess free volume that contributes to increased molecular mobility and ductile behavior. As equilibrium is approached, free volume decreases and the material behaves as a glassy solid. While there is little clinical consequence as regards internal fixation devices, possible transient changes in permeability and other properties could have implications in drug delivery and other applications.

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Introduction

Bioabsorbable internal fixation has been used as an alternative to metallic fixation in many clinical applications, including use in the foot [1], ankle [2], knee [3], hand [4], wrist [5], elbow [6], shoulder [7], spine [8], and craniofacial skeleton [9]. Benefits include no need to remove the implant after osseous healing, radiolucency, and no stress shielding. [10, 11] As with metal plates, it is desirable to adapt bioabsorbable plates to the osseous surface to maximize fracture stability. Metal plates are adapted by bending, using appropriate instrumentation. [12] Most bioabsorbable polymers used for internal fixation have a glass transition temperature, T_g, that is above body temperature so it is in the glassy regime where it can provide rigidity and stability. [13–15] Below T_g, bioabsorbable polymers are sufficiently brittle to limit the ability for ‘‘cold bending’’. Cold bending oriented bioabsorbable plates is possible but may weaken them. [16, 17]

Alternatively, a bioabsorbable implant can be heated to above T_g using a heat pack, heat pen, or water bath to temporarily render it malleable for adaptation. [17–19] Once below T_g, the device retains its adapted shape. This method is applied, principally, to unoriented implants because oriented devices contain internal stresses which may relax and cause distortion when heated.

A well-studied bioabsorbable polymer used clinically as a fracture plate material is LactoSorb® copolymer (Biomet, Inc., Warsaw, IN), derived from 82% poly-L-lactic acid (PLLA) and 18% polygolycolic acid (PGA) (molar basis). It has been estimated that over 100,000 patients have received implants fabricated from this material. [20] Numerous clinical studies, principally in the craniofacial arena, have been published with positive outcomes utilizing plates, sheets, and mesh panels of this material, with intraoperative heating used as the primary means of adaptation. [9, 21, 22] Approximately 10 years ago a study was published showing that heating this copolymer to a temperature greater that its T_g, and permitting it to cool under ambient conditions, resulted in an increase in the ductility of the material. [18] This effect was short-lived as in vitro studies showed that by one week in pH 7.4 buffer at 37°C, the mechanical properties of both heated and unheated specimens were essentially the same and showed equivalent temporal profiles of strength loss over a 12 week period. The authors, however, did not evaluate the mechanism in detail. Furthermore, only one copolymer formulation was studied, so whether this was a general phenomenon, or not, was not investigated.

Increasingly, bioabsorbable polymers are being used for applications such as tissue engineering matrices and drug delivery vehicles making a more complete understanding of factors that effect these materials critical for future development efforts. [23–25] The goals of this study were to (1) further investigate the relationship between heating and cooling cycles on the mechanical properties of PLLA/PGA copolymers, (2) explore the reversibility of this effect, (3) examine the clinical implications for fracture fixation devices, and (4) propose areas of study whereby this effect might be advantageous.

Materials and methods

Specimen description

LactoSorb® copolymer (Biomet, Inc., Warsaw, IN) is a substantially amorphous random copolymer of 82% PLLA and 18% PGA (molar basis) with an inherent viscosity of approximately 1.6 (0.25 g/100 mL chloroform, 30°C). [26] Specimens were unoriented and were fabricated by compression molding dried resin pellets at 160°C, under vacuum, into blanks, machining the blanks into wafers, followed by ethylene oxide sterilization and aeration. Small wafers were 25.4 × 6.4 × 1.0 mm while large wafers were 50.8 × 10.0 × 1.3 mm. Limited studies were also performed on small (nonsterile) wafers similarly fabricated from a 95% PLLA and 5% PGA copolymer (Boerhinger-Ingelheim, Ingelheim, Germany).

General heating regimen

A two-liter beaker containing water was set on a hot plate and magnetically stirred. The hot plate was adjusted to produce a water temperature of ~90°C. Wafers were placed in water-impermeable pouches, one specimen per pouch, and submersed in the water bath for 5 min, permitting the wafers to be heated while in a dry state.

Post-heat regimen: dry and wet incubation

After heating to 90°C, the small 82:18 copolymer specimens were removed from the pouches and incubated under one of three sets of conditions for up to 48 h: (1) room temperature (23°C) under vacuum, (2) 37°C in a forced-air oven, or (3) 37°C pH 7.4 phosphate buffer. Prior to transfer to the incubation systems, the specimens were exposed to ambient conditions for several minutes where they had opportunity to quickly cool to room temperature. Following incubation, the specimens were immediately mechanically tested in three-point bend (see below). This experiment concentrated on failure appearance, as described below. Ten unheated specimens were used as controls and five wafers were used for each set of the 90°C heat/incubation conditions.

Post-heat regimen: cooling rate

After heating the pouch-encased large 82:18 specimens to 90°C, the water bath was transferred to an unheated magnetic stir plate and the bath was allowed to cool to 45°C, recording the temperature decline with a thermocouple. The cooling rate was slowed by surrounding the beaker with thermal insulation or increased by setting the beaker in a refrigerator. For extremely fast cooling, the pouch (containing a thermocouple) was removed from the hot water bath and immediately submersed in room temperature water. Overall, the cooling times ranged from 20 s to nearly 8 h. Upon reaching final temperature, mechanical testing (see below) was immediately performed. Six or seven of the large 82:18 specimens were tested per each set of conditions. A limited set of similar experiments was performed on small 95:5 specimens, with five used for each set of conditions.

Post-heat regimen: quenching and dry incubation

After submersion in the 90°C bath for 5 min, the pouches containing small 82:18 specimens were immediately submersed (quenched) in another water bath set at one of the following temperatures: 37°C, 45°C, 50°C, or 55°C for 15 min, 1 h, or 2 h. Following this incubation, the pouches were removed and subsequently quenched in room temperature (23°C) water for 5 min, then immediately mechanically tested (see below). Six wafers were tested per each set of conditions.

Differential scanning calorimetry analysis

Differential scanning calorimetry (DSC) was performed using a TA Instruments (New Castle, Delaware) V4.0C scanning at 20°C/min from 30°C to 200°C. The software was used to automatically determine the T_g as well as the location and enthalpy associated with any melting peaks. Scans were performed on 82:18 specimens following one of three types of heat treatments, i.e., unheated; heated at 90°C for 5 min followed by an air quench; or similarly heated and quenched, followed by incubation in an oven at 45°C for 19 h. Measurements were performed in duplicate.

Contact angle measurement

Static water contact angles were determined by placing a 10 μL sessile drop of deionized water on the specimen and using an optical comparator (TEC-14, J&L Metrology, Springfield, VT) at 50X magnification equipped with a digital protractor to measure the angle at an ambient temperature of 24°C and relative humidity of 39%. Ten replicates were performed for each set of two conditions, i.e., 82:18 specimens unheated, or heated at 90°C for 5 min followed by an air quench.

Mechanical testing

The wafers were tested in three-point bend, under ambient room conditions, utilizing a Sintech 1/S uniaxial mechanical test machine (Sintech, Inc., Eden Prairie, MN). The fixture radii were 1.3 mm, with a support span of 8.9 mm and a deflection rate of 12.7 mm/min, as shown in Fig. 1. A relatively short support span was chosen to minimize the length of the region over which the bend transition occurred in an effort to better differentiate the failure modes of the heated and unheated specimens by their relative ductile/brittle characteristics. Specimen width and thickness, as well as the support span length, were provided as inputs to the analysis program. The following quantities were determined utilizing Testworks (Sintech, Inc.) software: modulus, energy to failure (area under the load-deflection curve), and peak deformation at failure (excursion of the central load fixture), with failure defined as the point at which load was reduced to 60% of peak value to be consistent with the prior study [18]. In addition, the wafer appearance in the central bend location was observed with a microscope and recorded. The varied appearances were divided into four principal failure modes: Mode 1) partial thickness crack across the entire tensile face of the specimen and the region was white and opaque, Mode 2) a white, opaque appearance without an observable crack, Mode 3) amber and translucent, with small, discrete regions that were white and opaque, without an observable crack and Mode 4) amber and translucent without evidence of crack formation or white regions. Thus, failure modes ranged from brittle (Mode 1) to ductile (Mode 4)

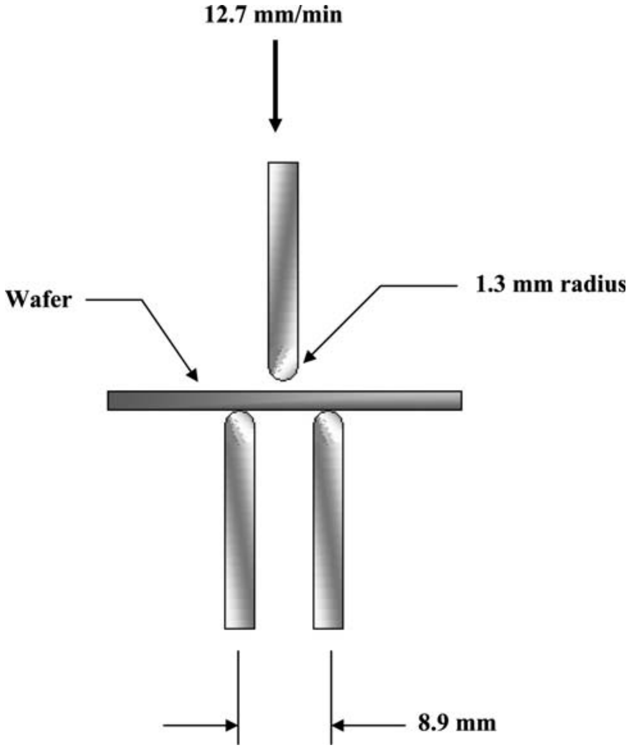

Fig. 1 Schematic of three-point bend test

Statistical analysis

Statistical analysis was performed using one-way analysis of variance followed by a post hoc Student-Newman-Keuls test. Statistical significance was taken for p values less than 0.05.

Results

Differential scanning calorimetry

Figure 2 shows representative DSC scans for the 82:18 copolymer for three conditions, namely (1) unheated, (2) heated for 5 min at 90°C then air-quenched, and (3) similarly heated and quenched, then incubated in an oven at 45°C for 19 h. The respective T_g values were 62.3 ± 0.0°C, 57.4 ± 0.4°C, and 60.1 ± 0.7°C (all significantly different). Each scan displayed an endothermic peak immediately following T_g whose magnitude was dependent on thermal history. Peak endothermic heat flow magnitudes were 1.22 ± 0.12 W/g (unheated), 0.63 ± 0.04 (heated and quenched), and 0.96 ± 0.12 (heated, quenched, incubated). Values for the unheated copolymer were significantly greater than that of the heated and quenched copolymer which was significantly less than those for the heated/quenched/incubated copolymer. However, the values corresponding to those of the unheated and heated/quenched/

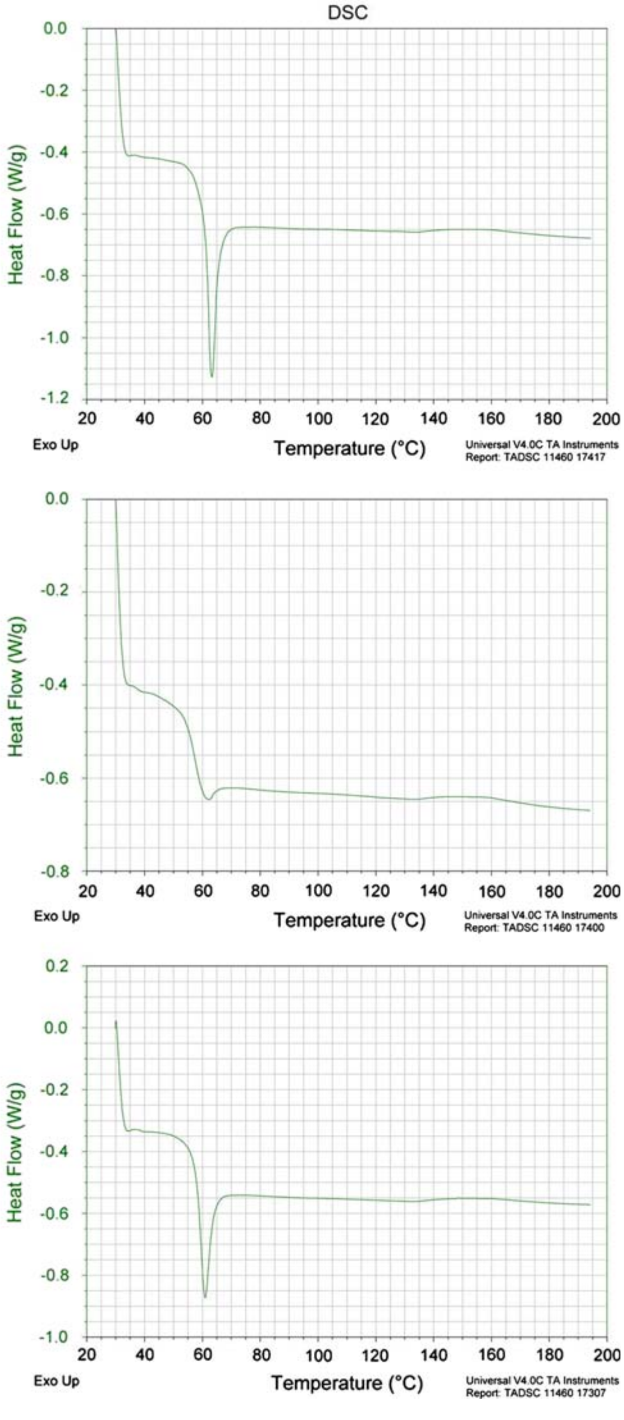

Fig. 2 Differential scanning calorimetry scan of 82:18 copolymer specimens. *Top*: Unheated, *Middle*: Heated to 90°C for 5 min and quenched to room temperature, *Bottom*: Heat and quenched as described, then incubated at 45°C for 19 h

incubated specimens were statistically equivalent. Thus, heating to above T_g and rapid cooling had the effect to reduce the T_g by about 5°C and all but eliminate the post-T_g enthalpic transition. Incubation at 45°C for 19 h partially restored the character of the DSC scan to that of its unheated state. There was little evidence of a melting peak, showing that this random copolymer had little propensity to crystallize.

Contact angle measurement

The contact angles of water on heated/air-quenched and unheated 82:18 specimens were 75.8 ± 3.3^{o} and 75.8 ± 1.8^{o}, respectively, which were not significantly different ($p = 0.980$).

The influence of post-heat wet and dry incubation on failure mode

Figure 3 shows representative photographs of each of Modes 1–4 mechanical failures. All small, unheated 82:18 copolymer wafers exhibited Mode 1 (brittle) failure following mechanical testing. Heating initially resulted in a Mode 4 (ductile) failure, however, storage under various conditions over a 48-h period resulted in a gradual reversion to Mode 1 (brittle) failure, as summarized in Table 1 and Fig. 4. Specimens stored under vacuum at 23°C, dry at 37°C, or in buffer at 37°C required 48 h, 24 h, and 4 h, respectively, to convert to the appearance of unheated specimens following mechanical testing.

The influence of post-heat cooling rate on mechanical properties

The temperature profiles of the cooling wafers are shown in Fig. 5. Figure 6a and b show representative load-deflection curves for large 82:18 copolymer specimens that were not heated, or were heated and then rapidly cooled, respectively. Both achieved a peak load of about 170 N and had similar initial slopes, but the unheated specimen attained only about a 1.5 mm deflection at failure while the heated (and rapidly cooled) one achieved about 5 mm. Also, after yield, the curve for the unheated specimen flattened while that for the heated (and rapidly cooled) specimen underwent immediate force reduction. A broad peak was apparent in the curve of the heated specimen beginning at about 2 mm of deflection. Although the distance between the test supports was sufficient to accommodate the central load fixture and the encroaching large specimen without direct interference, the physical proximity of these components slightly increased the load resistance at high values of deformation. This peak, however, added less than 10% to the area under the force-displacement curve so was not a confounding influence in the analysis.

Table 2 summarizes the cooling rate studies after heating. In general, slow cooling did not change the mechanical properties of the large 82:18 copolymer specimens compared to the unheated controls. Fast cooling, however,

Fig. 3 Representative photographs of small 82:18 copolymer wafers after three-Point bend testing illustrating the appearance modes. Clockwise from upper left: Mode I, Mode II, Mode III, Mode IV

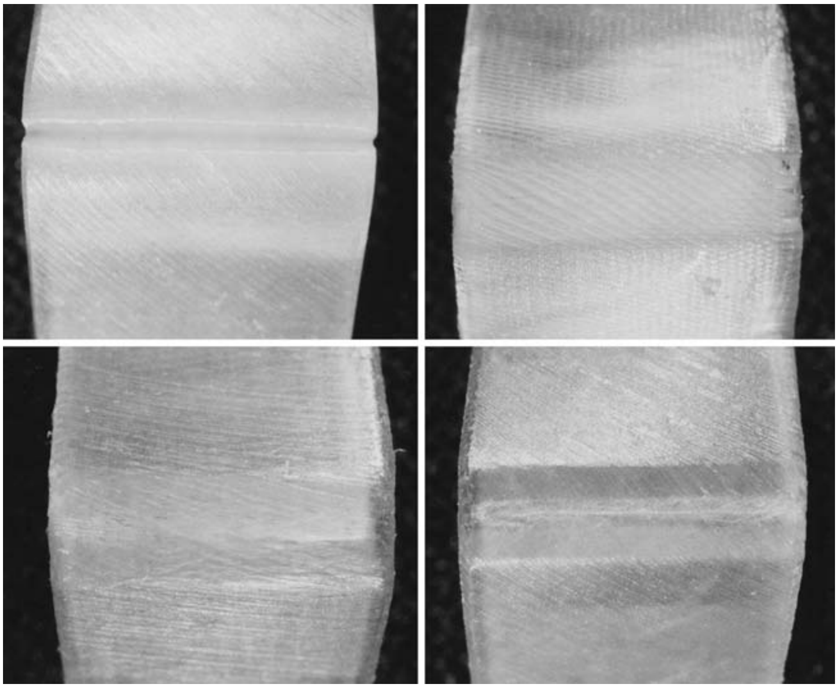

Table 1 Failure appearance mode of 82:18 copolymer small wafers after three-point bend testing as a function of post-90°C heating incubation method

Time (h)	Failure appearance mode[a] (Unheated controls (n = 10) Mode 1)		
	23°C vacuum (n = 5)	37°C dry (n = 5)	37°C buffer (n = 5)
0	4	4	4
1	3	2	2
2	N/A	2	2
4	2	2	1
24	2	1	1
48	1	1	1

[a] The ductile nature of the failure mode increases with increasing numerical score. See text for details

resulted in an increase in ductility as evidenced by increased failure energy and peak deformation at failure. To a limited extent, this was at the expense of a 15–20% decrement in modulus, although the relationship between modulus and cooling rate was not strong.

Figure 7 shows the relative (to unheated control) values of modulus, failure energy, and peak deformation at failure of the large 82:18 specimens versus cooling time. There were no significant differences between failure energy and peak deformation of the unheated control wafers compared to the heated specimens undergoing the longest cooling time (7.6 h). All faster cooling rates, however, produced significantly greater values, typically a 2- to 3-fold increase. The four slowest cooling rates did not result in a

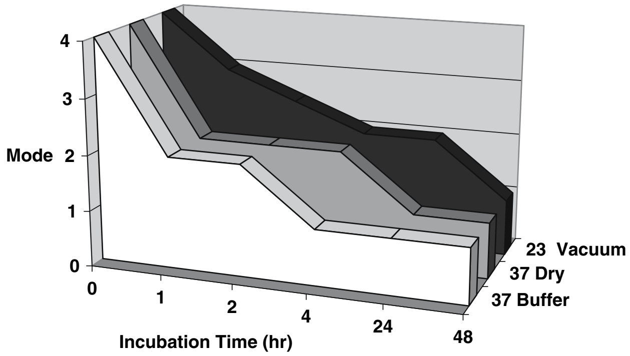

Fig. 4 Appearance of small 82:18 copolymer wafers in region of central load application after three-point bend test as a function of incubation time and condition. Decreasing numerical value of Mode corresponds to increasing brittle behavior

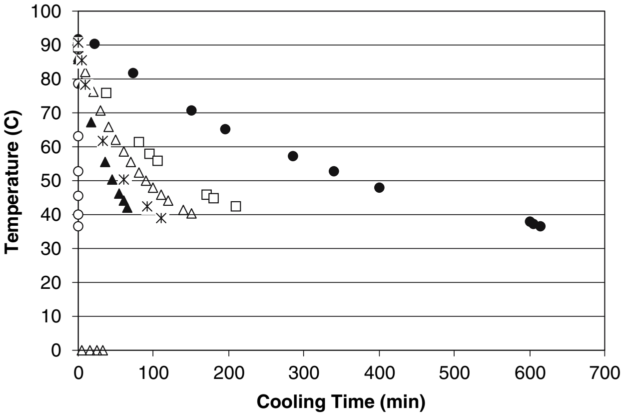

Fig. 5 Cooling profiles of the 82:18 copolymer large wafer specimens

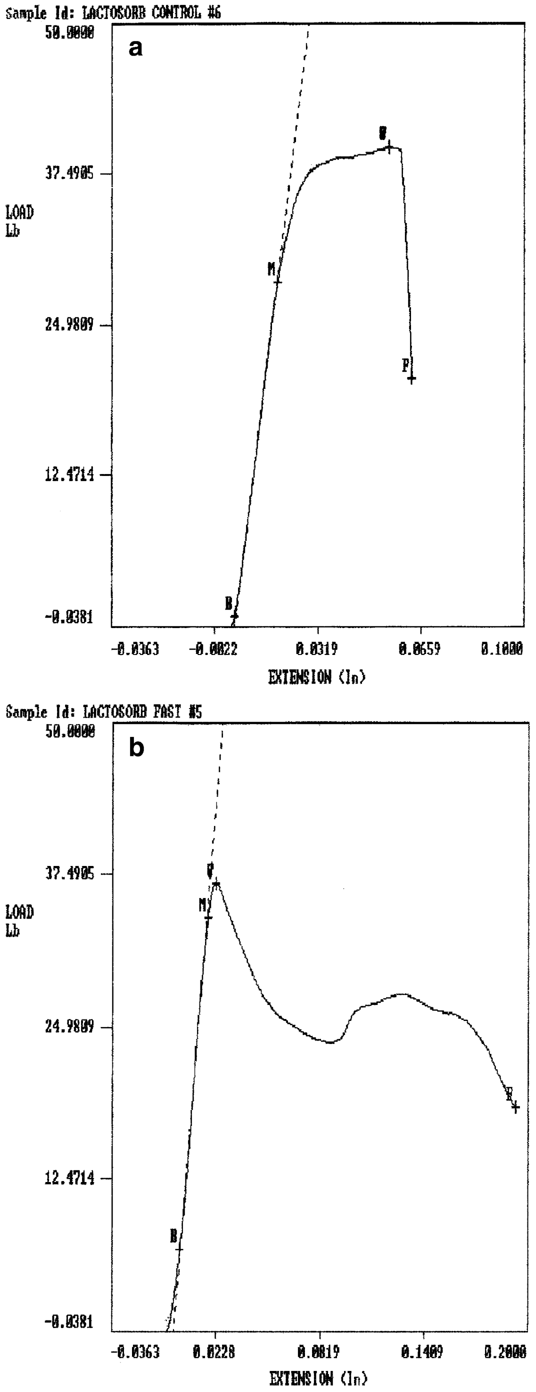

Fig. 6 (**a**) Load-displacement curve of large 82:18 wafer specimen: unheated control. (**b**) Load-displacement curve of large 82:18 wafer specimen: heated at 90°C then rapidly cooled

significant change in modulus. The shortest two cooling times (57.5 min and 0.33 min) resulted in a 15–20% decrease in modulus, however, this was only significant for the 57.5 min cooling time.

Table 2 also shows the effects of heating and cooling on the mechanical properties of small 95:5 specimens. Since the two copolymers shown in this table utilized different size specimens (82:18 large, 95:5 small), the failure energy and peak deformation results cannot be directly compared to each other, but trends within identically sized specimens of the same formulation are meaningful. The failure energy of the small 95:5 specimens showed a similar dependency on cooling rate as that of the 82:18 copolymer large wafers. At the relatively short cooling time of 57.5 min, the failure energy was double that of the unheated controls. At the longer cooling time of 115.6 min, the average failure energy was greater than that of the controls, but this difference was not significant. The 95:5 specimens, however, exhibited a different pattern of the effect of cooling rate on modulus than did the 82:18 copolymer. The moduli following cooling times of 115.6 min and 57.5 min were greater than that of the unheated controls by 15% and 7%, respectively. These differences were significant.

The influence of post-heat quenching and incubation on mechanical properties

The large 82:18 specimens remained dry in their pouches when removed from the 90°C bath and quenched and incubated in the lower temperature water baths. The mechanical properties were, to a limited extent, temperature and time dependent. Table 3 summarizes the data while Figs. 8–10 show plots of normalized (to unheated controls) data for failure energy, peak deformation, and modulus, respectively.

In all but one instance, the failure energy of the wafers was between one-and-one-half and two times that of the unheated controls. This was significantly different than control values for all but the three 45°C regimens. The heated specimens incubated at 45°C for 15 min and 60 min, while also having failure energies in this range, had large standard deviations, accounting for the lack of significance. The exception was the 45°C quench and 2-h incubation regimen, which returned the failure energy values to that of the controls. The peak deformation data followed similar trends.

As was the case with the cooling rate studies, there was not a strong relationship between the modulus and heating followed by quenching and incubation. In fact, only the 55°C quench followed by 15 min and 60 min incubations had a significantly different modulus (about 15–20% lower) than that of the unheated control.

Discussion

In the previous study by Pietrzak et al. [18], 82:18 specimens were heated in a water bath to above T_g, then removed and allowed to cool to ambient temperature over

Table 2 Mechanical properties of large 82:18 copolymer wafers heated to 90°C as a function of cooling rate

PLLA:PGA	Specimen type (qty)	Cooling time ~90°C to 45°C (min)	Modulus (GPa)	Failure energy (J)	Peak deformation (mm)
82:18	Large (6)	Unheated	2.82 ± 0.498	0.293 ± 0.0836	1.91 ± 0.432
82:18	Large (6)	456.6	2.77 ± 0.201	0.216 ± 0.0475	1.57 ± 0.373
82:18	Large (6)	178.2	2.71 ± 0.128	0.516 ± 0.0226*	4.06 ± 1.49*
82:18	Large(6)	115.6	2.57 ± 0.117	0.575 ± 0.101*	4.56 ± 0.622*
82:18	Large (7)	80.4	2.76 ± 0.410	0.519 ± 0.176*	4.62 ± 1.50*
82:18	Large (6)	57.5	2.22 ± 0.395*	0.615 ± 0.0587*	5.46 ± 0.399*
82:18	Large (6)	0.33	2.35 ± 0.245	0.487 ± 0.0429*	5.20 ± 0.307*
95:5	Small (5)	Unheated	3.06 ± 0.112	0.101 ± 0.0237	N/A
95:5	Small (5)	115.6	3.52 ± 0.0436*	0.123 ± 0.0305	N/A
95:5	Small (5)	57.5	3.28 ± 0.155*	0.236 ± 0.0678*	N/A

* denotes that mean was significantly different than that of corresponding control

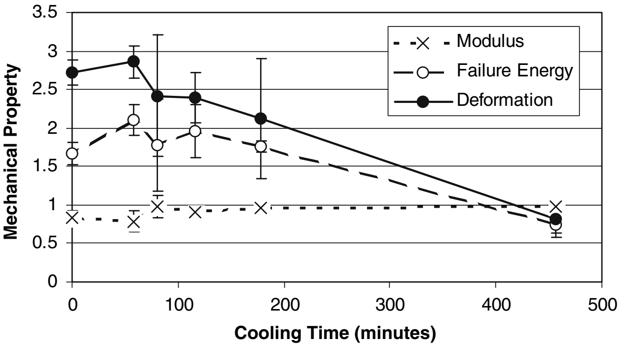

Fig. 7 Relative (to unheated control) mechanical properties of large 82:18 copolymer wafers after heating at 90°C for 5 min and cooling to 45°C over several periods of time. (x) = modulus, (o) = failure energy, (•) = peak deformation. Ave ± SD (n = 6 or 7)

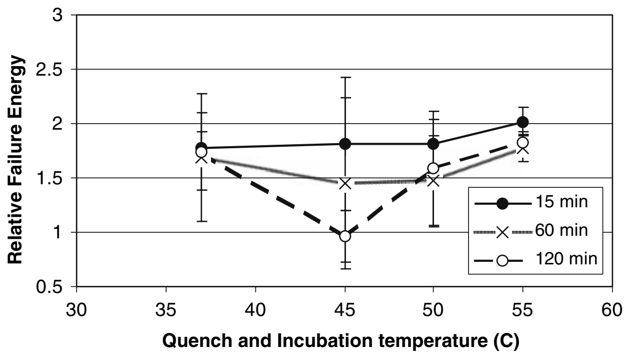

Fig. 8 Relative (to unheated control) failure energy of large 82:18 copolymer wafers after 90°C heating as a function of quench and incubation regimen. Ave ± SD (n = 6)

Table 3 Mechanical properties of large 82:18 copolymer wafers as a function of quench and incubation temperture

Time	Quench and incubation temperature (n = 6)			
	37°C	45°C	50°C	55°C
Control	M: 2.82 ± 0.498 Gpa	E: 0.293 ± 0.0836 J	D: 1.91 ± 0.432 mm	
15 min	M: 2.48 ± 0.433 Gpa	M: 2.85 ± 0.281 GPa	M: 2.61 ± 0.296 GPa	M: 2.23 ± 0.298 GPa*
	E: 0.519 ± 0.0441 J*	E: 0.532 ± 0.179 J	E: 0.532 ± 0.0667 J*	E: 0.591 ± 0.0373 J*
	D: 5.04 ± 0.381 mm*	D: 4.26 ± 1.27 mm*	D: 4.86 ± 0.257 mm*	D: 5.14 ± 0.160 mm*
60 min	M: 2.90 ± 0.308 Gpa	M:2.95 ± 0.152 GPa	M: 2.76 ± 0.0869 GPa	M: 2.33 ± 0.103 GPa*
	E: 0.495 ± 0.172 J*	E: 0.424 ± 0.230 J	E: 0.433 ± 0.121 J*	E: 0.519 ± 0.0362 J*
	D: 4.34 ± 1.30 mm*	D: 3.18 ± 1.70 mm	D: 4.38 ± 1.16 mm*	D: 5.10 ± 0.168 mm*
120 min	M:2.78 ± 0.113 Gpa	M: 2.86 ± 0.161 GPa	M: 2.69 ± 0.206 GPa	M: 2.49 ± 0.122 GPa
	E: 0.510 ± 0.104 J*	E: 0.281 ± 0.0689 J	E: 0.464 ± 0.156 J*	E: 0.536 ± 0.0282 J*
	D: 4.42 ± 1.05 mm*	D: 1.92 ± 0.340 mm	D: 4.37 ± 1.53 mm*	D: 4.98 ± 0.122 mm*

Note: M = modulus, E = failure energy, D = peak deformation

* denotes that mean was significantly different than that of control

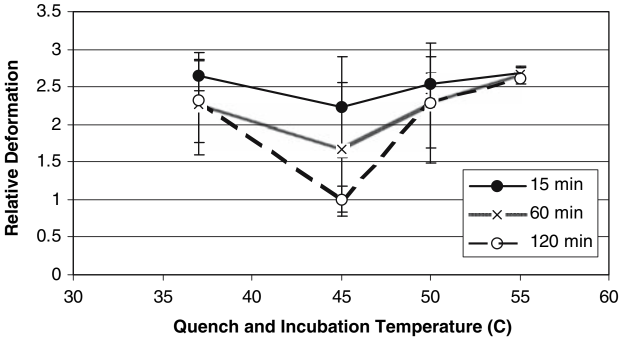

Fig. 9 Relative (to unheated control) peak deformation of large 82:18 copolymer wafers after 90°C heating as a function of quench and incubation regimen. Ave ± SD (*n* = 6)

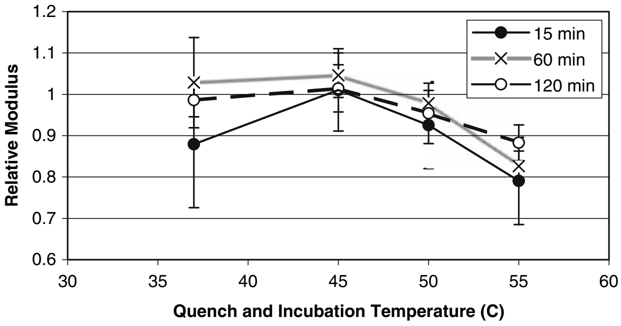

Fig. 10 Relative (to unheated control) modulus of large 82:18 copolymer wafers after 90°C heating as a function of quench and incubation regimen. Ave ± SD (*n* = 6)

the course of about 1 min. This resulted in an increase in ductility relative to unheated controls, which was largely gone by one week under in vitro conditions. The current study showed that this phenomenon is dependent on the rate of cooling, is a general phenomenon, and there can be a gradual return toward the preheated mechanical state within hours or days. These effects can be explained by a thermodynamic and kinetic treatment of the glass transition.

The glass transition describes a second-order thermodynamic transition of the amorphous regions of a polymer as may be characterized by measuring the change in a thermodynamic property, such as specific volume, or enthalpy, with temperature [27, 28]. As the transition is approached, there will be a change in the slope of the curve over a relatively narrow temperature range, with the T_g taken as the midpoint of this range. Below T_g the polymer behaves as a glass, i.e., hard, stiff, and brittle, and above it behaves as a rubbery solid, i.e., ductile, tough, and flexible. These changes in mechanical properties can be understood in the context of molecular mobility and free volume. There are various modes of macromolecular mobility, ranging from atomic vibrations about an equilibrium position to translational movement of entire molecules. [27] The energy barriers to motion increase with increasing involvement of the polymer chain. At a given temperature, there will be a Boltzman distribution of molecular energy, which increases with increasing temperature. As molecular energy exceeds the energy barriers to movement, there will be a concomitant shift from glassy to rubbery behavior and vice versa as the polymer is cooled to below T_g. Free volume may be defined as the specimen volume not occupied by that of the individual molecules and may be thought of as the volume available within which molecular motion may collectively occur. [27] The greater the free volume, the lower are the energy barriers to chain movement, hence, the lower will be T_g. Other factors that affect T_g include the attractive forces between molecules, chain mobility, chain stiffness, chain length, copolymer composition, the presence of plasticizers, and others. [27, 29, 30]

A glass is commonly thought of as an amorphous product produced by the rapid quenching of a melt. [31] Such a glass is not initially at thermodynamic equilibrium below its T_g and will undergo a slow transformation toward equilibrium, an enthalpy-driven process, with free volume playing a central role. [30, 32] For instance, when a polymer is rapidly cooled to below T_g, the free volume is initially greater than it would be at equilibrium. Under isothermal ($<T_g$) conditions, the free volume will decrease, over time, to an equilibrium value. The nearer the storage, or incubation, temperature is to the T_g, the faster will be the rate of approach to equilibrium. [30] The presence of water can also be a factor as absorbed water can act as a plasticizer, lowering the T_g, with the effect that, at a given storage temperature, the equilibrium approach may be accelerated. [30] Thus, one would expect that immediately after rapid cooling to below T_g, a polymer would possess relatively high ductility due to the large free volume and enhanced molecular mobility, and that, over time, the polymer would acquire increasingly brittle characteristics as free volume and mobility decrease toward equilibrium values.

The foregoing explains many of the experimental results of this study with the difference that, here, the polymer specimens were cooled not from the melt, but rather, from a temperature, T, that was typically between the glass and melt transitions, i.e., $T_g < T < T_m$. Extremely slow cooling (~8 h) of 82:18 specimens resulted in no mechanical changes relative to the unheated wafers. It is likely that sufficient time was available to allow the free volume to maintain itself in near-equilibrium as temperature decreased to below T_g. For specimens cooled rapidly, sufficient time was not provided for the decrease in free volume to keep pace with the decrease in temperature, resulting in excessive free volume and, concomitantly, increased ductility below T_g. There was, however, an approach to the unheated mechanical state whose rate increased with increasing temperature and in the presence of water. Kranz et al. [29] measured a water absorption in a similar polymer (80% lactide, 20% glycolide) of less than 1% (w/w) after 150 days at 37°C in a buffer environment, indicating that very small amounts of water absorption may be effective as a plasticizer in this regard.

Some 82:18 specimens underwent a two-stage quench, i.e., (1) from 90°C to 37°C, 45°C, 50°C, or 55°C, held at the quench temperature for up to 2 h, and (2) to room temperature followed by immediate mechanical testing. As such, both time and temperature conditions could be studied for their effects on recovery of mechanical properties. The results can best be interpreted with focus on failure energy and peak deflection since these quantities had better correlation with the heating and cooling cycles than did modulus. Specimens initially quenched to 37°C maintained increased ductility even after 2-h incubation at this temperature whereas the 45°C quenched specimens were statistically indistinguishable from the unheated controls after 60 min incubation at this temperature. This is consistent with rapid cooling to below T_g initially increasing ductility as well as with higher incubation temperatures being more conducive to a return to the equilibrium state. Interestingly, specimens quenched to 50°C or 55°C, both below the nominal T_g, then held at these temperatures for up to 2 h, showed no return to the preheated state. This fits into the overall pattern when interpreted in the context of the temperature range over which the glass transition occurs. The glass transition of the 82:18 copolymer occurs over a range which starts at approximately 50°C, or so. Thus, at 50°C or 55°C, the polymer cannot be fully considered to be below T_g. Consequently, the rapid cooling from 90°C to 50°C or 55°C was not a true quench. Rather, the transfer, following the incubation at 50°C or 55°C, to a room temperature water bath represented the only true quench for these specimens. We may hypothesize that at 50°C or 55°C the polymer still contains a relatively large total free volume regardless of the time of incubation at these temperatures. Upon quenching to room temperature, the free volume became excessive, as demonstrated by the enhanced ductility that was measured.

The DSC scans of the unheated; heated and quenched; and heated, quenched, and incubated (45°C for 19 h) 82:18 specimens paralleled those of the mechanical studies, showing partial recovery of the scan characteristics following incubation toward those of the unheated state. Greater free volume would reduce the energy barriers to chain movement, corresponding to lower T_g, as was the case for the 57.4°C mean for heated and quenched specimens compared to the 62.3°C mean for the unheated specimens. The mean T_g of the heated, quenched, and incubated specimens (60.1°C) was intermediate between these two extremes, showing partial recovery. The enthalpic transition associated with the negative peak in the DSC scan in the vicinity of T_g was likely associated with a microstructural transformation in the polymer. With the microstructure of the unheated specimen corresponding completely to that of the glassy state below T_g, the transformation would fully manifest upon passage through T_g, hence the large peak in the unheated DSC scan. Upon quench, the microstructure of the rubbery state would be temporarily preserved below T_g, with the polymer in a metastable state. If the polymer were then immediately heated through the T_g, little or no microstructural transformation would occur, hence, the small peak in the scan. If, however, the quenched polymer was incubated for a sufficiently long period at a suitable temperature, the microstructure would gradually transform to that characteristic of the glass. Subsequent heating would then result in the enthalpic transition resembling that of the glass transforming to a rubber, as was partially seen in the corresponding DSC scan.

Surface energy of a polymer substrate, as measured by contact angle, is known to be an important influence on the interaction between proteins and the surface [33]. Whether specimens were heated and rapidly cooled, or not heated at all, had no measurable effect on surface energy of the 82:18 specimens. This suggests that protein interactions with implants derived from this, or similar, material(s) may be unaffected by use of intraoperative heating and shaping.

Testing the 95:5 copolymer wafers showed that, indeed, such changes are, more or less, a general phenomenon. Interestingly, while there was an increase in ductility in response to heating and rapidly cooling the 95:5 copolymer specimens, there was actually a small, but significant, increase in modulus, opposite to the case for the 82:18 formulation. It would be expected that the 95:5 copolymer would have a greater propensity to crystallize than the 82:18 formulation due to its greater steric regularity along the polymer chain. [14] Furthermore, the 90°C, 5 min exposure could have functioned as a short annealing cycle for the 95:5 specimens during which crystallinity may have increased. [34] It is possible that microstructural differences between the two copolymers could have contributed to the slight differences that were observed in the effects of heating and rapid cooling on mechanical properties between these two copolymers.

Throughout this study, unheated specimens were used as controls with the assumption that they were in thermodynamic equilibrium below T_g. The specimens were machined from compression-molded plates, hence, had a thermal history. After application of pressure at 160°C, the plates were allowed to cool to room temperature, a process requiring about 20 min, which was likely short enough to manifest the effects seen in this study. However, once fabricated, these plate blanks were stored, with desiccant, in moisture-proof foil pouches, at room temperature, for several weeks before being machined into the geometry of the wafers. After wafers were fabricated, they were EtO sterilized, then aerated to remove residuals. The sterilization cycle exposed specimens to temperatures no greater than 46°C, hence, would not have been expected to influence results. Thus, more than six weeks elapsed between the time that the polymer was heated to above T_g and mechanical testing of the wafers. This was likely sufficient time for the specimens to have reached thermodynamic equilibrium prior to use in this study.

Clinically, bioabsorbable plates are typically heated in a dry state and then applied directly to the surface of the bone. [18, 19] In doing so, the heated plates are effectively quenched to below T_g, making it likely that mechanical changes will manifest. Minimal effect of heating and rapid cooling on stiffness, or modulus, was seen in this study, and when it was observed, the effect was relatively small. There was a large increase in toughness, on the order of 2- to 3-fold, in response to simulated intraoperative heat treatment. This was a positive finding in terms of ability to provide fixation, although given the transient nature of the effect, this is probably not clinically important. The aggregate of experiments performed here show that, depending on the post-heat conditions to which the implants are exposed, there can be a measurable approach to mechanical equilibrium as indicated by return toward the unheated state, within 48 h. Thus, to the extent that intraoperative heat adaptation modifies the mechanical properties of the bioabsorbable fracture plates, the effect is likely very short-lived in situ. Hence, as relates to fracture fixation, there appears to be little clinical relevance to the phenomenon described here.

There may be ways, however, that the temporary changes that follow intraoperative heating of bioabsorbable implants can provide clinical benefit, which may warrant further study. For instance, bioabsorbable implants can be impregnated with antibiotics and implanted, with the antibiotic eluting over time to produce a locally high concentration. [25] The diffusion coefficient for a diffusant in a polymer depends on the instantaneous free volume. [32] If an initial brief bolus of release is desired, followed by a slower, sustained delivery rate, it might be possible to heat the antibiotic-loaded device to above T_g immediately prior to implantation, then cool it quickly to convert it to a metastable state with a relatively high free volume to enhance early drug release. Then, as thermodynamic equilibrium is achieved and free volume becomes reduced, the release rate would correspondingly lessen. Bioabsorbable polymer scaffolds are an important part of tissue engineering [23]. Seeded cells interact with the matrix, differentiate, proliferate, form extracellular matrix, and help provide an environment conducive to angiogenesis. Whether the transient effects resulting from heating and rapid cooling alter the ability of such scaffolds to perform this role must await further study.

There were at least two limitations to this study. First, DSC was selectively, rather than broadly, used. More extensive use might have aided in the analysis and interpretation of results. Nevertheless, the DSC studies that were performed provided strong evidence to support the hypothesis that the mechanical changes following rapid cooling could be explained by free volume considerations and the kinetics and thermodynamics of the glass transition. Second, limited study was performed on a second copolymer formulation, making it difficult to fully extrapolate these results to other bioabsorbable polymers. While the results suggest that similar effects will occur in other bioabsorbable polymers, there may be subtle differences requiring further study.

Conclusions

Heating of poly-α-hydroxy acid bioabsorbable fixation devices, as a means for adaptation, can result in a transient increase in ductility. This is likely due to an excess in free volume which remains following rapid cooling to below T_g due to the time required for the macromolecules to complete the transition from the rubbery to the glassy state. While there is likely little clinical relevance of this effect as pertains to the mechanical requirements of internal fixation, such knowledge is useful to more fully understand the structure-function properties of bioabsorbable implants and may be useful in the development of new materials, implant designs, application methods, and indications.

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