

Strength retention behavior of oriented PLLA, 96L/4D PLA, and 80L/20D,L PLA

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The strength retention characteristics of oriented semicrystalline polylactides were monitored during hydrolytic degradation *in vitro*. The effects of the polymer type, the material's initial inherent viscosity (*iv*), the sample diameter and the residual monomer content on strength retention were analyzed. The analyzed polylactides had similar, but not identical, strength retention characteristics. It was concluded that a higher degree of initial crystallinity was a major variable determining the earlier and more profound strength loss of PLLA than 96L/4D PLA and 80L/20 D,L PLA. Samples with a higher initial *iv* were found to have a longer strength retention time than lower *iv* samples. Size-dependency was observed, as the strength retention time was shorter for the smaller diameter samples. This size-dependency was caused by faster *iv* decay. The amount of residual monomer content had a remarkable impact on strength retention. Neither the sample diameter, initial *iv* or residual monomer content were found to have an effect on the *iv* range in which there was a rapid decline in strength properties. Therefore, it was concluded that the inherent viscosity and/or molecular weight of oriented PLLA, 96L/4D PLA and 80L/20 D,L PLA is a major variable determining the strength retention of these materials.

Introduction

Poly- α -hydroxyacids degrade mainly because of hydrolysis. During their hydrolytic degradation, the water reacts with the ester bonds of the polymer backbone causing the immediate decay of molecular weight followed by the loss of other properties. The degradation rate is dependent on several factors, such as the polymer's intrinsic properties, external factors, impurities and additives.¹⁻¹⁶ The intrinsic properties include, e.g., the structure of the polymer backbone, the hydrophilicity, the molecular weight and the morphology of the polymer.^{1,9,10} External factors include, e.g., the degradation environment (*in vitro/in vivo*) and the media, the sterilization method, the storage history and the sample size.^{1,6,7,13,15-17} In addition, certain impurities such as the post-processing residual monomer content, and the presence of possible additives, such as bioactive bioceramic fillers, can either accelerate or hinder the rate of degradation.^{2-5,8,11,12} As a consequence of hydrolytic degradation, the molecular weight of the polymer will decrease. As the degradation progresses further, the molecular weight eventually reaches a threshold region, below which a rapid decline in mechanical properties occurs. A similar threshold region can also be detected by measuring the polymer's inherent viscosity (*iv*), which reflects the material's molecular weight. McManus et al. analyzed the strength retention of 70L/30D,L PLA and found that this threshold region for the *iv* was ca. 0.75 dl/g.¹⁷ Paakinaho et al. reported a broader threshold region of 0.6–0.8 dl/g for 85L/15G PLGA after their analysis.⁴

Both of these studies proved that the rapid decline in mechanical properties for two different poly- α -hydroxyacids occurs within a similar *iv* range.^{4,17}

This study compares the three different oriented PLAs: PLLA, 96L/4D PLA and 80L/20D,L PLA, using a methodology that allows, for the first time, the intrinsic differences in the strength retention of these polymers to be characterized. This study also defines the threshold *iv* above which 50% of the polymer's initial strength is retained, and includes analyses of the effects of the sample diameter, the initial *iv* of the processed polymer and the amount of residual monomer on strength retention *in vitro*.

Results

The effect of the polymer type on strength retention behavior. The effect of polymer stereochemistry on the strength retention characteristics during degradation was studied using oriented (draw ratio 3.7–3.8) \varnothing 1.1–1.2 mm samples composed of PLLA, 96L/4D PLA and 80L/20D,L PLA. When the shear and bending strength values were plotted against the incubation time, a remarkable drop was seen in the shear strengths at 25–45 weeks and in the bending strengths after 18–30 weeks *in vitro* hydrolysis (data not shown). No clear difference between the polymer compositions of the oriented samples was observed by this analysis method, and nor were there any observable differences in the strength retention dynamics. When the hydrolysis time was neglected from the analysis and the shear and bending strength

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values were plotted as a function of the corresponding inherent viscosities (Fig. 1) we saw very similar behavior for both 96L/4D PLA and 80L/20D,L PLA. The shear strength loss occurred at a lower iv level and thus later in degradation than the bending strength did. Both the stereocopolymers retained at least 70% of their initial shear strength until the iv values 0.65–0.55 dl/g, after which there was a steep decline in shear strength (Fig. 1A). They retained at least 50% of their initial shear strengths until the iv had dropped to 0.55–0.4 dl/g. When analyzing the bending strength retention of 96L/4D PLA and 80L/20D,L PLA (Fig. 1B) it was difficult to determine a precise starting point for the rapid decline. The loss in bending strength occurred gradually over a longer period of time and already started at 90% strength retention level, when the iv was as high as 0.9 dl/g. The iv level was 0.65–0.55 dl/g when about 50% of the initial bending strength was left, indicating that the bending strength dropped at higher iv levels than did the shear strength. We may speculate that in order to resist 3-point bending stress a polymer needs to have longer molecular chains in its structure than is the case in shear stress.

The results showed that for both the mechanical testing types, PLLA started to show strength loss at higher iv levels than the studied stereocopolymers. However, we found that there were not enough data points where the rapid shear strength loss occurred at the inherent viscosity range of 0.75–0.5 dl/g (equal to ca. 36–44 weeks in vitro) to fully analyze the behavior of the PLLA specimens, particularly in the case of the shear strength values, (Fig. 1A). The observed difference most likely stems from differences between the morphologies of the PLLA and the PLA stereocopolymers. The more regular polymer chains of the homopolymer PLLA may also withstand mechanical stresses in a slightly different manner than those in the less regular stereocopolymer structures.

The effect of the specimen's inherent viscosity on strength retention behavior. The effect that the initial iv of the processed specimens had on the strength retention time was analyzed using oriented Ø4.0 mm 96L/4D PLA and 80L/20D,L PLA rods. The analysis was conducted by comparing the shear strengths of high iv (EtO-sterilized) and low iv (gamma sterilized) samples derived from the same manufacturing lots, and thus the same raw material batch. Plotting the measured shear strength values as a function of degradation time (Fig. 2A) showed that the sterilization method had no noticeable effect on the initial shear strength levels of the analyzed sample types. All the samples retained their initial shear strength levels throughout the first 38 weeks of the degradation period (i.e., 9 mo), after which low iv (gamma sterilized) samples showed signs of decline in shear strength. This decline was visualized by plotting the shear strength (% of initial) as a function of inherent viscosity (Fig. 2B), but the shear strength values of the low iv 96L/4D PLA and 80L/20D,L PLA were still at least 90% of the initial stage at 52-week follow-up point.

The effect of the sample diameter on strength retention behavior. The effect of the sample diameter on the strength retention dynamics was analyzed by comparing the oriented Ø 1.2 mm and Ø 4.0 mm samples, whose other initial properties

were virtually identical (Table 1). The analysis was conducted on 96L/4D PLA and 80L/20D,L PLA polymers. When analyzing the shear strength as a function of degradation time it was found that the Ø 1.2 mm samples showed more rapid strength loss than the Ø 4.0 mm samples (Fig. 3A). It was also observed that the Ø 1.2 mm samples with a draw ratio of 3.8 had a noticeably higher initial shear strength than the Ø 4.0 mm samples with a slightly higher draw ratio of 4. This difference most probably stems from the fact that there is a more profound molecular orientation in the smaller diameter samples, which results in a more homogeneous molecular orientation in the direction of the draw. There was no obvious difference between the small and large samples when plotting the shear strength values (% of initial) as a function of the corresponding inherent viscosities (Fig. 3B). As our previous study has proven that these Ø 1.2 mm samples had a faster iv loss than the Ø 4.0 mm samples,¹⁸ the more profound strength loss shown in Figure 3A can be assumed to be a consequence of the faster degradation. The sample diameter did not, however, seem have any effect on the threshold iv at which the rapid strength loss begins (Fig. 3B).

Residual monomer content. The effect of the residual monomer content on shear strength retention was analyzed by using oriented Ø 1.5–3.1 mm 96L/4D PLA samples with different residual monomer contents. Due to the limited quantity of raw materials available, different sample diameters were used. Even the relatively low increase in monomer content which was studied (from 0.09% to 0.33%) shortened the time at which the strength remained at the initial level from 30 to 12 weeks (Fig. 4A). However, the profile of the plotted curve of the shear strength loss against hydrolysis time was similar.

When the remaining shear strength values (% of initial) were plotted as a function of inherent viscosity (Fig. 4B) it was seen that the strength retention was practically identical for all the analyzed samples. Regardless of the residual monomer content, the samples were able to retain at least 50% of their initial shear strength until the inherent viscosity had degraded to a value of ca. 0.5 dl/g.

Materials and Methods

The samples were manufactured in the same manner as earlier by means of single-screw melt extrusion followed by die drawing (orientation process).^{3,4,15} All the raw materials (poly-L-lactide [PLLA], 96L/4D polylactide [96L/4D PLA] and 80L/20D,L polylactide [80L/20 D,L PLA]) were of medical grade quality, had initial inherent viscosities in the range of 5–7 dl/g and were purchased either from Purac Biomaterials b.v. or Boehringer Ingelheim Pharma GmbH and Co. KG. After the processing steps, the samples were washed, dried, packed and sterilized either by gamma-irradiation (minimum 25 kGy) or by ethylene oxide (EtO) in the same way as was done in the previous literature.^{4,17} The initial properties of the specimens after manufacturing and sterilization are summarized in Table 1.

Hydrolytic degradation conditioning. The hydrolytic degradation analysis in vitro was performed as previously described.^{3,4,15} The degradation characteristics were studied by incubating

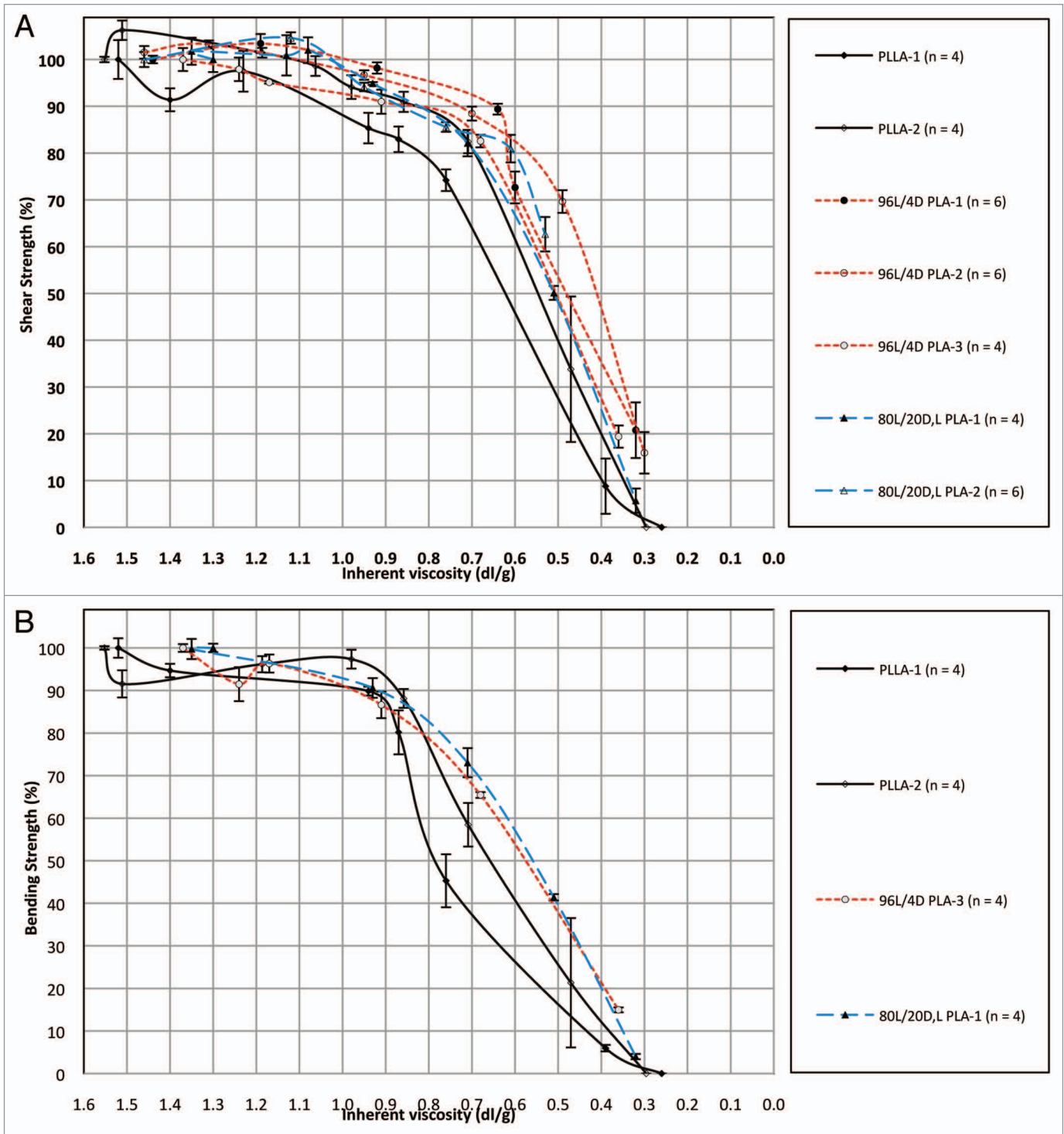


Figure 1. In vitro occurring strength retention of Ø1.1–1.2 mm oriented PLLA, 96L/4D PLA, and 80L/20D,L PLA samples plotted against determined inherent viscosity value measured from the same specimens; shear strength (A) and bending strength (B). Values are averages of the mentioned parallel samples and error bars indicate standard deviations for the measurements.

samples in phosphate-buffered saline (PBS; ionic concentrations Na^+ 156.2 mM, HPO_2^{-4} 24.9 mM, $\text{H}_2\text{PO}_4^{-4}$ 5.5 mM and Cl^- 100.9 mM). The pH was 7.4, the temperature of the media was maintained at 37 °C and the $V_{\text{solution}}/V_{\text{sample}}$ ratio was at least 20. The buffer solution was changed bi-weekly, and the pH was

measured (three parallel samples) using a Mettler Toledo MP225 pH-meter (Mettler-Toledo GmbH, Schwerzebbach, Switzerland).

Material characterization and testing. The inherent viscosity (iv) was measured by viscometric analysis (LAUDA Proline PV 24 viscosimeter with Ubbelohde Oa capillary at 25 °C in

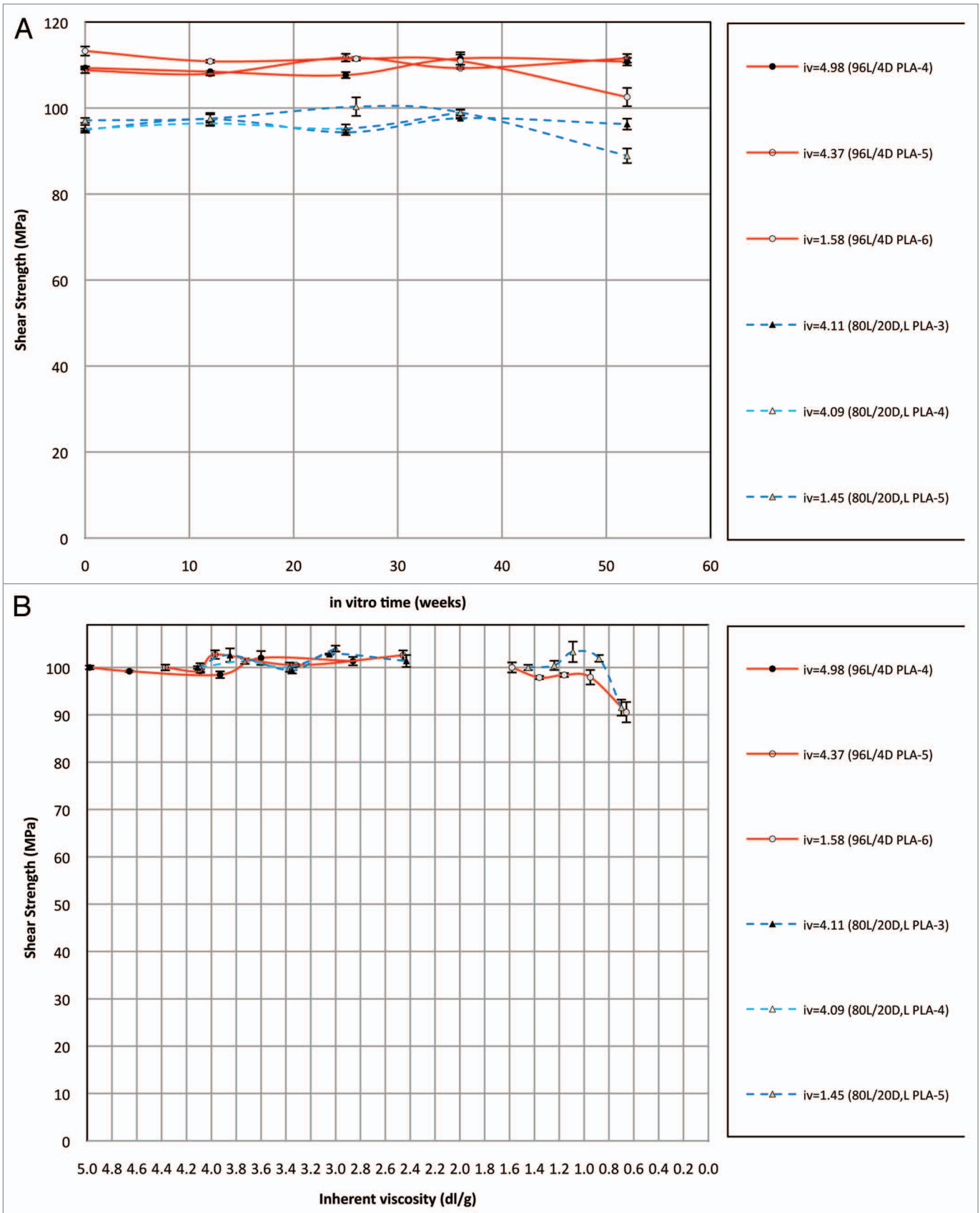


Figure 2. Effect of the polymers initial iv on shear strength retention of Ø4.0 mm oriented 96L/4D PLA and 80L/20D,L PLA samples. Shear strength as a function of degradation time (A) and inherent viscosity (B). Values are averages of the mentioned parallel samples and error bars indicate standard deviations for the measurements.

Table 1. The sample codes and the initial measured values for oriented and sterilized rods

Sample code and number of parallel samples in mechanical analyses at all time points	Sterilization method	3-Point bending strength [MPa]	Shear strength [MPa]	Inherent viscosity (dl/g)	residual monomer content (%)	Sample diameter (mm)	Draw ratio	Degree of crystallinity (%)
PLLA-1 (n = 4)	Gamma-irradiation	175 ± 4	143 ± 6	1.5	0.06	1.1	3.7	60
PLLA-2 (n = 4)	Gamma-irradiation	172 ± 1	134 ± 1	1.6	0.04	1.1	3.7	36
96L/4D PLA-1 (n = 6)	Gamma-irradiation	N.M.	140 ± 1	1.4	0.02	1.2	3.8	36
96L/4D PLA-2 (n = 6)	Gamma-irradiation	N.M.	142 ± 2	1.5	0.02	1.2	3.8	37
96L/4D PLA-3 (n = 4)	Gamma-irradiation	175 ± 2	148 ± 4	1.4	0.06	1.2	3.8	39
96L/4D PLA-4 (n = 3)	Ethylene Oxide	N.M.	109 ± 1	5.0	0.01	4	4	29
96L/4D PLA-5 (n = 3)	Ethylene Oxide	N.M.	109 ± 1	4.4	0.01	4	4	28
96L/4D PLA-6 (n = 3)	Gamma-irradiation	N.M.	113 ± 1	1.6	0.01	4	4	37
96L/4D PLA-7 (n = 4)	Gamma-irradiation	203 ± 2	143 ± 3	1.4	0.09	3.2	5.7	N.M
96L/4D PLA-8 (n = 4)	Gamma-irradiation	180 ± 3	135 ± 1	1.5	0.18	1.5	5.8	N.M
96L/4D PLA-9 (n = 4)	Gamma-irradiation	206 ± 4	139 ± 1	1.5	0.2	2	5.5	N.M
96L/4D PLA-10 (n = 4)	Gamma-irradiation	N.M	137 ± 3	1.6	0.33	2	5.5	N.M
80L/20D,L PLA-1 (n = 4)	Gamma-irradiation	161 ± 2	135 ± 4	1.3	0.03	1.1	3.8	7
80L/20D,L PLA-2 (n = 6)	Gamma-irradiation	N.M	136 ± 2	1.5	0.01	1.2	3.8	14
80L/20D,L PLA-3 (n = 3)	Ethylene Oxide	N.M	95 ± 0	4.1	0.01	4	4	1
80L/20D,L PLA-4 (n = 3)	Ethylene Oxide	N.M	95 ± 1	4.1	0.01	4	4	13
80L/20D,L PLA-5 (n = 3)	Gamma-irradiation	N.M	97 ± 1	1.5	0.01	4	4	19

The number of the parallel samples for each sample type is in the parenthesis after the sample code. Results are as averages. N.M., not measured.

a water bath) according to standard ISO 1628–1:2009, using chloroform as a solvent. In the sample preparation, a 20 ± 1 mg piece of the sample representing the whole cross-sectional cut of the sample was dissolved in chloroform. The concentration of this solution was 1 mg/ml. The degree of initial crystallinity was measured by differential scanning calorimetry (DSC Q1000, TA Instruments) as in,^{3,4} using 5–10 mg vacuum-dried samples. Analyses were made from first heating (10 to 200 °C) using a heating rate of 20 °C/min. In the analysis, the enthalpies of cold crystallization and melting were analyzed and the theoretical enthalpy value of 93.7 J/g for 100% crystalline PLA was used to calculate the degree of crystallinity, which was done using the equation $(\Delta H_{\text{melting}} - \Delta H_{\text{cryst.}}) / 93.7 \text{ J/g} \times 100\%$. The residual monomer content of the studied materials was measured with gas chromatography (Thermo Finnigan Trace GC with Autosampler 3000, ThermoQuest Italia S.p.A.) as described in.¹⁹ All mechanical testing was done at room temperature under wet conditions for virgin samples, immediately after which the specimens were removed from the buffer solution and rinsed using deionized water, in the same manner as reported in reference 3. It was decided to report the shear strength of all the sample materials, and the shear testing was performed according to the ASTM B 769–94 standard, for which the tools and calculations were modified to apply to cylindrical samples. The crosshead speed was 10 mm min⁻¹. Furthermore, the 3-point bending strength was also measured for the Ø1.1–1.2 mm samples. The bending strength was determined according to the ASTM D 790–84 (revision D 790-02) standard, which was modified to apply to

cylindrical samples. The bending span was 22 mm and the cross-head speed 2 mm min⁻¹. All the mechanical tests were conducted using an MTS 2/M uniaxial testing machine (MTS systems corporation, Minnesota, USA).

Discussion

Although the degradation of poly- α -hydroxyacids has been studied extensively over the recent decades, the effects of various factors and variables on the rate of hydrolytic degradation are not fully explained in the existing literature.^{1-9,11-17,19} The lack of measurement of crucial factors affecting the rate of hydrolytic degradation, such as the residual monomer content, may have had an impact on the results and conclusions of some previous studies. Therefore, a detailed and itemized analysis of the effects of various factors on the rate of degradation is relevant.

In our previous study the effects of several factors and variables on the degradation rate of the oriented polylactides were analyzed using the loss of inherent viscosity as a function of the degradation time.¹⁸ The analysis focused on the period of time which is the most critical in determining the strength retention characteristics of these materials in clinical applications. The study proved that the loss of inherent viscosity at the beginning of the degradation process was almost identical for the oriented PLLA, the 96L/4D PLA and the 80L/20D,L PLA.¹⁸

Due to the unexpected finding of a similar iv loss for the oriented polymers mentioned above, we wanted to analyze the same samples to reveal the strength retention characteristics of these

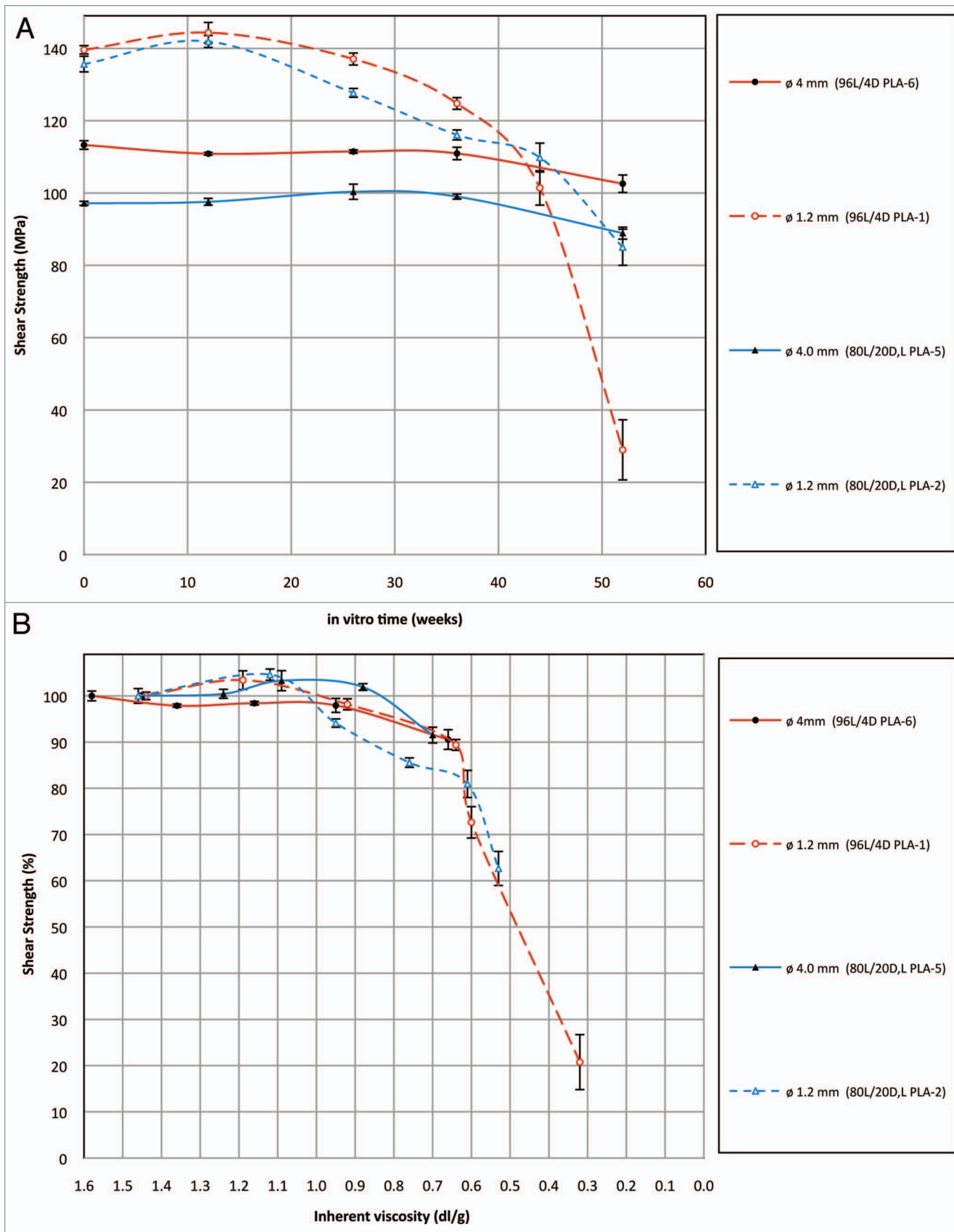


Figure 3. Effect of the sample diameter on shear strength retention of oriented 96L/4D PLA and 80L/20D,L PLA samples. Shear strength as a function of degradation time (A) and inherent viscosity (B). Values are averages of the mentioned parallel samples and error bars indicate standard deviations for the measurements.

materials and to define the effects of several material variables on the behavior of the strength properties during degradation. The previous literature has discussed how the copolymerization of D-lactic acid in an L-lactic acid-dominated polymer backbone decreases the degree of crystallinity.²⁰ It has also been shown that as the degree of crystallinity decreases, the loss in mass, which indicates degradation, is noticeably faster.⁹ Previous literature has also shown that an increasing amount of D-lactic acid in an L-lactic acid-dominated polymer backbone decreases the strength retention time.²¹ Li et al., however, reported that partially crystalline PLLA has a shorter strength retention time than initially amorphous PLLA.¹⁰ The published results are contradictory and thus the differences in the strength retention of PLLA, 96L/4D PLA, and 80L/20D,L PLA cannot be predicted based on previous literature. The itemized analysis of the current study did, however, indicate that such estimates can be done solely based on the materials' initial properties if the decay of the *iv* can be predicted, and if the effects of various initial variables on strength retention are correctly understood.

This study revealed that oriented PLLA, 96L/4D PLA, and 80L/20D,L PLA follow very similar but not completely identical trends in strength retention. The 96L/4D PLA and 80L/20D,L PLA samples were found to retain their strength properties at slightly lower *iv* values than the PLLA. The decline in mechanical properties also occurred in a more profound manner for PLLA than it did for the 96L/4D PLA and the 80L/20D,L PLA. Based on our previous study, in which these materials were found to have practically identical degradation rates in terms of *iv* decay,¹⁸ these new findings indicate that oriented PLLA has an intrinsically shorter strength retention time than 96L/4D PLA and 80L/20D,L PLA. This conclusion contradicts the previous literature, where the oriented PLLA was found to have a longer strength retention time than the oriented 96L/4D PLA and 85L/15D PLA.²¹ However, in that analysis neither the residual monomer contents nor the initial inherent viscosities of the samples were reported at the time. Therefore, the previously reported difference most likely originates from the non-comparable initial stages, rather than the natural characteristics of these polymers.

The observed differences in strength retention characteristics may be explained by the morphological differences. The analyzed 96L/4D PLA and 80L/20D,L PLA samples had a lower degree of initial crystallinity than the PLLA samples. Therefore, the earlier and more profound strength loss of the PLLA is in accordance with the results of Li et al., who found that an initially semi-crystalline PLLA has a shorter strength retention time than an initially amorphous PLLA.¹⁰ In fact, in this analysis the samples with the highest initial degree of crystallinity (PLLA-1) demonstrated the most profound shear and bending strength loss, in addition to which, the strength loss for PLLA-1 also occurred at the highest *iv* range. It can be also speculated that in order to withstand the mechanical stresses, the more regular polymer chains of homopolymer PLLA may also need to be longer (i.e., a higher *iv*) than the less regular stereocopolymer structures.

For all the analyzed polymers, the decline in bending strength occurred at a slightly higher *iv* than did the decline in shear

strength. This probably stems from the fact that, under our test conditions, the shear is a pure transformation as the test fixture fit was very tight (tolerance +0.1 mm), and therefore the sample has supposedly undergone almost pure shear forces. On the other hand, in a 3-point bending test the upper side of the sample undergoes compressive forces, the opposite side experiences tensile forces and in the middle of the sample there are longitudinal shear forces.

The effect of the sample's initial *iv* on its strength retention characteristics revealed that the strength retention time is very much dependent on the initial *iv* (or molecular weight) of the sterilized, final product. Thus, by selecting the sterilization method correctly in clinical applications the strength retention time can be tailored to meet the requirements, since it has been shown that regardless of the *iv* before gamma irradiation, afterwards the *iv* is practically at the same level.⁴ According to the present results, the EtO-sterilized (i.e., higher initial *iv*) samples were able to retain their initial shear strength practically unchanged over a 52-week follow-up period, whereas the onset of strength loss was observable for the lower *iv* samples which had undergone gamma-sterilization. This finding is in accordance with the previous literature.^{17,21,22} No noticeable differences between the oriented 96L/4D PLA and 80L/20D,L PLA samples could be observed.

It was found that the smaller-diameter samples have shorter strength retention times than the larger-diameter samples. It was concluded that the observed difference was caused by faster decay of the *iv* during hydrolytic degradation. This finding contradicts the conclusions of Grizzi et al., who reported that larger samples degrade faster than smaller samples.⁶ The analysis of Grizzi et al. does not, however, include the measurements of the samples' residual monomer contents and their analysis may also include a systematic error in data analysis, as was discussed in our previous study.¹⁸ Therefore, the conclusions about size-dependency and the rate of degradation reported by Grizzi et al. in reference 6 may be questionable. No remarkable differences between the oriented 96L/4D PLA and 80L/20D,L PLA samples could be observed in this study. However, due to the limitations of this study, the finding that smaller samples have a faster degradation rate than specimens with a larger diameter may only be limited to oriented polylactides with very low residual monomer content. Therefore, further analyses using injection molded or extruded samples may be required.

The significant effect of even minor amounts of residual monomer accelerating the rate of degradation found in this study is in accordance with the previous literature.^{4,8,12} The increase in residual content from 0.09% to 0.33% shortened the time at which the strength remained at the initial level from 30 to 12 weeks. Before this study it was, however, uncertain whether the amount of monomer also has an effect on the *iv* range of oriented 96L/4D PLA where the rapid decline in mechanical properties occurs. It was proven here that the noticeable drop in shear strength was identical, regardless of the residual monomer content.

Although the oriented PLLA, 96L/4D PLA, and 80L/20D,L PLA demonstrated slight, but evident differences in strength retention characteristics, the analysis conducted in this study indicates that there is a somewhat universal range of inherent

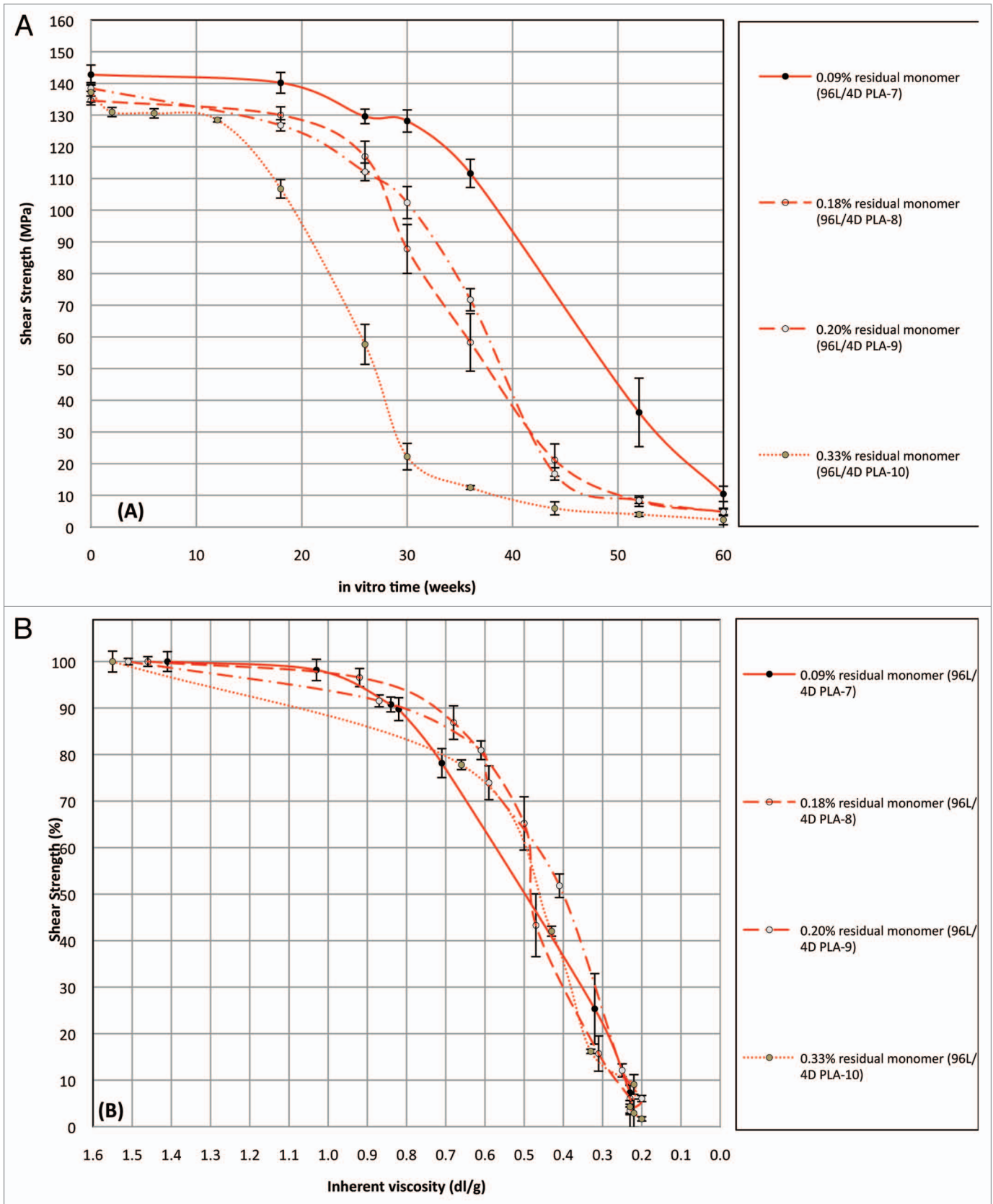


Figure 4. Effect of the residual monomer content on shear strength retention of \varnothing 1.5–3.1 mm 96L/4D PLA samples. Shear strength as a function of degradation time (A) and inherent viscosity (B). Values are averages of the mentioned parallel samples and error bars indicate standard deviations for the measurements.

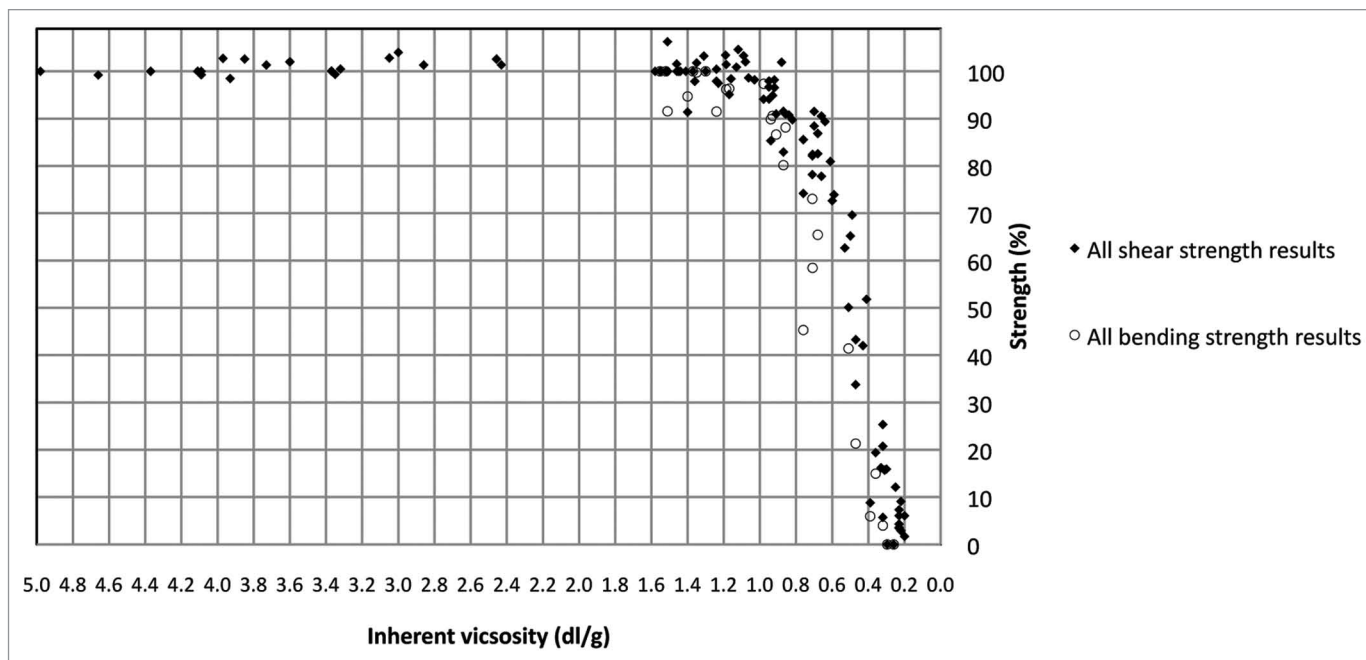


Figure 5. Summary graph of strength and inherent viscosity correlation of all samples analyzed in this study. Regardless from the variables affecting on the rate of iv decay, the strength loss occurs on similar iv range.

viscosity, above which these materials can retain most of their initial strength properties. This iv range represents a critical range of molecular weight above which polymer molecules are long enough to ensure mechanical strength, but below which the strength of the material will be gradually lost because the polymer molecules are too short to provide an adequate degree of molecular entanglement to give mechanical support. In order to clarify this correlation between strength and inherent viscosity (or molecular weight) all the results of this study were collected on the same graph (Fig. 5). This summarizes the strength retention characteristic of the analyzed samples. It can be seen that the inherent viscosity of oriented PLLA, 96L/4D PLA, and 80L/20 D,L PLA seems to be a major variable determining the strength retention of these materials. Therefore, it may be concluded that if the rate of molecular weight decay can be predicted reliably enough up to the point when the rapid decline in mechanical

properties occurs, the strength retention time of oriented PLLA, 96L/4D PLA, and 80L/20 D,L PLA may be estimated to a degree of accuracy which is useful for practical applications.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References

- Cameron RE, Kamvari-Moghaddam A. *Synthetic bioresorbable polymers*. In: Buchanan F, ed. *Degradation Rate of Bioresorbable Materials: Prediction and Evaluation*, Cambridge, England: Woodhead publishing limited, 2008:43-66.
- Lin P, Fang H, Tseng T, Lee W. Effects of hydroxyapatite dosage on mechanical and biological behaviors of poly(lactic acid) composite materials. *Mater Lett* 2007; 61:3009-13; <http://dx.doi.org/10.1016/j.matlet.2006.10.064>
- Niemelä T. Effect of β -tricalcium phosphate addition on the in vitro degradation of self-reinforced poly-L-lactide. *Polym Degrad Stabil* 2005; 89:492-500; <http://dx.doi.org/10.1016/j.polydegradstab.2005.02.003>
- Paakinaho K, Heino H, Väisänen J, Törmälä P, Kellomäki M. Effects of lactide monomer on the hydrolytic degradation of poly(lactide-co-glycolide) 85L/15G. *J Mech Behav Biomed Mater* 2011; 4:1283-90; <http://dx.doi.org/10.1016/j.jmbbm.2011.04.015>; PMID:21783137
- Yang Z, Best SM, Cameron RE. The influence of alpha-tricalcium phosphate nanoparticles and microparticles on the degradation of poly(D,L-lactide-co-glycolide). *Adv Mater* 2009; 21:3900-4; <http://dx.doi.org/10.1002/adma.200901093>
- Grizzi I, Garreau H, Li S, Vert M. Hydrolytic degradation of devices based on poly(DL-lactic acid) size-dependence. *Biomaterials* 1995; 16:305-11; [http://dx.doi.org/10.1016/0142-9612\(95\)93258-F](http://dx.doi.org/10.1016/0142-9612(95)93258-F); PMID:7772670
- Landes CA, Ballon A, Roth C. In-patient versus in vitro degradation of P(L/DL)LA and PLGA. *J Biomed Mater Res B Appl Biomater* 2006; 76:403-11; PMID:16184534; <http://dx.doi.org/10.1002/jbm.b.30388>
- Ellä V, Nikkola L, Kellomäki M. Process-induced monomer on a medical-grade polymer and its effect on short-term hydrolytic degradation. *J Appl Polym Sci* 2011; 119:2996-3003; <http://dx.doi.org/10.1002/app.33027>
- Li S. Hydrolytic degradation characteristics of aliphatic polyesters derived from lactic and glycolic acids. *J Biomed Mater Res* 1999; 48:342-53; PMID:10398040; [http://dx.doi.org/10.1002/\(SICI\)1097-4636\(1999\)48:3<342::AID-JBM20>3.0.CO;2-7](http://dx.doi.org/10.1002/(SICI)1097-4636(1999)48:3<342::AID-JBM20>3.0.CO;2-7)
- Li S, Garreau H, Vert M. Structure-property relationships in the case of the degradation of massive aliphatic poly-(alpha-hydroxy acids) in aqueous media. *J Mater Sci Mater Med* 1990; 1:123-30; <http://dx.doi.org/10.1007/BF00700871>
- Nakamura T, Hitomi S, Watanabe S, Shimizu Y, Jamshidi K, Hyon SH, Ikada Y. Bioabsorption of poly-lactides with different molecular properties. *J Biomed Mater Res* 1989; 23:1115-30; PMID:2808460; <http://dx.doi.org/10.1002/jbm.820231003>

12. Paakinaho K, Ellä V, Syrjälä S, Kellomäki M. Melt spinning of poly(l/d)lactide 96/4: Effects of molecular weight and melt processing on hydrolytic degradation. *Polym Degrad Stab* 2009; 94:438-42; <http://dx.doi.org/10.1016/j.polymdegradstab.2008.11.010>
13. Pamula E, Menaszek E. In vitro and in vivo degradation of poly(L: -lactide-co-glycolide) films and scaffolds. *J Mater Sci Mater Med* 2008; 19:2063-70; PMID:17968505; <http://dx.doi.org/10.1007/s10856-007-3292-2>
14. Pistner H, Bendix DR, Mühlhng J, Reuther JF. Poly(L-lactide): a long-term degradation study in vivo. Part III. Analytical characterization. *Biomaterials* 1993; 14:291-8; PMID:8476999; [http://dx.doi.org/10.1016/0142-9612\(93\)90121-H](http://dx.doi.org/10.1016/0142-9612(93)90121-H)
15. Saikku-Bäckström A, Tulamo RM, Pohjonen T, Törmälä P, Riihjä JE, Rokkanen P. Material properties of absorbable self-reinforced fibrillated poly-96L/4 D-lactide (SR-PLA96) rods; a study in vitro and in vivo. *J Mater Sci Mater Med* 1999; 10:1-8; PMID:15347988; <http://dx.doi.org/10.1023/A:1008828925090>
16. van Dijk M, Tunc DC, Smit TH, Higham P, Burger EH, Wuisman PI. In vitro and in vivo degradation of bioabsorbable PLLA spinal fusion cages. *J Biomed Mater Res* 2002; 63:752-9; PMID:12418020; <http://dx.doi.org/10.1002/jbm.10466>
17. McManus AJ, Moser RC, Dabkowski RB, Thomas KA. Enhanced retention of polymer physical characteristics and mechanical strength of 70:30 poly(L-lactide-co-D,L-lactide) after ethylene oxide sterilization. *J Biomed Mater Res B Appl Biomater* 2007; 82:325-33; PMID:17238162; <http://dx.doi.org/10.1002/jbm.b.30737>
18. Huttunen M. Analysis of the factors affecting the inherent viscosity of oriented polylactides during hydrolytic degradation. *J Mater Sci Mater Med* 2013; 24:1131-44; PMID:23471499; <http://dx.doi.org/10.1007/s10856-013-4886-5>
19. Daculsi G, Goyenvalle E, Cognet R, Aguado E, Suokas EO. Osteoconductive properties of poly(96L/4D-lactide)/beta-tricalcium phosphate in long term animal model. *Biomaterials* 2011; 32:3166-77; <http://dx.doi.org/10.1016/j.biomaterials.2011.01.033>; PMID:21315446
20. Bigg DM. Polylactide copolymers: Effect of copolymer ratio and end capping on their properties. *Adv Polym Technol* 2005; 24:69-82; <http://dx.doi.org/10.1002/adv.20032>
21. Kellomäki M, Pohjonen T, Törmälä P. Self reinforced polylactides: Optimization of degradation and mechanical properties. In: Arshady R, ed. *Biodegradable Polymers*. London, United Kingdom: Citys Books, 2003:211-235.
22. Migliaresi C, Fambri L, Cohn D. A study on the in vitro degradation of poly(lactic acid). *J Biomater Sci Polym Ed* 1994; 5:591-606; PMID:8086385; <http://dx.doi.org/10.1163/156856294X00220>