SYNTHESES AND PROPERTIES OF POLY(α-HYDROXY ACID)S WITH POLY(ETHER) CORES

by

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JEFFREY L. ATKINSON

CHEMISTRY

ABSTRACT

Novel biomaterials composed of a polyglycidol backbone with polyester branches consisting of poly(lactide) or poly(lactide-co-glycolide) are synthesized and characterized. Thermal stability, mechanical properties, and hydrolytic degradation of these polymers are essential factors of their processing and practical application. Data from the analysis of the polymer properties is used to determine structure-property relationships for the branched polyesters.

Poly(glycidol) (PG), poly(glycidol)-g-L-lactide (PG-g-La), and poly(glycidol)-g-glycolide (PG-g-Gly) are synthesized for evaluation of the core material and simple branched systems. Thermogravimetry, Fourier transform infrared spectroscopy, and isoconversional kinetic analysis are used to evaluate the kinetic and mechanistic aspects of nonoxidative thermal degradation. It is found that PG degrades in a single mass loss step, whereas, PG-g-La and PG-g-Gly degrade in two. It is demonstrated that the first step in degradation of PG-g-La and PG-g-Gly is associated with decomposition of the pendant groups and the second is due to degradation of the PG backbone.

Poly(lactide)s and poly(lactide-co-glycolide)s with different number of arms are synthesized from L-lactide and glycolide monomers using stannous (II) 2-ethylhexanoate and alcohols containing 1, 2, 25 and 51 hydroxyl groups. 1-dodecanol is used to produce the 1-arm polymer, poly(ethylene glycol) for the 2-arm polymer, and polyglycidols of appropriate molecular weight are used to initiate the 25- and 51-arm branched polyesters.
Polymer composition and molecular weight are characterized by $^1$H NMR and gel permeation chromatography (GPC). Thermal properties of the polymers are studied using differential scanning calorimetry (DSC). Thermal degradation behavior is investigated using a combination of thermogravimetry, FTIR spectroscopy, and isoconversional kinetic analysis. Polymer processing and use are evaluated by melt rheology, dynamic mechanical analysis (DMA), and in vitro degradation. Melt rheology demonstrates branched polymers have favorable processing temperatures. DMA demonstrates melt-processed polymer samples have similar storage and loss modulus values at room temperature and body temperature. Hydrolytic degradation and erosion is investigated in phosphate buffer pH 7.4 at 37 °C for 28 days. Degraded samples are analyzed by gravimetry, DSC, dilute solution viscometry (Cannon-Fenske), and GPC.

Keywords: degradation, kinetics, thermogravimetric analysis (TGA), dynamic mechanical analysis (DMA), poly(lactide), poly(glycidol)
DEDICATION

For Jacqui, Dixon, Erin, Anna Lea, and Meagan
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<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>DDS</td>
<td>drug delivery system</td>
</tr>
<tr>
<td>DSC</td>
<td>differential scanning calorimetry</td>
</tr>
<tr>
<td>$E'$</td>
<td>storage modulus in tensile mode</td>
</tr>
<tr>
<td>$E''$</td>
<td>loss modulus in tensile mode</td>
</tr>
<tr>
<td>EEGE</td>
<td>Ethoxy ethyl glycidyl ether</td>
</tr>
<tr>
<td>$E_{\alpha}$</td>
<td>activation energy</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier-transform infrared spectroscopy</td>
</tr>
<tr>
<td>G</td>
<td>shear modulus</td>
</tr>
<tr>
<td>$G'$</td>
<td>storage modulus in shear mode</td>
</tr>
<tr>
<td>$G''$</td>
<td>loss modulus in shear mode</td>
</tr>
<tr>
<td>Gly</td>
<td>glycolide</td>
</tr>
<tr>
<td>GPC</td>
<td>gel permeation chromatography</td>
</tr>
<tr>
<td>$\Delta H_c$</td>
<td>heat of crystallization</td>
</tr>
<tr>
<td>$\Delta H_m$</td>
<td>heat of melting</td>
</tr>
<tr>
<td>i</td>
<td>initial time</td>
</tr>
<tr>
<td>La</td>
<td>L-Lactide</td>
</tr>
<tr>
<td>m</td>
<td>number of intervals for analysis</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$m_d$</td>
<td>mass after drying</td>
</tr>
<tr>
<td>$m_h$</td>
<td>hydrated mass</td>
</tr>
<tr>
<td>$m_i$</td>
<td>initial weight</td>
</tr>
<tr>
<td>$\bar{M}_n$</td>
<td>number-average molecular weight</td>
</tr>
<tr>
<td>$\bar{M}_w$</td>
<td>weight-average molecular weight</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>PEG</td>
<td>poly(ethylene glycol)</td>
</tr>
<tr>
<td>PEO</td>
<td>poly(ethylene oxide)</td>
</tr>
<tr>
<td>PG</td>
<td>poly(glycidol)</td>
</tr>
<tr>
<td>PGA</td>
<td>poly(glycolide)</td>
</tr>
<tr>
<td>PG-g-Gly</td>
<td>poly(glycidol)-g-glycolide</td>
</tr>
<tr>
<td>PG-g-La</td>
<td>poly(glycidol)-g-L-lactide</td>
</tr>
<tr>
<td>PLA</td>
<td>poly(lactide)</td>
</tr>
<tr>
<td>PLGA</td>
<td>poly(lactide-co-glycolide)</td>
</tr>
<tr>
<td>PLLA</td>
<td>poly(L-lactide)</td>
</tr>
<tr>
<td>Sn(oct)$_2$</td>
<td>tin 2-ethylhexanoate</td>
</tr>
<tr>
<td>tan $\delta$</td>
<td>loss tangent</td>
</tr>
<tr>
<td>$T_g$</td>
<td>glass transition temperature</td>
</tr>
<tr>
<td>TGA</td>
<td>thermogravimetric analysis</td>
</tr>
<tr>
<td>$T_m$</td>
<td>melting temperature</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>peak degradation temperature</td>
</tr>
<tr>
<td>$T_{p,c}$</td>
<td>peak crystallization temperature</td>
</tr>
<tr>
<td>$T_{p,m}$</td>
<td>peak melting temperature</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>WA</td>
<td>water absorbed</td>
</tr>
<tr>
<td>$X_c$</td>
<td>percent crystallinity</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>percent conversion</td>
</tr>
<tr>
<td>$\eta^*$</td>
<td>complex viscosity</td>
</tr>
<tr>
<td>$\eta_{inh}$</td>
<td>inherent viscosity</td>
</tr>
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</table>
INTRODUCTION

When designing polymers for medical and pharmaceutical applications, one needs to consider a host of properties, including biocompatibility, mechanical and thermal properties, products, and rates of degradation. These properties can be critical under conditions of storage, during initial introduction into the body and throughout the lifetime of the device, or drug product as well as under processing conditions such as hot melt extrusion, which puts stringent requirements on the thermal stability of polymers used in pharmaceutical formulations. The thermo-mechanical properties are determined by the polymer composition (monomer selection), molecular weight, initiator type, process conditions, and presence of additives. These factors control the hydrophilicity/water uptake, crystallinity, melt and glass-transition temperatures, molecular-weight distribution (polydispersity), end groups, sequence distribution (random versus block), rate of hydrolysis, degradation products, and presence of residual monomer or additives in the polymer.\textsuperscript{[1]} Biocompatibility of the polymer, impurities in the polymer, and degradation products must be considered in polymer design as they can affect the suitability of the polymer for internal use because the body is exposed to it for an extended period of time or for multiple treatments.\textsuperscript{[2]}

More than four decades have passed since the first publication on the application of poly(lactic acid) (PLA) in medicine by Kulkarni et al.\textsuperscript{[3]} in 1966. Since then aliphatic polyesters based on lactic and glycolic acids have been studied and used extensively as biomaterials and drug delivery carriers. Polylactides, polyglycolides and the copolymers
of lactide and glycolide are used for sutures, fracture fixation and drug delivery including parenteral implants and microspheres.\[^{[4]}\] High molecular weight PLA is required for some applications, for example, orthopedics, but, the high melt viscosity and poor thermal stability of PLA can result in degradation during processing.\[^{[4, 5]}\] Additionally, when PLA or poly(lactide-co-glycolide) (PLGA) are used in drug delivery systems they often demonstrate polyphasic drug release, low encapsulation efficiencies of hydrophilic molecules, and negative effects on protein stability.\[^{[6]}\] For polyesters made of lactic and/or glycolic acid, properties are adjusted primarily by varying the molecular weight and/or monomer ratio during co-polymerization.\[^{[7]}\] Modifications to the polymer properties using the above methods do not always lead to the desired release profile and/or polymer degradation rate. To achieve better control of the release profile and polymer degradation rate, two major modifications to PLGA polymers have been proposed in the literature\[^{[8]}\]: 1. increasing the hydrophilicity of the polymer resulting in faster water uptake and swelling of the polymer matrix; 2. accelerating the degradation rate by using a branched architecture. Also, inclusion of a hydrophilic block/core increases the hydrophilicity of the polymer which should increase and enhance the stability of hydrophilic bioactive agents like proteins within the polymer matrix.

Branched structures are known to have different thermal, mechanical, and degradable properties than their linear counterparts. Degradation in branched polyesters should be faster than in linear polyesters since the degradation products will be soluble in water within a few cleavage steps. Lower glass transition temperatures (\(T_g\)) and melt viscosities are observed for multi-arm polymers than for linear polymers of similar molecular weight which may enable processing at lower temperatures.\[^{[9]}\]
The properties of the branched polymer can be tuned by manipulating the type and amount of backbone material used. Examples of this are PLAs and PLGAs synthesized using poly(ethylene glycol) (PEG), polyethylene oxide (PEO), glycerol, tetra(ethylene glycol), 1,1,1-tri(hydroxyl methyl)propane, pentaerythritol, mannitol/sorbitol, star-shaped PEG/PEO, Poly(amidoamine), depsipeptide-lactide, polysaccharide (dextran), poly(vinyl alcohol) and polyglycidol as macroinitiators. For each of the different backbone materials it was shown that $T_g$, $T_m$, crystallinity and degradation rate of the branched polymers could be controlled by changes to the molecular architecture such as varying the molecular weight of the main chain or branches and degree of branching. It has been shown that the properties of the polyol used in the backbone strongly influence the degradation mechanism so it is adjustable from random to nonrandom hydrolysis (i.e., preferential hydrolysis at preformed break-points such as branch points) of the polyester chains.

The polymerization of glycidol was first reported by Sandler and Berg in 1966. Vandenburg demonstrated that the structure of PG had extensive branching due to transfer reactions. A method for synthesizing linear PG by protecting the glycidol hydroxyl group with ethyl vinyl ether, polymerizing the protected glycidol then removing the protecting group has been reported more recently. The resulting linear PG is a polyether and can be considered a polyfunctional poly(ethylene glycol) (PEG) since the repeat unit has the same $-\text{CH}_2-\text{CH}_2-\text{O}-$ composition with a methyl alcohol pendant group. PG is hydrophilic, has been shown to have biocompatibility that is as good as or better than that of PEG, and has protein adsorption resistance equal to PEG.
PG were chosen as the hydrophilic core materials for the branched polymers in this study. PEG is one of the most studied and widely used biocompatible polymers. PG is expected to have many of the same favorable properties as PEG due to the structural similarity. Additionally, since PG contains a pendant alcohol group in each repeat unit it has the functionality to have polyester branches equal to the number of repeat units in the PG backbone. This functionality allows for the synthesis of highly branched polyesters. The advantage of using PG as the backbone is that the polymers can be extensively modified, PG molecular weight, ratio of PG to polyester, ratio of lactide to glycolide, molecular weight of arms, etc., to achieve the desired thermo-mechanical, degradation, and drug release properties.

The objective of this dissertation research is to investigate the properties of the novel branched polymers synthesized with a PG core and PLA or PLGA arms. Gel permeation chromatography (GPC) and $^1$H NMR are used to determine molecular weight and composition. Differential scanning calorimetry (DSC) is used to evaluate glass transition, melting point, and crystallinity. Thermogravimetric analysis (TGA) and TGA-FTIR are employed to obtain information about the thermal stability, degradation products, and mechanistic insights. Isoconversional kinetic analysis of the TGA data is also performed to extract kinetic information on thermal degradation. Dynamic mechanical analysis (DMA) is used to access the mechanical properties as a function of temperature. Melt rheology is used to determine the mechanical properties affecting melt processing. In vitro degradation in a phosphate buffer system is performed to evaluate hydrolytic degradation.
The research is divided into three parts which either have been published or submitted for publication. The first manuscript details the study on the thermal degradation of the core material PG and the model compounds poly(glycidol)-g-L-lactide (PG-g-La) and poly(glycidol)-g-glycolide (PG-g-Gly). Figure 1 shows the structures of the polymers investigated in the first manuscript. To better understand the effect on thermal properties and degradation of branched PLA and PLGA with hydrophilic polyl cores, the study described in the second manuscript compares the thermal properties and degradation of linear poly(L-lactide) (PLLA) and PLGA with multi-arm PEG-PLLA, PEG-PLGA, PG-PLLA, and PG-PLGA. In the third manuscript, the dynamic mechanical and hydrolytic degradation properties of PLLA, PLGA, PEG-PLLA, PEG-PLGA, PG-PLLA and PG-PLGA are evaluated. The structures of the polymers with semi-crystalline (Figure 2) and amorphous (Figure 3) character investigated in second and third manuscripts are shown below. Table 1 contains a summary of some of the polymer properties.
Polyglycidol (PG)

Poly(glycidol)-g-L-lactide (PG-g-La)
or
Poly(glycidol)-g-glycolide (PG-g-Gly)

Figure 1. Structures of poly(glycidol), poly(glycidol)-g-L-lactide, and poly(glycidol)-g-glycolide.
Figure 2. Structures of linear and branched poly(lactide-co-glycolide)s with semi-crystalline characteristics.
Figure 3. Structures of amorphous linear and branched poly(lactide-co-glycolide)s.
<table>
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<tr>
<th>Polymer</th>
<th>[LLA]/[Gly]/ [PEG or PG]</th>
<th>Microstructure</th>
<th>$\bar{M}_{n,NMR,arm}$</th>
<th>$\bar{M}_{n,GPC}$</th>
<th>$\bar{M}_{w,GPC}$</th>
<th>$T_g$</th>
<th>$T_{m,p}$</th>
<th>$T_{\text{max}}$</th>
</tr>
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<tbody>
<tr>
<td>PG2</td>
<td>0/0/100</td>
<td>linear, amorphous</td>
<td>–</td>
<td>1300</td>
<td>1800</td>
<td>-18</td>
<td>–</td>
<td>383</td>
</tr>
<tr>
<td>PG-g-La</td>
<td>95/0/5 c)</td>
<td>linear, amorphous</td>
<td>–</td>
<td>2200</td>
<td>4300</td>
<td>15</td>
<td>–</td>
<td>268, 328</td>
</tr>
<tr>
<td>PG-g-Gly</td>
<td>0/95/5 c)</td>
<td>linear, amorphous</td>
<td>–</td>
<td>2300</td>
<td>3300</td>
<td>6</td>
<td>–</td>
<td>267, 347</td>
</tr>
<tr>
<td>PG4</td>
<td>0/0/100</td>
<td>linear, amorphous</td>
<td>–</td>
<td>2600</td>
<td>5200</td>
<td>-16</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PEG</td>
<td>0/0/100</td>
<td>linear, amorphous</td>
<td>–</td>
<td>900</td>
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a) Molar ratio from $^1$H NMR  
b) Results rounded to the nearest hundred  
c) Theoretical  
d) Calculated using $(\bar{M}_{n,GPC} - \bar{M}_{p,GPC})/2$  
e) Number of arms = 2 (theoretical)  
f) Number of arms ≈ 25 from $^1$H NMR  
g) Number of arms ≈ 49 from $^1$H NMR
NONOXIDATIVE THERMAL DEGRADATION OF POLY(GLYCIDOL), POLY(GLYCIDOL)-g-L-LACTIDE AND POLY(GLYCIDOL)-g-GLYCOLIDE

by

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Format adapted and errata corrected for dissertation
Abstract

Three polymers of pharmaceutical/medical relevance are synthesized: poly(glycidol) (PG), poly(glycidol)-g-L-lactide (PG-g-La), and poly(glycidol)-g-glycolide (PG-g-Gly). Because the thermal stability of these polymers is an essential factor of their processing and practical application, the study focuses on kinetic and mechanistic aspects of non-oxidative thermal degradation. The study is conducted by combining thermogravimetry, Fourier transform infrared spectroscopy, and isoconversional kinetic analysis. It is found that PG degrades in a single mass loss step, whereas, PG-g-La and PG-g-Gly degrade in two. It is demonstrated that the first step in the degradation of PG-g-La and PG-g-Gly is associated with decomposition of the pendant groups and the second is due to degradation of the PG backbone.

Keywords:
degradation, FTIR; kinetics; thermogravimetric analysis (TGA); poly(glycidol)

Introduction

When designing polymers for medical and pharmaceutical applications, one needs to consider a host of properties, including biocompatibility, mechanical and thermal properties, products and rates of degradation. These properties can be critical under conditions of storage, initial introduction into the body and throughout the lifetime of the device, or drug product as well as under processing conditions such as hot melt extrusion, which puts stringent requirements on the thermal stability of polymers used in
pharmaceutical formulations. The thermo-mechanical properties are determined by the polymer composition (monomer selection), molecular weight, initiator type, process conditions, and presence of additives. These factors control the hydrophilicity/water uptake, crystallinity, melt and glass-transition temperatures, molecular-weight distribution (polydispersity), end groups, sequence distribution (random versus block), rate of hydrolysis, degradation products, and presence of residual monomer or additives in the polymer.\[^1\] Biocompatibility of the polymer, impurities in the polymer, and degradation products should be considered in polymer design as they could affect the suitability of the polymer for internal use because the body is exposed to it for an extended period of time or for multiple treatments.\[^2\]

Poly(glycidol) (PG), poly(lactide) (PLA) and poly(glycolide) (PGA) have attracted significant research interest during the last two decades. PG because of its biocompatibility, protein adsorption resistance, and functionality; PLA and PGA because of their biocompatibility, biodegradability, and mechanical properties. All are interesting because of their potential medical and pharmaceutical applications.

The polymerization of glycidol was first reported by Sandler and Berg in 1966.\[^3\] Vandenburg\[^4\] demonstrated that the structure of PG had extensive branching due to transfer reactions. A method for synthesizing linear PG by protecting the glycidol hydroxyl group with ethyl vinyl ether, polymerizing the protected glycidol then removing the protecting group has been reported more recently.\[^5\] The resulting linear PG is a polyether and can be considered a polyfunctional poly(ethylene glycol) (PEG) since the repeat unit has the same \(-\text{CH}_2\text{CH}_2\text{O}–\) composition with a methyl alcohol pendant
group. PG is hydrophilic, has been shown to have biocompatibility as good as or better than that of PEG and has protein adsorption resistance equal to PEG.\textsuperscript{[6]}

PLA, PGA and their co-polymers (PLGA) have been successfully used in several biomedical applications such as drug delivery systems, implant materials, and bioabsorbable surgical sutures.\textsuperscript{[7]} Despite the good properties and successes of poly(\(\alpha\)-hydroxy acid)s such as PLA, PGA and PLGA, these polyester delivery vehicles are known to have low encapsulation efficiencies of hydrophilic molecules, a negative effect on protein stability, and polyphasic release profiles.\textsuperscript{[8]} One of the most common strategies in the literature to overcome the problems with poly(\(\alpha\)-hydroxy acid) is to increase the hydrophilicity of the polyesters by incorporating hydrophilic blocks such as PEG or poly(ethylene oxide) (PEO) into the polymers. Studies of these block co-polymers indicate they may overcome some of the shortcomings of PLGA.\textsuperscript{[9-11]}

Using PG to introduce a branched architecture with hydrophilic properties into \(\alpha\)-hydroxy acid polyesters is another strategy to improve the properties. Branched structures are known to have different thermal, mechanical, and degradable properties than their linear counterparts. Poly(glycidol)-g-poly(lactide) (PG-g-PLA) has been synthesized and some of the thermal and mechanical properties have been evaluated.\textsuperscript{[12]} The study was limited to a single molecular weight, racemic PG backbone while varying the molecular weight of the PLA branches. It was shown that the \(T_g\), \(T_m\) and crystallinity of PG-g-PLA could be changed by varying the PLA chain molecular weight.\textsuperscript{[12]} More research is needed to understand how the ratio of PG to \(\alpha\)-hydroxy acid polyester branches affect the thermal and mechanical properties as well as the degradation of the
polymer so that the properties may be tailored for different medical and pharmaceutical uses.

Temperature changes can stimulate a variety of processes in polymers,\textsuperscript{13} including thermal degradation that can take place at the temperatures of processing and storage. Thermogravimetric analysis (TGA) is a technique widely used to study the thermal degradation of polymers. By combining TGA with FTIR, one can also obtain information about degradation products and some mechanistic insights. TGA can also produce data suitable for extracting kinetic information on thermal degradation. A simple and efficient way of accomplishing this task is to subject TGA data to isoconversional kinetic analysis.\textsuperscript{13} The purpose of the present study is to investigate the thermal degradation of PG and its lactide and glycolide derivatives using the aforementioned techniques. To our knowledge, there have been no studies of the kinetic and mechanistic aspects of the thermal degradation of this type of polymer despite their promise of important medical and pharmaceutical applications.

**Experimental Section**

**Materials**

Racemic glycidol (Aldrich), iodoethane (Alfa Aesar), ethyl vinyl ether (ACROS), and 2-methoxyethanol (ACROS) were purified by distillation. Cesium hydroxide monohydrate (ACROS), p-Toluenesulfonic acid monohydrate (ACROS), sodium bicarbonate (Sigma), anhydrous magnesium sulfate (Fisher Scientific), toluene (Fisher Scientific), hydrochloric acid (Fisher Scientific), tin (II) 2-ethyl hexanoate (Sigma) were
purchased and used without further purification. L-Lactide (La) and glycolide (Gly) were a gift from Lakeshore Biomaterials, Birmingham, AL and were used without further purification.

**Synthesis**

The reaction scheme for the synthesis of Poly(glycidol) (PG), Poly(glycidol)-g-L-lactide (PG-g-La), and Poly(glycidol)-g-glycolide (PG-g-Gly) is shown in Scheme 1.

**Protected Glycidol**

Ethoxy ethyl glycidyl ether (EEGE or protected glycidol) was synthesized by reacting glycidol with ethyl vinyl ether according to Fitton *et al.*  The organic layer was separated from the aqueous layer, dried over anhydrous MgSO$_4$ and filtered. Excess ethyl vinyl ether was evaporated under reduced pressure. The product was purified by distillation.

**Cesium 2-methoxyethalcoholate Initiator**

Cesium hydroxide monohydrate was dissolved in 2-methoxyethanol and magnetically stirred in a reaction flask. The solution was stirred at 90 °C for 1.5 h under a nitrogen purge then stirred at 90 °C under vacuum for an additional 2 h. The reaction mixture was cooled to 60 °C and stirred for an additional 12 h at 60 °C.
Scheme 1. Synthesis of poly(glycidol), poly(glycidol)-g-L-lactide and poly(glycidol)-g-glycolide.
Polyglycidol Polymerization Procedure

The polymerization of protected glycidol was performed by adding the appropriate molar amounts of the EEGE monomer to fresh cesium alcoholate initiator. The reaction mixture was stirred and heated at 60 °C for 72 h. At the end of the 72 h iodoethane was added in excess to terminate the reaction and stirring continued at 60 °C for 2 h. Any excess monomer and iodoethane were stripped under vacuum, then the reaction mixture was allowed to cool to room temperature. The poly(ethoxy ethyl glycidyl ether) (PEEGE) was dissolved in toluene and filtered. The solvent was then evaporated. Deprotection was accomplished by adding 3 mL of aqueous HCl (35%) to 540 mg of PEEGE in 34 mL of THF at room temperature and stirring for 2 h as described by Spassky et al.\textsuperscript{[15]} THF and HCl were removed using vacuum. The PG product was dissolved in water and filtered through molecular weight cut-off filters to obtain a product with a narrow molecular weight range between 1000 and 3000 Da. The water was evaporated and the polyglycidol was dried \textit{in vacuo} at 80 °C. Molecular weight was determined by gel permeation chromatography (GPC) using a Waters instrument with an Alltech ELSD-2000 evaporative light-scattering detector and a Phenomenex® Polysep-GFC-P-2000 column. The molecular weight was as follows: $\bar{M}_n = 860$, $\bar{M}_w = 1391$ g mol$^{-1}$, $\bar{M}_w/\bar{M}_n = 1.62$. Polyglycidol structure was confirmed by $^1$H NMR. The $^1$H NMR signals for PG are $\delta = 3.4-3.7$ ppm. No signals of the ethoxyethyl protecting group were observed in the spectrum indicating the full removal of the protecting group.
Poly(glycidol)-g-L-lactide and Poly(glycidol)-g-glycolide

The PGs with pendant ester groups were synthesized by ring-opening reaction of L-lactide or glycolide using PG as a macroinitiator and tin 2-ethylhexanoate (Sn(oct)$_2$) as the catalyst (Scheme 1). PG was dried under vacuum at 80 °C for 24 h. Glycolide or L-lactide was then added to the reaction flask containing PG and heated at 130 °C for 2 h to melt the reactants. A fresh solution of tin 2-ethylhexanoate in methylene chloride was added to the melt in a hood under dry nitrogen. The methylene chloride was removed under vacuum then reaction the flask was purged with dry nitrogen. The reaction mixture was heated at 130 °C for 3 h then cooled to room temperature. Molecular weights of PG-g-La and PG-g-Gly were determined by GPC using a Waters instrument with an Alltech ELSD-2000 evaporative light-scattering detector and a Phenomenex® Polysep-GFC-P-2000 column. The molecular weight was as follows: PG-g-La, $\bar{M}_n = 2218, \bar{M}_w = 4255$ g mol$^{-1}$, $\bar{M}_w/\bar{M}_n = 1.92$; PG-g-Gly, $\bar{M}_n = 2258, \bar{M}_w = 3337$ g mol$^{-1}$, $\bar{M}_w/\bar{M}_n = 1.48$. Polymer structures were confirmed by $^1$H NMR. The $^1$H NMR signals for PG-g-La are $\delta = 1.30$ ppm (La: CH$_3$), $\delta = 3.4-3.8$ ppm (PG: CH, main chain CH$_2$), $\delta = 4.10$ ppm (La: terminal CH), $\delta = 4.26$ ppm (PG: side chain CH$_2$), and $\delta = 5.05$ ppm (La: CH). PG-g-Gly $\delta = 3.3-3.6$ ppm (PG: CH, main chain CH$_2$), $\delta = 4.01, 4.07, 4.25,$ and $4.27$ ppm (PG: side chain CH$_2$), and $\delta = 4.62, 4.64, 4.65,$ and $4.67$ ppm (Gly: CH$_2$). The appearance of the new signal at $\delta = 4.26$ ppm indicates the introduction of the lactide groups onto the PG backbone. Likewise, the signals at $\delta = 4.01, 4.07, 4.25,$ and $4.27$ ppm indicate the introduction of glycolide groups onto the PG backbone.
Analysis

Differential Scanning Calorimetry

All calorimetric measurements were performed using a heat flux DSC (Mettler-Toledo, 823®). Indium and zinc standards were used to perform temperature, heat flow and tau-lag calibrations. Samples were prepared by weighing \( \approx 10 \) mg into 40 µL aluminum pans. Thermal scanning was performed from -40 to 600 °C at a heating rate of 10 °C min\(^{-1}\) under a nitrogen purge at a flow rate of 80 mL min\(^{-1}\).

Thermogravimetry

Thermal degradation kinetics were measured as temperature and time dependent mass loss using a Mettler-Toledo TGA/SDTA851®. Samples were prepared by weighing \( \approx 5 \) mg samples into 40 µL aluminum pans and drying under vacuum for 48 h at 80 °C. Non-isothermal measurements of the samples were performed under a nitrogen purge at a flow rate of 70 mL min\(^{-1}\) from 25 to 620 °C while heating at rates of 2.5, 5.0, 7.5, 10.0 and 12.5 °C min\(^{-1}\). The buoyancy effect in TGA was accounted for by performing a blank run of the empty pan and subtracting the empty pan results from the respective mass loss measurements for the polymer samples.

FTIR Spectroscopy

The gaseous products of nonoxidative thermal degradation were monitored using TGA coupled with Fourier transform infrared spectroscopy (TGA-FTIR). TGA-FTIR analysis was performed on a Mettler-Toledo TGA/SDTA851® module interfaced with a
Nicolet Nexus 470 FTIR spectrometer. Samples were prepared by weighing ≈ 8 mg samples into 40 µL aluminum pans and drying under vacuum for 48 h at 80 °C prior to TGA-FTIR analysis. Before each TGA-FTIR run the system was purged with nitrogen for a minimum of 1 h. The dry samples were then run in the TGA under a nitrogen purge at a flow rate of 65 mL min\(^{-1}\) from 25 to 600 °C while heating at a rate of 10 °C min\(^{-1}\). Evolved gases flowed from the furnace of the TGA through a heated transfer line at 230 °C to the FTIR gas cell. FTIR spectra of the degradation products were taken at 4 cm\(^{-1}\) resolution. Each spectrum was an average of 32 scans.

NMR Spectroscopy

A Bruker DRX-400 spectrometer was used to obtain \(^1\)H NMR spectra at a frequency of 400 MHz. D\(_2\)O was used as a solvent to prepare solutions of 5 mg mL\(^{-1}\) for each synthesized polymer.

Isoconversional Kinetic Analysis

The mass data obtained by TGA were subjected to isoconversional kinetic analysis.\(^{[16]}\) As demonstrated in a recent review paper,\(^{[13]}\) this type of analysis offers an efficient approach to understanding the complex kinetics that are typically encountered in thermally activated processes in polymeric systems. The data were treated by an advanced isoconversional method developed by Vyazovkin\(^{[17, 18]}\) that allows one to determine a dependence of the effective activation energy \((E_\alpha)\) on the extent of conversion \((\alpha)\). The latter value was determined as a fractional mass loss from TGA data.
Compared to the most common isoconversional methods of Flynn and Wall\cite{19} and Ozawa,\cite{20} the method has two principal advantages. First, it can treat data obtained under arbitrary variation in temperature, $T(t)$ which permits analyzing data acquired on cooling as well as accounting for self-heating/cooling detectable by the thermal sensor of the instrument. For a set of $n$ experiments performed under different temperature programs, $T_i(t)$, the effective activation energy is evaluated at any given $\alpha$ by finding $E_\alpha$, which minimizes the function\cite{17,18}

$$\Psi(E_\alpha) = \sum_{i=1}^{n} \sum_{j=i}^{n} \frac{J[E_\alpha, T_i(t_{a,j})]}{J[E_\alpha, T_j(t_{a,i})]}$$  \hspace{1cm} (1)$$

where

$$J[E_\alpha, T_i(t_{a,j})] = \int_{t_{a,i} - \Delta t}^{t_{a,i}} \exp\left[-\frac{E_\alpha}{RT_i(t)}\right] dt$$ \hspace{1cm} (2)$$

The second advantage is due to carrying out numerical integration over small time segments (Equation 2) that eliminates a systematic error\cite{18} found in the Flynn and Wall and Ozawa methods when $E_\alpha$ varies significantly with $\alpha$. In Equation 2, $\alpha$ is varied from $\Delta \alpha$ to 1-$\Delta \alpha$ with a step $\Delta \alpha = m^{-1}$, where $m$ is the number of intervals chosen for computation. The integral, $J$ in Equation 2, is evaluated by using the trapezoid rule. The minimization routine is repeated for each value of $\alpha$ to determine the dependence $E_\alpha$ on $\alpha$. 
Results and Discussion

Differential Scanning Calorimetry

PG, PG-g-La, and PG-g-Gly were examined using DSC to identify thermal transitions from -40 to 600 °C. The glass transition temperatures for PG, PG-g-La and PG-g-Gly were -18, 15, and 6 °C respectively. No other thermal transitions were observed in the temperature range until degradation started, indicating that all three polymers were amorphous.

Thermogravimetry

Figure 1 and 2 display respectively typical TGA and DTG data for the thermal degradation of all three polymers. As seen from Figure 1 and 2, PG degrades in a single mass loss step and has the largest thermal stability of all three polymers. It starts actively losing mass somewhere above 250 °C. Its mass loss rate reaches a maximum at $T_{\text{max}}$ = 383 °C. PG-g-La and PG-g-Gly start losing mass above 150 °C and degrade in two steps. The degradation complexity of PG-g-La and PG-g-Gly is well seen in DTG data, which are known to be a better indicator of the number of processes, reactions, or physical phenomenon occurring. The maximum rate of the mass loss in the first step is found at $T_{\text{max}, 1}$ = 268 °C (PG-g-La) and 267 °C (PG-g-Gly). For the second mass loss rate, the rate maxima are found at $T_{\text{max}, 2}$ = 328 °C (PG-g-La) and 347 °C (PG-g-Gly). Since the second mass loss process occurs in the temperature range of the degradation of PG, one can expect this process to be associated with the degradation of the polymer backbone. The occurrence of the second rate maxima for PG-g-La and PG-g-Gly at a lower
Figure 1. Mass loss curves obtained on heating the polymers at 10°C min\(^{-1}\).
Figure 2. Derivative mass curves for the polymers heated at 10°C min⁻¹. The numbers denoted by arrows represent the temperatures of the maximum mass loss rate, $T_{\text{max}}$. 
temperature than for PG is consistent with the well-known effect of the thermal destabilization of polyethers due to branching.\textsuperscript{[22]} Then, the first mass loss step can perhaps be linked to the degradation of the pendant groups. It is also worthy of note that PG degrades leaving a little over 5\% residue, whereas, PG-g-La and PG-g-Gly produce more than 20\% of char. Increasing amount of low volatility residue is usually indicative of inter- and intra-molecular reactions such as cross-linking and cyclization.

**Fourier Transform Infrared Spectroscopy**

Information about the nonoxidative thermal degradation products as a function of temperature for each of the 3 polymers was obtained by analyzing evolved gas from the TGA furnace flow into the FTIR gas cell. Figure 3 presents Gram-Schmidt plots demonstrating the IR absorption intensity for degradation products of the three polymers.

The thermal degradation of PG occurs as a single mass loss step with the highest amount of volatile products being released at 383 °C for these experimental conditions. The unimodal shape of the Gram-Schmidt plot confirms the single-step degradation of PG. The FTIR spectra of the evolved products of PG degradation at multiple temperatures are shown in Figure 4. There are no previous thermal degradation studies of PG that identify the main degradation products. PG can be considered a polyfunctional analog of PEG which has been extensively studied. The main thermal decomposition products of PEG have been identified as alcohols, alkenes, cyclic and non-cyclic ethers, formaldehyde, acetic aldehyde, oligomers with aldehydic ends, ethylene oxide, water, carbon monoxide (CO), and carbon dioxide (CO\textsubscript{2}).\textsuperscript{[23-27]}
Figure 3. Gram-Schmidt plot showing the intensity of the evolution of degradation products ($\nu = 400-4000 \text{ cm}^{-1}$) during the thermal decomposition of the polymers.
Figure 4. FTIR of gas phase degradation products of PG at multiple temperatures.
degradation of PG should yield similar degradation products. At $T_{\text{max}}$ for the degradation of PG the FTIR absorption bands have been identified as follows: sym. ring deformation (epoxy rings), CH$_2$ rocking at 850 cm$^{-1}$, asym. ring deformation (epoxy rings), CH$_3$ rocking at 930 cm$^{-1}$, ring breathing, C-O stretching in primary alcohol at 1060 cm$^{-1}$, C-O-C asym. stretching at 1110 cm$^{-1}$, CH$_2$ twisting, CH$_2$ wagging, ring breathing, O-H bending in epoxy rings and alcohols at 1270 cm$^{-1}$, CH$_2$ wagging at 1370 cm$^{-1}$, C═O stretch at 1720 (ketone) and 1800 cm$^{-1}$ (aldehyde), CO at 2110 and 2180 cm$^{-1}$, CO$_2$ at 2320 and 2360 cm$^{-1}$, C-H stretching in acyclic ethers and aldehydes at 2850 cm$^{-1}$, C-H stretching in epoxy rings at 2950 cm$^{-1}$, C-H stretching at 2600-3100 cm$^{-1}$, and H$_2$O at 3583 cm$^{-1}$. By comparing the time-resolved IR spectra the first degradation products are alcohols, ethers, and epoxides followed by aldehydes, ketones and CO, the last product to evolve is CO$_2$. Alcohols, ethers, and epoxides are visible in the IR from 350 to 600 °C; aldehydes, ketones, and CO are seen from 360 to 495 °C; CO$_2$ is seen from 380 to 395 °C. The results suggest that PG degradation is most likely a combination of unzipping and random chain scission mechanisms.

Thermal degradation of PG-g-La occurs in two-steps where the first step starts at 175 °C, reaches a maximum at 268 °C, the first and second degradation steps overlap strongly, the maximum for the second step occurs at 347 °C, and the second step ends at 380 °C. The Gram-Schmidt plot demonstrating the IR absorption intensity of the PG-g-La degradation products is shown in Figure 3. The bimodal shape of the Gram-Schmidt plot is consistent with the two-step degradation of PG-g-La. Poly(D,L-lactide) ($\bar{M}_n = 4900$, $\approx$ 34 lactide units) has been found to have a $T_{\text{max}}$ of 272 °C.$^{[28]}$ It is expected that
the lactide pendant groups on the PG-g-La degrade at a $T_{\text{max}}$ less than 272 °C. $T_{\text{max}}$ for the first stage of PG-g-La degradation is 268 °C which is consistent with the expectation above. In previous thermal degradation studies of PLA in the temperature range of 230-440 °C oligomers, lactide, acetaldehyde, and CO were observed as degradation products at all temperatures in the range.$^{[29, 30]}$ CO$_2$ was observed above 277 °C and methylketene was observed above 320 °C. The main decomposition reaction postulated was a non-radical, backbiting ester exchange (Scheme 2). CO$_2$ generation was attributed to the chain scission of PLA involving alkyl-oxygen homolysis producing radicals (Scheme 3)$^{[29, 30]}$. The primary pyrolysis products of the lactide pendant groups in PG-g-La should be the same as PLA.

The FTIR spectra of the evolved products at multiple temperatures are shown in Figure 5. CO$_2$ is the first decomposition product observed in the degradation of PG-g-La. This result indicates that the non-radical ester exchange is not the primary degradation route in PG-g-La but rather the radical decomposition route R1 (Scheme 3). This may be explained due to steric hinderance in the backbiting ester exchange reaction although ester exchange may occur between the lactide groups along the PG backbone. Ester exchange between the lactide groups would not result in degradation products. The activation energy of the alkyl-oxygen bond scission (R1) is slightly lower than the acyl-oxygen bond scission (R2), therefore, CO$_2$ would be generated before CO.$^{[30]}$

At the $T_{\text{max}}$ for the first decomposition step the FTIR absorption bands have been identified as follows: C═C wagging, ring skeletal vibration, CH$_3$ rocking at 900 cm$^{-1}$, C-O stretch, O-C-C stretching at 1100 cm$^{-1}$, C-C-O stretch at 1190 cm$^{-1}$, CH$_2$ twisting, CH$_2$
Scheme 2. Non-radical reactions for the thermal degradation of PLA based on references [29, 30].
Scheme 3. Radical reactions for the thermal degradation of PLA based on references [29,30].
Figure 5. FTIR of gas phase degradation products of PG-g-La at multiple temperatures.
wagging, C-C-O stretch, C-O stretch at 1270 cm\(^{-1}\), C-H bending in CH\(_3\) groups at 1360 cm\(^{-1}\), C═O stretch at 1720 cm\(^{-1}\), CO at 2100 and 2180 cm\(^{-1}\), CO\(_2\) at 2330 and 2360 cm\(^{-1}\), aldehydic C-H stretch at 2740 cm\(^{-1}\), C-H stretching in CH\(_2\) groups at 2850-3050 cm\(^{-1}\), and C-H stretching in CH\(_3\) groups at 2990 cm\(^{-1}\). The presence of lactide and cyclic oligomers are indicated by C-O stretching at 1100 and 1270 cm\(^{-1}\), C═O stretching at 1720 cm\(^{-1}\) (ester), CH\(_2\) stretching and bending at 2990 and 1360 cm\(^{-1}\), and a ring skeletal vibration at 900 cm\(^{-1}\). The C-H bending in CH\(_3\) groups at 1360 cm\(^{-1}\), C═O stretch at 1700-1820 cm\(^{-1}\), aldehydic C-H stretch at 2740 cm\(^{-1}\) and C-H stretching in CH\(_3\) groups at 2990 cm\(^{-1}\) indicate aldehyde degradation products. Pyrolysis products from this stage of degradation correspond with the degradation of the lactide groups.

By comparing the FTIR spectra of PG-g-La at \(T_{\text{max},2}\) and \(T_{\text{max},1}\) changes in degradation products are observed. The primary changes in the FTIR spectra from \(T_{\text{max},1}\) to \(T_{\text{max},2}\) are as follows: (1) C═O stretch peak shift from 1720 cm\(^{-1}\) to 1790 cm\(^{-1}\) indicating a shift in volatile products from ester to aldehydes, (2) CO\(_2\) peak is less intense signaling less CO\(_2\) is produced, (3) Absorption from 2600 to 3100 cm\(^{-1}\) becomes more intense and defined indicating more volatile products containing C-H stretching, C-H stretching in acyclic ethers and aldehydes (2850 cm\(^{-1}\)), and C-H stretching in epoxy rings (2950 cm\(^{-1}\)), and (4) H\(_2\)O (3580 cm\(^{-1}\)) peak intensity increases indicating water is produced more abundantly at higher temperatures. These changes in the spectrum correspond to the degradation of the PG backbone as the second step in the degradation of PG-g-La.

Thermal degradation of PG-g-Gly is also a two-step process where the first step starts at 180 °C, reaches a maximum at 267 °C, the first and second degradation stages
overlap, the maximum for the second step is at 347 °C, and the second-step ending at 380 °C. The Gram-Schmidt plot for demonstrating the IR absorption intensity of the PG-g-Gly degradation products is seen in Figure 3. The FTIR spectra of the evolved products at multiple temperatures are shown in Figure 6. Due to the similarity of glycolide and lactide it is expected that the glycolide pendant groups on the PG-g-Gly degrade at a similar temperature. \( T_{\text{max}} \) for the first stage of PG-g-Gly degradation is 267 °C which is consistent with the expectation above. McNeill and Leiper\(^{31} \) suggest that PGA degrades by the same ester exchange mechanism as PLA, excepting the cis-elimination (NR4) due to the lack of \( \beta \)-hydrogens, yielding glycolide and cyclic oligomers (Scheme 2). However, they also observed \( \text{CO}_2 \) production at lower temperatures and suggested decarboxylation of terminal carboxyl groups to be the source (Scheme 4).\(^{31} \) Formaldehyde and CO were only observed at higher temperatures leading them to conclude that they were products of chain scission (Scheme 3).\(^{31} \) The primary pyrolysis products of PGA have been identified as \( \text{CO}, \text{CO}_2 \), formaldehyde, glycolide, and cyclic oligomers.\(^{31} \) It is assumed that the primary pyrolysis products of glycolide should be similar to those of PGA.

\( \text{CO}_2 \) is the first decomposition product observed (Figure 6) in the degradation of PG-g-Gly, however, decarboxylation of terminal carboxyl groups would not occur in PG-g-Gly due to the alcohol end-groups. The generation of \( \text{CO}_2 \) as the first decomposition product may be explained in the same manner as in PG-g-La. Degradation occurs primarily through the radical decomposition route R1.
Figure 6. FTIR of gas phase degradation products of PG-g-Gly at multiple temperatures.

Scheme 4. Decarboxylation reaction for the thermal degradation of PGA proposed by McNeill.\textsuperscript{31}
At the $T_{\text{max}}$ for the first decomposition step the FTIR absorption bands have been identified as follows: ring skeletal vibration at 850 cm$^{-1}$, C-O stretch, O-C-C stretching at 1060 cm$^{-1}$, C-C-O stretch at 1190 cm$^{-1}$, CH$_2$ twisting, CH$_2$ wagging, C-C-O stretch, C-O stretch at 1280 cm$^{-1}$, C═O stretch at 1800 cm$^{-1}$ (ester and aldehyde), CO at 2100 and 2190 cm$^{-1}$, CO$_2$ at 2320 and 2360 cm$^{-1}$, and C-H stretching at 2600-3100 cm$^{-1}$. The presence of glycolide monomer and cyclic oligomers are indicated by C-O stretching at 1060 and 1280 cm$^{-1}$, C=O stretching at 1801 cm$^{-1}$, C-H stretching and bending at 2600-3100 cm$^{-1}$, and a ring skeletal vibration at 850 cm$^{-1}$. Aldehydic degradation products are difficult to identify due to the overlap of the C=O stretching for glycolide and associated aldehydes. Volatile decomposition products from the first stage of degradation may be attributed to the degradation of the glycolide pendant groups.

A change in degradation products can be identified by comparing the FTIR spectra of PG-g-Gly at $T_{\text{max}, \ 2}$ and $T_{\text{max}, \ 1}$ (Figure 6). The primary changes in the FTIR spectra from $T_{\text{max}, \ 1}$ to $T_{\text{max}, \ 2}$ are as follows: (1) CO$_2$ peak is less intense signaling less CO$_2$ is produced, (2) Absorption from 2600-3100 cm$^{-1}$ becomes more intense and defined indicating more volatile products containing C-H stretching, C-H stretching in acyclic ethers and aldehydes (2850 cm$^{-1}$) and C-H stretching in epoxy rings (2950 cm$^{-1}$), and (3) H$_2$O (3580 cm$^{-1}$) peak intensity increases indicating water is produced more abundantly at higher temperatures. These changes in the spectrum correspond to the degradation of the PG backbone as the second step in the degradation of PG-g-Gly.
Kinetic Analysis

As a result of applying of an advanced isoconversional method the dependencies of the effective activation energy on conversion were determined (Figure 7-9). For all three polymers the earliest degradation stages ($\alpha \rightarrow 0$) are characterized by low activation energies in the vicinity of 50 kJ mol$^{-1}$. Lower values at the initial stages are frequently observed in thermal degradations of polymers.$^{[13, 16]}$ They are usually associated with the process of initiation at weak linkages such as head to head and peroxide groups. For the degradation of PG (Figure 7), the $E_\alpha$ value quickly rises past the initial stage and levels around 150 kJ mol$^{-1}$ in the range $\alpha=0.2 – 0.7$. The constancy of the effective activation energy indicates that the degradation kinetics is likely to be limited by a single reaction step. As mentioned above, degradation of PG is markedly similar to degradation of PEG. The $E_\alpha$ dependence obtained by an isoconversional method for PEG was found$^{[23]}$ to be increasing from 140 to 180 kJ mol$^{-1}$. The aforementioned $E_\alpha$ value, 150 kJ mol$^{-1}$, for PG is within 10% error of the mean activation energy for the first 40% of degradation of PEG. However, according Vrandecic et al.$^{[32]}$ the isoconversional activation energies do not practically depend on conversion but decrease with decreasing $M_w$ of PEG being around 120 kJ mol$^{-1}$ for $M_w=3,400$. While smaller, this value is within 20% error of that for PG. The similarity of the activation energies supports the idea of the similarity of the reaction mechanisms and limiting steps for degradation of PG and PEG.

The evolution of the effective activation energy for degradation of PG-g-La is shown in Figure 8. The $E_\alpha$ values seem practically constant throughout most of the first
Figure 7. $E_\alpha$ dependence (circles) for degradation of PG. Solid line shows conversion vs. temperature data at an average heating rate, 7.5°C min$^{-1}$. 
Figure 8. $E_\alpha$ dependence (circles) for degradation of PG-g-La. Solid line shows conversion vs. temperature data at an average heating rate, 7.5°C min$^{-1}$.
Figure 9. $E_\alpha$ dependence (circles) for degradation of PG-g-Gly. Solid line shows conversion vs. temperature data at an average heating rate, $7.5^\circ$C min$^{-1}$. 
mass loss step ($\alpha=0.1 - 0.4$) averaging to $\approx 90$ kJ mol$^{-1}$. As mentioned earlier, the
degradation products of the first mass loss step demonstrate notable similarity with those
for degradation of PLA. However, the activation energy found in the present study is
noticeably smaller than values reported for degradation of PLA: a constant value $120^{[30]}$
increasing with $\alpha$ from 160 to 190$^{[33]}$, and from $120 - 170^{[34]}$ kJ mol$^{-1}$. Apparently the
difference in the activation energies results from the fact that degradation of PLA and the
lactide pendant of PG-g-La have different limiting steps. As the degradation of PG-g-La
approaches the second mass loss step, the effective activation energy quickly rises,
reaching $\approx 150$ kJ mol$^{-1}$. This value is identical with the plateau $E_\alpha$ value for degradation
of PG (Figure 7). The similarity is consistent with the assumption that the second mass
loss step is associated with the degradation of the polymer backbone.

Figure 9 displays the $E_\alpha$ dependence for degradation of PG-g-Gly. The process
appears to be more complex kinetically than degradation of the two other polymers.
During the first mass loss step, the initial increase in the $E_\alpha$ values in the range $\alpha=0 - 0.2$
is followed by a quick drop and stabilization of the value at $\approx 100$ kJ mol$^{-1}$ in the range
$\alpha=0.3 - 0.6$. Considering the demonstrated mechanistic similarity of the first mass loss
step and degradation of PGA, one can expect the similarity of the activation energies for
these two processes. This seems to be the case here. For PGA, the activation energy was
reported$^{[31]}$ to be $\approx 90$ kJ mol$^{-1}$. Within 10% error, the value is consistent with the plateau
value $\approx 100$ kJ mol$^{-1}$, which represents the largest part of degradation of PG-g-Gly. The
initial rise of the $E_\alpha$ values to 150 kJ mol$^{-1}$ is not expected. It might indicate that
degradation of glycolide pendant is complicated by a contribution from the backbone
degradation, which is characterized by activation energy 150 kJ mol\(^{-1}\). As degradation reaches the second mass loss step the effective activation energy quickly rises to the level of the values characteristic for the degradation of PG (Figure 7). The behavior is rather similar to what was observed in degradation of PG-g-La (Figure 8). Again, the results are consistent with the assumption that the second mass loss step is due to the degradation of the polymer backbone.

**Conclusion**

Thermogravimetry coupled to FTIR was used to study the nonoxidative thermal degradation of PG, PG-g-La and PG-g-Gly. The degradation of PG occurred in a single step while the degradation of PG-g-La and PG-g-Gly occurred in two steps corresponding to a side-group elimination mechanism. FTIR analysis of the gaseous degradation products of PG indicated alcohols, ethers, epoxides, aldehydes, ketones, CO, CO\(_2\), and water. The degradation mechanism is most likely a combination of an unzipping and random chain scission. Degradation products of PG-g-La and PG-g-Gly corresponded to the degradation of the lactide or glycolide pendant groups by chain scission at the alkyl-oxygen bond in the first step followed by the degradation of the PG backbone in the second step. For the second step, the closeness of the degradation temperatures and similarity of the degradation products provide further evidence that this step is due to the PG backbone degradation.

The thermal degradation kinetics were analyzed by using an advanced isoconversional method. The results indicate that the PG degradation kinetics are likely
limited by a single reaction step. PG-g-La and PG-g-Gly degradation kinetics are limited by at least two reaction steps, the first being associated with the loss of the pendent lactide or glycolide groups while the second mass loss is due to the degradation of the PG backbone. Clearly, grafting pendant groups to the PG backbone yields polymers with lower thermal stability.
References


THERMAL PROPERTIES AND DEGRADATION BEHAVIOR OF LINEAR AND BRANCHED POLY(L-LACTIDE)S AND POLY(L-LACTIDE-CO-GLYCOLIDE)S

by

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Format adapted and errata corrected for dissertation
Abstract

Poly(lactide)s and poly(lactide-co-glycolide)s with different number of arms are synthesized from L-lactide and glycolide monomers using stannous (II) 2-ethylhexanoate and alcohols containing 1, 2, 25 and 51 hydroxyl groups. 1-dodecanol is used to produce the 1-arm polymer, poly(ethylene glycol) for the 2-arm polymer and polyglycidols of appropriate molecular weight are used to initiate the 25- and 51-arm branched polyesters. The polymers are characterized by $^1$H NMR and GPC. The thermal properties of the polymers are studied using DSC. Their degradation behavior is investigated using a combination of thermogravimetry, FTIR spectroscopy, and isoconversional kinetic analysis.

Keywords:

degradation; kinetics; thermogravimetric analysis (TGA); poly(lactide); poly(glycidol)

Introduction

Mechanical and thermal properties, degradation rates and products, and biocompatibility are properties to be considered when designing polymers for medical devices or as pharmaceutical excipients. Initiator, catalyst, monomer(s), additives, process conditions, molecular weight, and polymer architecture affect the biocompatibility, hydrophobicity, crystallinity, polydispersity, end groups, degradation products, rate of hydrolysis, thermal transition temperatures, and mechanical properties. If a polymer is used in a medical application, patients may be exposed to it for multiple treatments or long periods of time. Consequently, biocompatibility of not only the
polymer but polymer impurities and degradation products as well determine the suitability of a polymer for medical use.

Thermal degradation of polymers due to an increase in temperature may occur during processing and storage. Some medical devices and pharmaceutical formulations are processed using melt extrusion at high temperatures which necessitates thermal stability at the processing temperatures. Therefore, it is important to understand the thermal degradation of polymers used in these applications. One technique used to study the thermal degradation of polymers is thermogravimetric analysis (TGA). By using Fourier-transform infrared (FTIR) spectroscopy in conjunction with TGA, information regarding the volatile degradation products and some mechanistic insights may be obtained. Kinetic information on thermal degradation can also be extracted from TGA data. Subjecting TGA data to isoconversional kinetic analysis is a simple and efficient way of accomplishing this task.

Aliphatic polyesters such as poly(lactide) (PLA) and its copolymer with glycolide, poly(lactide-co-glycolide) (PLGA) have been widely used in medical applications such as sutures, implants, and drug delivery. However, high molecular weight PLA is required for some applications, for example, orthopedics, but, the high melt viscosity and poor thermal stability of PLA can result in degradation during processing. Additionally, when PLA or PLGA are used in drug delivery systems they often demonstrate polyphasic drug release, low encapsulation efficiencies of hydrophilic molecules, and poor protein stability. One common approach to overcome these problems is to incorporate hydrophilic blocks into the polyesters, which also introduces a branched or multi-arm structure. Inclusion of a hydrophilic block/core increases the hydrophilicity of the
polymer which should increase and enhance the stability of hydrophilic bioactive agents like proteins within the polymer matrix. The degradation by hydrolysis in branched polyesters should be faster than in linear polyesters since the degradation products will be soluble in water within a few cleavage steps. Multi-arm architectures typically have lower glass transition temperatures ($T_g$) and melt viscosities than linear polymers of similar molecular weight.$^{[10]}$

Several ways of synthesizing multi-arm PLAs with hydrophilic cores have been reported. Poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO) have been used to synthesize 2-arm polymers.$^{[11-13]}$ Star-shaped PLAs and PLGAs have been synthesized using low molecular weight multifunctional alcohols like glycerol,$^{[7, 14]}$ tetra(ethylene glycol),$^{[15]}$ 1,1,1-tri(hydroxyl methyl)propane,$^{[15]}$ pentaerythritol,$^{[15-17]}$ mannitol/sorbitol,$^{[18]}$ and star-shaped PEG/PEO.$^{[19, 20]}$ Poly(amidoamine) dendrimers have also been used to synthesize highly branched star-shaped PLA.$^{[21]}$ Comb PLAs and PLGAs have been synthesized using several different backbone materials such as depsipeptide-lactide,$^{[22, 23]}$ polysaccharide (dextran),$^{[24-26]}$ poly(vinyl alcohol),$^{[9, 13, 27-29]}$ and polyglycidol (PG)$^{[30]}$.

PEG and PG were chosen as the hydrophilic core materials for the branched polymers in this study. PEG is one of the most studied and widely used biocompatible polymers. PG is expected to have many of the same favorable properties as PEG due to the structural similarity. Preliminary in vitro and in vivo tests of PG showed that the biocompatibility of PG is as good as or better than that of PEG.$^{[31]}$ PG also has similar protein adsorption resistance when compared with PEG.$^{[31]}$ Additionally, since PG contains a pendant alcohol group in each repeat unit it has the functionality to have
polyester branches equal to the number of repeat units in the PG backbone. This functionality allows for the synthesis of highly branched polyesters.

The synthesis and thermal degradation of the model compounds poly(glycidol)-g-(L-lactide) (PG-g-La) and poly(glycidol)-g-glycolide (PG-g-Gly) were previously reported.\textsuperscript{[32]} It was reported that the polymers degraded by a two-step process, side-group elimination followed by backbone degradation.\textsuperscript{[32]} In an effort to better understand the effect on thermal properties and degradation of branched PLA and PLGA with hydrophilic polyol cores, the present study compares the thermal degradation of poly(L-lactide) (PLLA), PLGA, PEG-PLLA, PEG-PLGA, PG-PLLA, and PG-PLGA using the aforementioned techniques.

**Experimental Section**

**Materials**

Racemic glycidol (Aldrich), iodoethane (Alfa Aesar), ethyl vinyl ether (Acros), and 2-methoxyethanol (Acros) were purified by distillation. Cesium hydroxide monohydrate (Acros), \(p\)-toluenesulfonic acid monohydrate (Acros), sodium bicarbonate (Sigma), anhydrous magnesium sulfate (Fisher Scientific), toluene (Fisher Scientific), hydrochloric acid (Fisher Scientific), tin (II) 2-ethyl hexanoate (Sigma), PEG (\(M_w = 1500\) g·mol\(^{-1}\), Acros), 1-dodecanol (Acros) were purchased and used without further purification. L-Lactide (LLA) and glycolide (GA) were a gift from Lakeshore Biomaterials, Birmingham, AL and were used without further purification.
Synthesis of linear and branched polyesters

The synthesis of polylactones via ring-opening polymerization using stannous octoate as a catalyst is well known. It has also been reported that when alcohols are added to the reaction they react with tin(II) 2-ethylhexanoate (SnOct$_2$) forming a variety of Sn compounds such as Sn hydroxides, stannoxanes, and lactate complexes that contribute to initiating the polymerization.$^{[33]}$ Here, we report the synthesis of PLA and PLGA polymers with different number of arms using coinitiators containing 1, 2, 25, and 51 hydroxyl groups. Figure 1 shows the structures of the coinitiators. 1-Dodecanol was used to produce the 1-arm linear polymers and copolymers. PEG with $\bar{M}_w = 1500$ g mol$^{-1}$ was used to synthesize the 2-arm linear polymers and copolymers. PGs of appropriate molecular weight were used to produce the 25-arm and 51-arm branched polyesters.

Synthesis of the PG initiator has been reported previously.$^{[32]}$ Narrow molecular weight fractions of 1000-3000 g mol$^{-1}$ (25-arm) and 3000-5000 g mol$^{-1}$ (51-arm) were obtained by dissolving the PG product in water and filtering through molecular weight cut-off filters.

The reaction scheme for the synthesis of the linear and branched polyesters is shown in Scheme 1. The hydroxyl containing coinitiators were dried under vacuum at 80 °C for at least 24 h prior to addition of the monomer LLA or LLA and GA (molar ratio of 75:25, LLA:GA) to the reaction vessel containing the co-initiator then heated at 130 °C for 2 h to melt the reactants. SnOct$_2$ was added to the melt in a hood under dry nitrogen. The reaction mixture was heated at 130 °C for 24 h then cooled to room temperature.
1-dodecanol

Polyethylene glycol (PEG)

Polyglycidol (PG)
n=25 or 51

\[ n = \frac{M_{p,GPC}^{PG} - M_{PG \text{ endgroup}}}{M_G} \]

*Figure 1.* Structures of hydroxyl containing coinitiators.

*Scheme 1.* Synthesis of linear and branched poly(lactide) and poly(lactide-co-glycolide)
The polymers will be denoted PLLAx, PLGAx, PEG-PLLAx, PEG-PLGAx, PGy-PLLAx or PGy-PLGAx where x is the number average molecular weight of the polyester or polyester branch and y is the peak molecular weight of the polymeric cointiators in kg mol$^{-1}$.

**Analytical Methods**

**NMR Spectroscopy**

A Bruker DRX-400 spectrometer was used to obtain $^1$H NMR spectra at a frequency of 400 MHz. Samples of polyglycolide and poly(ethylene glycol) were dissolved in D$_2$O to prepare solutions of 5 mg mL$^{-1}$. Branched and linear PLLA or PLGA were dissolved in chloroform-d$_1$ (Acros Organics, deuteration degree $\geq$ 99.8%) at a concentration of approximately 10 mg mL$^{-1}$.

**GPC**

Molecular weight of the PEG and PG was determined by GPC. Samples were prepared at 1 mg mL$^{-1}$ in Nanopure water then injected onto a Waters instrument using Nanopure water as the mobile phase at a flow rate of 1 mL min$^{-1}$. Separation and detection of polymer species were accomplished using a Phenomenex® Polysep-GFC-P-2000 column and an Alltech ELSD-2000 evaporative light-scattering detector. PEG reference standards were used to generate the peak position calibration curve for molecular weight estimation of the samples.

Samples of the linear and branched polyesters were prepared in chloroform at 1 mg mL$^{-1}$ for analysis by GPC. Samples were injected into the chloroform mobile phase
(1 mL min$^{-1}$) using a Perkin Elmer instrument with two columns in series (Waters HR2 Styragel and Waters HR5E Styragel, respectively) and a Perkin Elmer Series 200a refractive index detector. The column oven and detector temperature were maintained at 40 °C. Narrow-fraction poly(styrene) reference standards were used to generate the peak position calibration curve for molecular weight estimation.

DSC

All calorimetric measurements were performed using a heat flux DSC (Mettler-Toledo, 823°). Indium and zinc standards were used to perform temperature, heat flow, and tau-lag calibrations. Samples were prepared by weighing approximately 10 mg into 40 µL aluminum pans. An empty aluminum pan was used as the reference. Thermal scans were performed using a heating rate of 10 °C min$^{-1}$ and a cooling rate of -50 °C min$^{-1}$ under a nitrogen purge at a flow rate of 80 mL min$^{-1}$. Samples were heated from 25 °C to 200 °C to erase the thermal history, then cooled to 0 °C and heated back to 200 °C. Cooling from 200 °C to 0 °C and heating from 0 °C to 200 °C was performed a total of two times prior to cooling the sample to -70 °C. A thermal scan from -70 °C to +625 °C was then performed to identify all thermal transitions in this temperature range.

Thermogravimetry

Thermal degradation kinetics were measured as temperature and time dependent mass loss using a Mettler-Toledo TGA/SDTA851°. Samples were prepared by weighing 6-8 mg samples into 40 µL aluminum pans and drying under vacuum for 48 h at 80 °C. Nonisothermal measurements of the samples were performed under a nitrogen purge at a
flow rate of 65-70 mL min\(^{-1}\) from 25 to 620 °C while heating at rates of 2.5, 5.0, 7.5, 10.0, and 12.5 °C min\(^{-1}\). The buoyancy effect in TGA was accounted for by performing a blank run of the empty pan and subtracting the empty pan results from the respective mass loss measurements for the polymer samples.

**FTIR Spectroscopy**

The gaseous products of nonoxidative thermal degradation were monitored using TGA coupled with FTIR spectroscopy (TGA-FTIR). TGA-FTIR analysis was performed on a Mettler-Toledo TGA/SDTA851\(^{\circ}\) module interfaced with a Nicolet Nexus 470 FTIR spectrometer. Samples were prepared by weighing 6-8 mg samples into 40 µL aluminum pans and drying under vacuum for 48 h at 80 °C prior to TGA-FTIR analysis. Before each TGA-FTIR run the system was purged with nitrogen for a minimum of 1 h. The dry samples were then run in the TGA under a nitrogen purge at a flow rate of 65-70 mL min\(^{-1}\) from 25 to 620 °C while heating at a rate of 10 °C min\(^{-1}\). Evolved gases flowed from the furnace of the TGA through a heated transfer line at 230 °C to the FTIR gas cell. FTIR spectra of the degradation products were taken at 4 cm\(^{-1}\) resolution. Each spectrum was an average of 32 scans.

**Isoconversional Kinetic Analysis**

The TGA data were subjected to isoconversional kinetic analysis\(^{[34]}\). This type of analysis was demonstrated\(^{[3]}\) to be an effective tool for learning about complex kinetics frequently encountered in thermally activated processes in polymeric systems. An advanced isoconversional method developed by Vyazovkin\(^{[35, 36]}\) was applied to the TGA
data to evaluate a dependence of the effective activation energy \( (E_\alpha) \) on the extent of conversion \( (\alpha) \). The latter value was estimated as a fractional mass loss. Compared with the most common integral isoconvensional methods\(^{[37]} \) the method has two key advantages. First, it is applicable to data obtained under arbitrary variation in temperature, \( T(t) \), which enables processing data obtained on cooling as well as accounting for self-heating/cooling assessable by the instrument. For \( n \) experiments conducted at different temperature programs, \( T_i(t) \), the effective activation energy is determined at any given \( \alpha \) by finding \( E_\alpha \), which minimizes the function\(^{[35, 36]} \)

\[
\Psi(E_\alpha) = \sum_{i=1}^{n} \sum_{j=1}^{\alpha} J[E_\alpha, T_i(t_\alpha)]
\]

where

\[
J[E_\alpha, T_i(t_\alpha)] = \int_{t_{\alpha-\Delta\alpha}}^{t_\alpha} \exp \left[ -\frac{E_\alpha}{RT_i(t)} \right] dt
\]

The second advantage arises from performing numerical integration over small time segments (Equation 2) that eliminates a systematic error\(^{[36]} \) found in the most common integral isoconvensional methods\(^{[37]} \) when \( E_\alpha \) depends strongly on \( \alpha \). In Equation 2, \( \alpha \) is varied from \( \Delta\alpha \) to 1-\( \Delta\alpha \) with a step \( \Delta\alpha = m^{-1} \), where \( m \) is the number of intervals selected for computation. The integral \( J \) in Equation 2 is determined by using the trapezoid rule. The procedure of minimization is repeated for each value of \( \alpha \) to evaluate the dependence \( E_\alpha \) on \( \alpha \).
Results and Discussion

Structure and Molecular Weight

The PEG and PG coinitiators were analyzed by $^1$H NMR and GPC to confirm the structure and molecular weight. The resonances from the CH$_2$ in the ethylene oxide repeat units of PEG are found at $\delta = 3.6$ ppm. In the $^1$H NMR spectra for PG, no signals of the ethoxyethyl protecting group are observed, indicating the full removal of the protecting group. The $^1$H resonances in PG are found at $\delta = 3.4$-3.7 ppm. The GPC curves for the PEG and both the PG initiators gave monodisperse molecular weight distributions. $\bar{M}_n$, $\bar{M}_w$, and $\bar{M}_w/\bar{M}_n$ for the polymeric coinitiators are found in Table 1.

$^1$H NMR and GPC were used to determine the structure and molecular weight of the linear and branched polyesters. The NMR spectra for PLLA, PLGA, PEG-PLLA, and PEG-PLGA corresponded well with the literature. Resonances were as follows. PLLA: $\delta = 1.5$ ppm (LA: CH$_3$), and 5.1-5.2 ppm (LA: CH). PLGA: $\delta = 1.5$ ppm (LA: CH$_3$), 4.5-4.9 ppm (GA: CH$_2$), and 5.1-5.3 ppm (LA: CH). PEG-PLLA: $\delta = 1.5$ ppm (LA: CH$_3$), 3.5-3.6 ppm (EO: CH$_2$), and 5.1-5.2 ppm (LA: CH). PEG-PLGA: $\delta = 1.5$ ppm (LA: CH$_3$), 3.5-3.6 ppm (EO: CH$_2$), 4.5-4.8 ppm (GA: CH$_2$), and 5.0-5.2 ppm (LA: CH). The structure of the branched polyesters was confirmed by the following signals in the $^1$H NMR: $\delta = 1.5$ ppm (LA: CH$_3$), 3.4-3.8 ppm (PG: CH, main chain CH$_2$, CH$_2$ unreacted side chain), 4.0-4.5 ppm (LA: terminal CH, PG: CH$_2$ reacted side chain), 4.6-4.9 ppm (GA: CH$_2$, if branch contains GA) and 5.1-5.4 ppm (LA: CH). The broadness and increase in intensity of the signal at $\delta = 4.0$-4.5 ppm indicates the introduction of the lactide/glycolide groups onto the PG backbone since there is an increase in number of
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a) Molar ratio from $^1$H NMR
b) Results rounded to the nearest hundred
c) Degree of substitution
d) Calculated using $(\bar{M}_{n,GPC} - \bar{M}_{p,GPC})/2$
e) Theoretical
end groups in the branched polymers. Figure 2 shows a representative NMR trace for PG-PLGA with the peak assignments.

GPC analysis yielded unimodal molecular weight distributions for the linear polymers but not the branched polymers. Figure 3 shows a representative GPC chromatogram for the branched polymer. The peak has a tail with additional modality. Residual monomer is not observed in the $^1$H NMR, therefore, the low molecular weight species are likely to be short chain polyesters initiated by water in the catalyst. Linear, low molecular weight species were approximated by determining the area percent of the tail. Linear species are approximated to be 14% in PG2-PLGA2 and 31% in PG4-PLLA2. Only the main peak was integrated so the reported GPC molecular weight data reflects only the peak not the tail. $^1$H NMR further confirms this hypothesis. By $^1$H NMR, the linear species are approximated to be 16% in PG2-PLGA2 and 36% in PG4-PLLA2. $\bar{M}_n$, $\bar{M}_{n,\text{arm}}$, degree of substitution (DS), and amount of linear species cannot be accurately calculated from the $^1$H NMR spectra for the 25 and 51-arm polymers due to the overlap of the PG signals for CH, main chain CH$_2$, and CH$_2$ unreacted side chain as well as the overlap of end groups for branched and linear polymer, however, an estimate may be calculated using the following equations:

$$I_{\text{end groups}} = I_{c,f} - I_c$$  \hspace{1cm} (3)

$$\text{DP} = \frac{I_e / 2 + I_d / 4 + I_{\text{end groups}}}{I_{\text{end groups}}}$$  \hspace{1cm} (4)

$$\text{LLA cont. / mol}\% = \frac{I_e / 2}{I_e / 2 + I_d / 4}$$  \hspace{1cm} (5)

$$\text{GA cont. / mol}\% = \frac{I_d / 4}{I_e / 2 + I_d / 4}$$  \hspace{1cm} (6)
\[ \bar{M}_{n,\text{arm}} = M_{\text{LLA}} \times (\text{LLA cont./ mol\%}) \times \text{DP} + M_{\text{GA}} \times (\text{GA cont./mol \%}) \times \text{DP} \]  

(7)

\[ R_{\text{end group}} = \frac{\text{End group}_{\text{branch}}}{\text{End group}_{\text{Total}}} = \frac{2I_c}{I_{c,f}} \]  

(8)

\[ I'_{\text{PG,reacted}} = \frac{I_{a,b}}{3R_{\text{end group}} + 5(1 - R_{\text{end group}})} \]  

(9)

\[
\text{DS} = \frac{I_c'}{I_{\text{PG,reacted}}}
\]  

(10)

\[
N_{\text{arm}} = \frac{M_{\text{PG}}^{\text{GPC}} - M_{\text{PG end group}}}{M_{G}}
\]  

(11)

\[
\bar{M}_{n,\text{NMR}} = \bar{M}_{\text{PG}}^{\text{GPC}} + \bar{M}_{n,\text{arm}} \times \text{DS} \times N_{\text{arm}}
\]  

(12)

where \( M_{\text{LLA}} = 144 \text{ g mol}^{-1} \), \( M_{\text{GA}} = 116 \text{ g mol}^{-1} \), \( M_{\text{PG end group}} = 75 \text{ g mol}^{-1} \), and \( M_{G} = 74 \text{ g mol}^{-1} \). It is assumed the end groups are all lactide units since glycolide is more reactive. This may also explain the difference in DS between PG4-PLLA2 (DS = 96%) and PG2-PLGA2 (DS = 103%). If GA were to react with the PG prior to LLA then there would be less steric hindrance at the hydroxyl groups on the PG to react allowing for substitution/polymerization at each glycidol repeat unit.

**DSC**

Thermal transitions in the synthesized polymers were identified using DSC. Samples were heated from 25 to 200 °C (first scan) to erase the thermal history. Cooling to 0 °C occurred at 50 °C min\(^{-1}\). Heating from 0 to 200 °C was then performed twice (second and third scans) prior to scanning from -70 to +625 °C (forth scan). Table 2 summarizes the thermal properties of the synthesized polymers determined by DSC including, \( T_g \), peak melting temperature (\( T_{p,m} \)), peak crystallization temperature (\( T_{p,c} \)),...
Figure 2. $^1$H-NMR spectrum of PG2-PLGA4
Figure 3. GPC trace of PG4-PLLA2 and PG2-PLGA2
<table>
<thead>
<tr>
<th>Polymer</th>
<th>$T_g$ [$^\circ$C]</th>
<th>$T_{p,c}$ [$^\circ$C]</th>
<th>$\Delta H_c$ [J g$^{-1}$]</th>
<th>$T_{p,m}$ [$^\circ$C]</th>
<th>$\Delta H_m$ [J g$^{-1}$]</th>
<th>$X_c$ [%]</th>
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<tr>
<td>PLLA35</td>
<td>53</td>
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<tr>
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<td>172</td>
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<tr>
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<td>40</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
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thermal effects of crystallization ($\Delta H_c$), and melting ($\Delta H_m$). The reported $T_g$s are an average of the measurements taken during the second, third and forth scans. $T_{p,m}$, $\Delta H_m$ and $X_c$ are reported for the first and second scan. Crystallinity of the polymers was estimated using the following equation:

$$X_c = \frac{\Delta H_m}{\Delta H_m^0} \cdot 100$$

(13)

where $\Delta H_m$ is the measured melting enthalpy and $\Delta H_m^0 = 106$ J g$^{-1}$ is the literature value for the melting enthalpy of the 100% crystalline PLLA homopolymer.$^{[38]}$

Any structural feature that decreases chain mobility increases the $T_g$ of the polymer, and, conversely, an increase in chain mobility results in a reduction of $T_g$. Chain mobility is affected by the polymer composition, size and flexibility of substituents, crystallinity, cross-linking, inter- and intramolecular forces, and molecular weight. Additionally, $T_g$ in branched polymers has been shown to be affected by the chemical properties of end groups, branching junctions, and end group free volume.$^{[39]}$

The $T_g$s of the polymers in this study followed the order of PLLA35 > PEG-PLLA7 > PEG-PLGA6 ≈ PLGA20 > PG4-PLLA2 > PLGA12 > PG2-PLGA2. The polymers in this study can be compared on the basis of linearity, crystallinity, and composition.

The PLLA35 was expected to have the highest $T_g$ since the crystalline regions in the polymer would reduce the segmental motion in the amorphous regions thereby increasing $T_g$. Molecular weight also plays a role since $T_g$ initially increases with molecular weight due to chain entanglement then levels off so changes in $T_g$ are minimal above a particular molecular weight. Random copolymerization of lactide with glycolide disrupts the regular and symmetrical geometry of the homopolymer forming an amorphous polymer. In addition, poly(glycolide) is known to have markedly lower $T_g$
than poly(lactide).\textsuperscript{[40]} Thus, the order PLLA35 > PLGA20 > PLGA12 for $T_g$s of the linear aliphatic polyesters in this study is anticipated.

The PEG initiated polyesters may also be considered 2-arm branched polymers along with the PG initiated multi-arm branched polymers. $T_g$s for the branched polymers were in the following order: PEG-PLLA7 > PEG-PLGA6 > PG4-PLLA2 > PG2-PLGA2. Li \textit{et al.}\textsuperscript{[41]} demonstrated that long PLLA blocks in PEG-PLLA block copolymers crystallize in the presence of short PEG blocks. It follows that PEG-PLLA7 has a higher $T_g$ than PEG-PLGA6 because of the crystalline regions in PEG-PLLA7.

PEG-PLLA7 was observed to have a higher $T_g$ than PG4-PLLA2. The difference is due to the increase in free volume from the large increase in end groups and loss of crystallinity. This indicates that the number of end groups impacts the $T_g$ more than molecular weight, structure compactness, and restricted mobility due to the branch points. PG2-PLGA2 has the lowest $T_g$ of the branched polymers. PG4-PLLA2 has a moderately higher $T_g$ due to a combination of higher total molecular weight and higher PLLA composition in the arms.

It is interesting to note that the $T_g$ of PEG-PLGA6 is the same as PLGA20 and the $T_g$ of PEG-PLLA7 is higher than PLGA20. The observation that $T_g$ for the PEG-PLGA6 is the same as the $T_g$ for the higher molecular weight statistical copolymer PLGA20 is best explained by the polydispersities of PLGA20 and PEG-PLGA6. Polydispersities for PLGA20 and PEG-PLGA6 are 3 and 1.9 respectively, therefore, the increased number of shorter chains in the PLGA20 may have caused the $T_g$ to be lower. The $T_g$ of block
copolymer PEG-PLLA7 is 6 °C higher than PLGA20, a copolymer with approximately double the weight average molecular weight. This is explained both in terms of polydispersity and crystallinity. The polydispersity for PEG-PLLA7 is 1.9 compared to 3 for PLGA20, therefore, the shorter chains in PLGA20 will lower the $T_g$. Also, the crystallinity in the PEG-PLLA7 polymer chain has a much larger effect on $T_g$ than molecular weight.

$T_{p,m}$ of the semi-crystalline polymers in this study decreases in the order of PLLA35 > PEG-PLLA7 > PG4-PLLA2. Selected DSC traces are shown in Figure 4 and 5 for the first and second scans, respectively. Melting temperature is affected by the crystallinity of the polymer. When the polymer structure is regular and symmetrical the chains pack together and crystallize. Chain ends either produce lattice imperfections in crystallities or are not incorporated into the crystalline regions resulting in a lower $T_{p,m}$ for branched polymers (equivalent to a polymer containing significant portions of low molecular weight species). It should then be expected that the linear homopolymer PLLA have the highest $T_{p,m}$ due to the regular, symmetric chains uninterrupted with another polymer block. PEG-PLLA7 can be anticipated to have a higher $T_{p,m}$ than the highly branched PG4-PLLA2 due to its longer PLLA segments (PLLA segments of $\approx$7,300 vs. $\approx$1600 g mol$^{-1}$) and fewer end groups (2 vs. 51). The effect of heating and cooling the semi-crystalline polymers is seen in Figure 4 and 5. The only thermal transition observed for PLLA35 and PEG-PLLA7 during the first scan was a single melting endotherm, no $T_g$ was observed. A $T_g$, cold crystallization exotherm, and melting endotherm were observed in the second, third, and forth scans for PLLA35 and PEG-
Figure 4. First scan DSC curves for linear and branched PLLA heated at 10°C min⁻¹
Figure 5. Second scan DSC curves for linear and branched PLLA heated at 10°C min⁻¹.
PLLA7. Also, the melting peak split into two peaks in the second, third, and forth scans for PEG-PLLA7. The splitting of the melting peak may indicate different crystallite morphologies and sizes being formed upon heating. It is of note that the temperature used for polymerization is below $T_{p,m}$ and above $T_g$ where nuclei are stable allowing for crystal growth. Thus, the PLLA segments in PEG-PLLA7 would have had time to arrange themselves into low energy structures during polymerization, which could account for the unimodal endothermic melting peak in the first scan. The rapid cooling after the first DSC scan quenched the polymer into a semi-crystalline state then the PLLA segments continued to crystallize during heating resulting in cold crystallization. Weak endotherms have been observed at temperatures lower than 150 °C in linear PLLA with molecular weights less than 3000 g mol$^{-1}$. In highly branched polymers with PLLA branches having a molecular weight of 3000 g mol$^{-1}$, no melting transition was observed.$^{[21]}$ However, in this study, a $T_g$ and bimodal melting endotherm for the highly branched PG4-PLLA2 were observed in the first scan (Figure 4) indicating some regions of the polymer crystallized during polymerization. A melting transition was not observed during the second scan (Figure 5) consistent with reduced chain movement due to steric hindrance weakening the crystallizability of the highly branched polymer when quenched.

**Thermogravimetry with FTIR Spectroscopy**

Nonoxidative thermal stability and degradation products as a function of temperature were studied for each of the polymers using the combination method of
TGA-FTIR. Analysis of evolved degradation products from the pyrolysis of PEG, PG, and PLLA using TGA-FTIR has been reported previously.\cite{32,42-47}

Mass loss for the PEG coinitiator used in this study occurs in a single step with $T_{\text{max}} = 400 \, \degree C$. The main thermal decomposition products of PEG have been identified as alcohols, alkenes, cyclic, and non-cyclic ethers, formaldehyde, acetic aldehyde, oligomers with aldehydic ends, ethylene oxide, water, carbon monoxide (CO) and carbon dioxide (CO$_2$).\cite{43-46}

The thermal degradation of PG2 and PG4 occurs as a single mass loss step starting somewhere above 250 °C with $T_{\text{max}}$ at 383 and 384 °C, respectively. Thermal degradation of PG yields similar degradation products to PEG.\cite{32} The main degradation product signals of PG based on the TGA-FTIR analysis were identified\cite{32} as follows: sym. ring deformation (epoxy rings), CH$_2$ rocking at 850 cm$^{-1}$, asym. ring deformation (epoxy rings), CH$_3$ rocking at 930 cm$^{-1}$, ring breathing, C-O stretching in primary alcohol at 1060 cm$^{-1}$, C-O-C asym. stretching at 1110 cm$^{-1}$, CH$_2$ twisting, CH$_2$ wagging, ring breathing, O-H bending in epoxy rings and alcohols at 1270 cm$^{-1}$, CH$_2$ wagging at 1370 cm$^{-1}$, C═O stretch at 1720 (ketone) and 1800 cm$^{-1}$ (aldehyde), CO at 2110 and 2180 cm$^{-1}$, CO$_2$ at 2320 and 2360 cm$^{-1}$, C-H stretching in acyclic ethers and aldehydes at 2850 cm$^{-1}$, C-H stretching in epoxy rings at 2950 cm$^{-1}$, C-H stretching at 2600-3100 cm$^{-1}$, and H$_2$O at 3583 cm$^{-1}$. By comparing the time-resolved IR spectra, the first degradation products are alcohols, ethers, and epoxides followed by aldehydes, ketones, and CO, the last product to evolve is CO$_2$.

In previous thermal degradation studies of poly(lactic acid) (PLA) the degradation appeared to be a single step process with $T_{\text{max}} = 351$-374 °C. CO, CO$_2$, oligomers,
lactide, and acetaldehyde were observed as the primary degradation products.\cite{48, 49} Nonradical and radical reaction pathways have been proposed.\cite{48, 49} The nonradical, backbiting ester exchange was proposed as the main decomposition pathway.\cite{48, 49} It has been shown that residual Sn catalyst has a significant effect on thermal degradation of PLLA at temperatures as low as 160 °C.\cite{8} Sn atoms are assumed to be bound to the alkoxide groups at chain ends at the end of polymerization. The Sn-alkoxide then catalyzes the depolymeration reaction where an alkoxide anion attacks the carbonyl carbon of the penultimate lactate unit and a lactide is eliminated (Scheme 2). As this repeatedly occurs, the result is an unzipping depolymerization.\cite{8, 50, 51}

Poly(glycolide) (PGA) degradation has been reported as a single step process starting at approximately 200 °C with $T_{\text{max}} \approx 360$ °C.\cite{52} The primary pyrolysis products of PGA have been identified as CO, CO$_2$, formaldehyde, glycolide, and cyclic oligomers.\cite{52} CO and formaldehyde were observed at higher temperatures, thus, it was concluded that they were products of chain scission.\cite{52} CO$_2$ at lower temperatures was a result of terminal carboxyl group decarboxylation while increased CO$_2$ at higher temperatures indicates chain scission. Glycolide and cyclic oligomer formations follow the same ester exchange mechanism degradation pathway as PLA.\cite{52} PLGA, the random copolymer of lactide and glycolide is expected to undergo thermal degradation by the same pathway as PLLA and PGA with thermal properties intermediate to those of PLLA and PGA.

Figure 6 shows typical TGA and DTG data for the thermal degradation of PLLA and PLGA. As seen in Figure 6, the linear polymers degrade in single mass loss step
Scheme 2. Sn catalyzed unzipping depolymerization of linear and branched poly(lactide) and poly(lactide-co-glycolide).\textsuperscript{[50,51]}

\[ R = \text{CH}_3, \text{L-lactide (LLA)} \]
\[ R = \text{H, glycolide (GA)} \]
Figure 6. Mass loss and derivative mass curves for 1-arm polymers heated at 10°C min⁻¹. The numbers denoted by arrows represent the temperatures of the maximum mass loss rate, $T_{\text{max}}$. 
with mass loss starting somewhere above 150 °C. Mass loss rate reaches a maximum at 265, 277, and 263 °C for PLGA12, PLGA20, and PLLA35, respectively. These results are in good agreement with the results achieved by Jamshidi et al. \cite{8} for Sn containing PLLA. The FTIR spectra of the evolved degradation products at multiple temperatures for PLGA20 and PLLA35 are shown in Figure 7. Time-resolved FTIR spectra for PLLA35 are representative of those observed for PLGA12. At $T_{max}$ for PLLA and PLGA, the FTIR absorption bands have been identified as follows: ring skeletal vibration at 830 cm$^{-1}$, CH$_3$ rocking at 930 cm$^{-1}$, C-O stretch, O-C-C stretching at 1060 cm$^{-1}$, C-C-O stretch at 1100 cm$^{-1}$, CH$_2$ twisting, CH$_2$ wagging, C-C-O stretch, C-O stretch at 1240 cm$^{-1}$, C-H bending in CH$_3$ groups at 1360 cm$^{-1}$, C═O stretch at 1790 cm$^{-1}$, C-H stretching in CH$_2$ groups at 2850-3050 cm$^{-1}$, C-H stretching in CH$_3$ groups at 3000 cm$^{-1}$. The presence of lactide/glycolide and cyclic oligomers are indicated by C-O stretching at 1060, 1100, and 1240 cm$^{-1}$, C═O stretching at 1790 cm$^{-1}$, CH$_2$ stretching and bending at 2990 and 1360 cm$^{-1}$, and a ring skeletal vibration at 830 cm$^{-1}$. Resonances from lactide/glycolide are observed in the FTIR spectra somewhere above 200 °C. No CO$_2$ was observed at low temperatures for either PLLA or PLGA indicating that decarboxylation of terminal carboxyl groups did not occur as it does in PGA. This was expected since the end groups for the polymers in this study should be hydroxyl groups. CO$_2$ was not observed as a positive absorbance, however, the negative absorbance at 2320 and 2360 cm$^{-1}$ became less negative near $T_{max}$ indicating CO$_2$ as a degradation product. The presence of CO$_2$ is considered an indicator for the radical degradation pathway and is typically not observed until elevated temperatures are reached.\cite{[48], [49]} No additional signals are observed, only the intensities of the aforementioned signals change. This confirms the result that the Sn
Figure 7. FTIR of gas phase degradation products at multiple temperatures for a) PLGA20 and b) PLLA35.
catalyzed depolymerization is the primary degradation route for PLLA and establishes that this is the primary route for PLGA as well.

PEG-PLLA7 and PEG-PLGA6 also start losing mass above 150 °C and degrade in two steps (Figure 8). Previous studies of PEG containing tri-block polymers have been reported. Drumond et al. observed a two-stage degradation process for two series of PEG-PLLA tri-block polymers initiated with a PEG diol ($\overline{M}_n = 600$ or $4000$ g mol$^{-1}$). The first stage was attributed to the “unzipping” of the PLLA segment and the second stage was attributed to the thermal chain scission of PEG. The mass loss in the PEG 4000 series corresponded to the weight percent of each segment but was not observed for the PEG 600 series. Our results using a PEG ($\overline{M}_w = 1500$ g mol$^{-1}$) are in agreement with the observations by Drumond et al. The maximum rate of mass loss in the first step for PEG-PLLA7 is $T_{\text{max},1} = 265$ °C and $T_{\text{max},1} = 276$ °C for PEG-PLGA6. These degradation temperatures for PEG-PLLA7 and PEG-PLGA6 are in good agreement with the 1-arm PLLA and PLGA described above. The FTIR spectra of the evolved degradation products of PEG-PLGA6 and PEG-PLLA7 are shown in Figure 9. Degradation products at $T_{\text{max},1}$ are similar to those observed for PLLA and PLGA allowing one to associate the first step with the degradation of the polyester arms. A maximum for the second step is not observed but rather appears as a change in the slope. It is seen in the TGA data for PEG-PLLA7 that approximately 2% mass loss occurs between 275 and 380 °C (See Figure 8 inset). This is also observed in the TGA curve for PEG-PLGA6 between 290 and 390 °C. Because this mass loss occurs in the same temperature range as PEG degradation and the mass loss equates to the PEG mass percent
Figure 8. Mass loss and derivative mass curves for 2-arm polymers heated at 10°C min\(^{-1}\). The numbers denoted by arrows represent the temperatures of the maximum mass loss rate, \(T_{\text{max}}\).
Figure 9. FTIR of gas phase degradation products at multiple temperatures for a) PEG-PLLA7 and b) PEG-PLGA6.
of the polymer composition, it may be attributed to the thermal degradation of the PEG coinitiator.

Previously, we reported the thermal degradation of the model compounds PG-g-La and PG-g-Gly, which degraded by a two-step process corresponding to a side-group elimination followed by degradation of the polymer backbone. In the previous studies, the backbone was PG2 and comprised approximately 50 wt. % of the polymer composition. \( T_{\text{max},1} \) was found to equal 268 °C (PG-g-La) and 267 °C (PG-g-Gly) with \( T_{\text{max},2} = 328 \) °C (PG-g-La) and \( T_{\text{max},2} = 347 \) °C (PG-g-Gly). It is anticipated that the polymers in the current study with PG backbones have similar thermal degradation processes.

PG2-PLGA2 starts losing mass above 150 °C while PG4-PLLA2 starts losing mass above 130 °C and both polymers with the PG backbone degrade in two steps (Figure 10). Although the two-stage degradation is noticeable upon inspection of the mass loss curve, the second stage is better seen in the DTG curve. DTG data are known to be more sensitive to the number of processes, reactions or physical phenomenon occurring. The maximum rate of the mass loss in the first step is found at \( T_{\text{max},1} = 264 \) °C (PG2-PLGA2) and 268 °C (PG4-PLLA2). \( T_{\text{max},1} \) values for PG2-PLGA2 and PG4-PLLA2 are similar to those found for the 1-arm PLLA and PLGA. The FTIR spectra of the evolved degradation products of PG2-PLGA2 and PG4-PLLA2 are shown in Figure 11. Degradation products at \( T_{\text{max},1} \) for PG2-PLGA2 and PG4-PLLA2 match those of PLLA and PLGA at \( T_{\text{max}} \) thus the first degradation step may be attributed to the degradation of the polyester arms. For the second mass loss, the rate maxima are found at \( T_{\text{max},2} = 325 \) °C (PG2-PLGA2) and 332 °C (PG4-PLLA2). The second mass loss step
Figure 10. Mass loss and derivative mass curves for 25- and 51-arm polymers heated at 10°C min⁻¹. The numbers denoted by arrows represent the temperatures of the maximum mass loss rate, $T_{\text{max}}$. 
Figure 11. FTIR of gas phase degradation products at multiple temperatures for a) PG4-PLLA2 and b) PG2-PLGA2.
in the multi-arm polymers occurs in the temperature range of PG degradation and accounts for approximately 5% mass loss. The rate maxima for PG2-PLGA2 and PG4-PLLA2 at a lower temperature than for PG were observed for the model compounds PG-g-La and PG-g-Gly studied previously and is a well-known effect of the thermal destabilization of polyethers due to branching.\(^{[32, 54]}\) It is also of note that PEG, PLLA, PLGA, PEG-PLLA, PEG-PLGA leave very little if any char while PG2, PG4, PG2-PLGA2, and PG4-PLLA2 degradations leave approximately 5% residue. Thus, the char is clearly associated with the PG.

Of particular interest is the similarity of the \(T_{\text{max}}\) for the degradation of the linear and branched PLLA and PLGA. Neither the ratio of lactide, glycolide, coinitiator, nor the number or lengths of branches, have a significant impact on the degradation temperature of the polymers. This provides further evidence that Sn-catalyzed depolymerization is the main thermal degradation pathway for polylactones synthesized using Sn catalysts.

**Isoconversional Kinetic Analysis**

The application of an advanced isoconversional method to the TGA resulted in obtaining the dependencies of the effective activation energy on conversion that are shown in Figure 12, 13, and 14. The polymers studied demonstrate remarkable similarities in the respective \(E_\alpha\) dependencies. In all cases, the effective activation energies at the early degradation stages (\(\alpha < 0.1\)) are around 80 – 100 kJ mol\(^{-1}\). There also appears to be a trend for \(E_\alpha\) to decrease with the progress of degradation. For all three 1-arm (linear) polymers (Figure 12), the initial value of \(E_\alpha\) is about 95 kJ mol\(^{-1}\) that
Figure 12. $E_\alpha$ dependencies for degradation of 1-arm polymers.
Figure 13. $E_\alpha$ dependencies for degradation of 2-arm polymers.
Figure 14. $E_\alpha$ dependencies for degradation of 25 (PG2-PLGA2) and 51 (PG4-PLLA2) - arm polymers.
indicates that the respective degradation processes are likely to have similar initiation steps. For PLLA35 and PLGA12, the $E_\alpha$ values rise to 120 kJ mol$^{-1}$. The activation energies for degradation of PLLA35 are smaller than the values reported for degradation of regular PLLA: a constant value of 120$^{[49]}$ and values increasing with $\alpha$ from 160 to 190$^{[47]}$ or from 120 to 170$^{[55]}$ kJ mol$^{-1}$. The difference is not necessarily significant considering that the confidence intervals for $E_\alpha$ are typically in the range 10 – 20 %. There do not seem be any literature reports on the effective activation energies for the thermal degradation of PLGA. Bearing in mind that the activation energy of degradation for PGA was reported$^{[52]}$ to be ≈ 90 kJ mol$^{-1}$, one may expect the $E_\alpha$ values for PLGA to be somewhat lower than those for PLLA. This assumption would be consistent with the $E_\alpha$ values found for PLGA20 that continuously decrease from 100 to 60 kJ mol$^{-1}$ remaining below the $E_\alpha$ values for PLLA35. However, the $E_\alpha$ values found for PLGA12 tend to be larger than those for PLLA35 in the range $\alpha > 0.3$. Although the difference in the $E_\alpha$ values for PLLA35 and for the individual PLGA polymers is comparable to the relatively big confidence intervals, the larger difference between PLGA12 and PLGA20 is unexpected and difficult to rationalize. Note that performing the isoconversional computations on different data sets for PLGA12 and PLGA20 did not affect the observed difference in the $E_\alpha$ values so that it must be associated with the nature of the polymers rather than with an experimental issue.

The two 2-arm polymers, PEG-PLLA7 and PEG-PLGA6, demonstrate practically identical $E_\alpha$ dependencies that decrease moderately from 105 to 70 kJ mol$^{-1}$ (Figure 13). Apparently the degradation pathways of these polymers are quite similar. The behavior is also rather similar to that observed for 1-arm PLGA20 and PLLA35, which is not
surprising considering that degradation of PEG-PLGA6 and PEG-PLLA7 is primarily due to degradation of PLGA and PLLA, respectively. The fact that the difference in the $E_\alpha$ dependencies of PEG-PLGA6 and PEG-PLLA7 is so small is likely due to the very small difference in the molecular weights of PLGA6 and PLLA7.

The $E_\alpha$ dependencies found for 25- and 51-arm polymers also do not show any significant difference within the respective confidence intervals (Figure 14). The activation energies for the initial stages of degradation are in the vicinity of 90 kJ·mol$^{-1}$ but rise slightly reaching $\approx 110$ kJ·mol$^{-1}$ at around $\alpha = 0.2$. The increase is followed by a gradual decrease down to approximately 60 kJ·mol$^{-1}$. Clearly, the $E_\alpha$ dependencies follow the same pattern as other PLLA and PLGA copolymers (Figure 12 and 13). This again indicates that degradation kinetics of these copolymers are limited by the degradation rates of the PLLA or PLGA arms.

**Conclusion**

Branched and linear PLAs and PLGAs were synthesized using coinitiators with varying numbers of hydroxyl groups. It was determined that the highly branched polymers with PG backbones could be produced with a high DS at the branch points on PG. Having some amount of glycolide in the side chain may allow for better substitution but more work is needed to evaluate this. As expected, branching lowers the $T_g$ of the polymers. However, branching does not appear to affect the degradation temperature of these polyesters when synthesized using a Sn catalyst. The depolymerization reaction catalyzed by Sn is the main thermal degradation pathway. Thermal degradation of PEG- and PG-initiated polymers occurred in two steps with mass loss of the polyester occurring
in the first step and polyether degradation in the second step. Polyester degradation was confirmed both by degradation temperature similarity and by FTIR. Polyether degradation was identified by the inflection points on the mass loss curve and by the amount of mass loss after the inflection point.

An advanced isoconversional method was used to analyze the thermal degradation kinetics. The results indicate similarities in the $E_\alpha$ dependencies. Initial $E_\alpha$ values for all the polymers are approximately 80-100 kJ mol$^{-1}$, indicating that the initial degradation steps are similar, and $E_\alpha$ trends downward as the degradation proceeds. The $E_\alpha$ dependencies for the branched polymers follow the same pattern as linear PLLA and PLGA. These observations indicate that the degradation kinetics of linear and branched PLLA and PLGA are not dependent on polymer architecture. This is in agreement with the suggestion that Sn-catalyzed depolymerization is the main thermal degradation pathway for linear and branched polylactones synthesized using Sn catalysts.

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References


DYNAMIC MECHANICAL ANALYSIS AND HYDROLYTIC DEGRADATION BEHAVIOR OF LINEAR AND BRANCHED POLY(L-LACTIDE)S AND POLY(L-LACTIDE-CO-GLYCOLIDE)S

by

JEFFREY L. ATKINSON AND SERGEY VYAZOVKIN

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Format adapted for dissertation
Abstract

Linear and branched poly(lactide)s and poly(lactide-co-glycolide)s are synthesized using stannous (II) 2-ethylhexanoate and alcoholic coinitiators resulting in polymers with 1, 2, 25 or 51 arms. 1-dodecanol is used to produce the 1-arm polymer, poly(ethylene glycol) is used for the 2-arm polymers and poly(glycidol)s of appropriate molecular weight are used to initiate the 25- and 51-arm branched polyesters. The polymers are evaluated by melt rheology and dynamic mechanical analysis (DMA). In vitro degradation is investigated in phosphate buffer pH 7.4 at 37 °C for 28 days for moisture uptake and mass loss. Degraded samples are analyzed by gravimetry, differential scanning calorimetry (DSC), dilute solution viscometry (Cannon-Fenske), and gel permeation chromatography (GPC).

Introduction

Polylactide (PLA) and its copolymers with glycolide, poly(lactide-co-glycolide) (PLGA) have been used in several medical applications such as sutures, implants, and drug delivery due to their wide range of physical properties and degradation rates.[1] Despite the good properties and successes, PLA and PLGA are known to have high melt viscosity and poor thermal stability resulting in degradation during processing,[2, 3] as well as low encapsulation efficiencies of hydrophilic molecules, a negative effect on protein stability and polyphasic release profiles when used in drug delivery systems (DDS). Low encapsulation efficiencies of hydrophilic drugs are due to the hydrophobicity of PLA and PLGA.[4] Protein instability in a PLA or PLGA DDS is
primarily a result of degradation. Hydrolysis of PLGA leads to an accumulation of lactic and glycolic acid within the drug delivery device resulting in a low pH microenvironment causing denaturation of encapsulated proteins.\textsuperscript{[4]}

When designing a polymer to overcome these shortcomings it is important to consider the factors affecting the thermo-mechanical properties and degradation rate. These factors are: polymer composition (monomer selection), molecular weight, initiator type, process conditions, and presence of additives. Hydrophilicity/water uptake, crystallinity, melt and glass-transition temperatures, molecular-weight distribution (polydispersity), end groups, sequence distribution (random versus block), and presence of residual monomer or additives in the polymer are controlled by the factors listed above.\textsuperscript{[5]}

One of the most common approaches for improving the properties of PLA or PLGA is to incorporate a hydrophilic core or block. Generally, a polyol is used as the macroinitiator for the synthesis of PLA and PLGA, thus the polyol becomes the polymer backbone with PLA or PLGA arms. Use of hydrophilic cores has been shown to affect the degradation rate of the PLA and PLGA polymers. Lower glass transition temperatures ($T_g$) and melt viscosities are observed for multi-arm polymers than for linear polymers of similar molecular weight which may enable processing at lower temperatures.\textsuperscript{[6]} Also, stability of proteins in the polymer matrix should be enhanced with the increased hydrophilicity of the polymer matrix.

By manipulating the type and amount of backbone material the properties of the branched polymer can be tuned. Examples of this are PLAs and PLGAs synthesized
using poly(ethylene glycol)\textsuperscript{[7]} (PEG), poly(ethylene oxide) \textsuperscript{[8]} (PEO), glycerol,\textsuperscript{[2, 9]} tetra(ethylene glycol),\textsuperscript{[10]} 1,1,1-tri(hydroxyl methyl)propane,\textsuperscript{[10]} pentaerythritol,\textsuperscript{[10-12]} mannitol/sorbitol,\textsuperscript{[13]} star-shaped PEG/PEO,\textsuperscript{[13, 14]} poly(amideamine),\textsuperscript{[15]} depsipeptide-lactide,\textsuperscript{[16, 17]} polysaccharide (dextran),\textsuperscript{[18-20]} poly(vinyl alcohol),\textsuperscript{[4, 21-24]} and poly(glycidol)\textsuperscript{[18]} (PG) as macroinitiators. For each of the different backbone materials it was shown that $T_g$, $T_m$, crystallinity and degradation rate of the branched polymers could be controlled by making changes to the molecular architecture such as varying the molecular weight of the main chain or branches and degree of branching.\textsuperscript{[16-18, 21, 25]} It has been shown that the properties of the polyol used in the backbone strongly influence the degradation mechanism so it is adjustable from random to nonrandom hydrolysis (preferential hydrolysis at preformed break-points such as branch points) of the polyester chains.\textsuperscript{[23]}

The synthesis, thermal properties, and thermal degradation of polylactide and poly(lactide-co-glycolide) polymers with different number of arms using coinitiators containing hydroxyl groups of 1, 2, 25 and 51 was previously reported.\textsuperscript{[26]} 1-Dodecanol was used to produce the 1-arm linear polymers and copolymers. PEG with $M_w=1500$ g mol$^{-1}$ was used to synthesize the 2-arm linear polymers and copolymers. PGs of appropriate molecular weight were used to produce the 25- and 51-arm branched polyesters. PEG and PG were chosen as the hydrophilic core materials for the branched polymers in this study due to their biocompatibility, structural similarity, and protein adsorption resistance.\textsuperscript{[27]} Here we report the dynamic mechanical and hydrolytic degradation properties of the previously described PLLA, PLGA, PEG-PLLA, PEG-
PLGA, PG-PLLA and PG-PLGA polymers in an effort to understand the effects of molecular architecture on these properties.

**Experimental Section**

**Synthesis of Linear and Branched Polyesters**

We previously reported\textsuperscript{[26]} the synthesis of PLLA and PLGA polymers with different number of arms via ring-opening polymerization using stannous octoate with cointiators containing hydroxyl groups of 1, 2, 25, and 51. Linear (single arm) polymers PLLA35, PLGA12, and PLGA20 were initiated using 1-dodecanol. PEG with $\bar{M}_w = 1500$ g mol\textsuperscript{-1} was used to synthesize the 2-arm linear polymers and copolymers. PGs of appropriate molecular weight were used to produce the 25- and 51-arm branched polyesters. The polymers were previously designated using the following abbreviations: PLLA35, PLGA20, PLGA12, PEG-PLLA7, PEG-PLGA6, PG4-PLLA2, and PG2-PLGA2. Numbers following the abbreviation of the polyester represent the number average molecular weight of the polyester or polyester branch while the numbers following the PG designation represent the peak molecular weight of the PG in kg mol\textsuperscript{-1} previously reported\textsuperscript{[26]}

**Dynamic Mechanical Analysis**

Polymer bars were prepared by heating the amorphous polymers (PLGA12, PLGA20, PEG-PLGA6, and PG2-PLGA2) to 75-85 °C and pressing into sheets with a thickness of 1.0 to 1.6 mm. The slabs were then cut into strips 6-8 mm wide. Semi-
crystalline polymers (PLLA35, PEG-PLLA7, and PG4-PLLA2) were heated above the melting temperature, cooled by 10-20 °C, pressed into a sheet 1.0 to 1.5 mm thick, cut into strips 6-8 mm wide, then cooled to room temperature. Dynamic mechanical testing was performed using a Triton Technology Tritec 2000 DMA. Calibration was performed using the built in calibration programs for spring stiffness and damping, force factor, and balance/zero. Experiments were run in tension mode at a frequency and displacement of 1 Hz and 10 microns, respectively. Samples were run in duplicate, reported results are an average of the duplicate runs. PLLA samples were loaded at room temperature, heated to 60 °C, clamped, and cooled below 0 °C with liquid nitrogen. Testing was carried out from 0 to 120 °C at a heating rate of 5 °C min⁻¹. PEG-PLLA7 samples were loaded at room temperature, heated to 50 °C, clamped, and cooled below 0 °C with liquid nitrogen. Testing was carried out from 0 to 60 °C at a heating rate of 5 °C min⁻¹. PLGA12, PLGA20, PEG-PLGA6, PG2-PLGA2, and PG4-PLLA2 samples were loaded at room temperature, heated to 50 °C, clamped, and cooled below -40 °C with liquid nitrogen. Testing was carried out from -40 to 60 °C at a heating rate of 5 °C min⁻¹.

Melt Rheology

Rheological measurements were performed using a TA Instruments AR2000, rheometer with an 8-mm parallel plate geometry. Inertia calibration and gap compensation were performed daily prior to measurements. Samples were loaded on the peltier plate and heated above their $T_g$, trimmed, gapped, and cooled to 30 °C. Temperature scans were performed from 30 to 150 °C at a heating rate of 5 °C min⁻¹, and
frequency of 1 Hz. Samples were run in duplicate, reported results are an average of the duplicate runs. The temperature range for melt rheology of PLLA is limited between the melting point and the onset of degradation, therefore, rheological measurements were only performed on the amorphous polymers PLGA12, PLGA20, PEG-PLGA6, PG2-PLGA2, and PG4-PLLA2 (some semi-crystalline character).

**In-vitro Degradation**

Polymer samples were made by heating the amorphous polymers to 75-85 °C and pressing into sheets with thicknesses of approximately 1 mm. The slabs were then cut into 7 mm squares. Semi-crystalline polymers were heated above the melting temperature, cooled by 10-20 °C, pressed into a sheet approximately 1 mm thick, and cut into 7 mm squares. Samples were weighed and immersed in 10 mL of phosphate buffered saline solution (PBS, pH 7.4, 6.7 mM) in 14 mL (17 \( \times \) 100 mm) polypropylene round-bottom tubes with lids. The samples were placed in a reciprocating shaker bath maintained at 37 °C and 120 rpm. The PBS solution was replaced periodically during the degradation study. At 1, 7, 14, 21, and 28 days samples were removed, blotted to remove excess PBS, weighed, and dried in a vacuum oven (room temperature, 25 in Hg) until constant weight was observed (7-14 days). Water uptake was evaluated by calculating the percent water absorbed as follows:

\[
WA, \% = \frac{m_h - m_d}{m_d} \times 100
\]  

(1)

Where \( m_h \) is the hydrated mass and \( m_d \) is the mass after drying. Mass loss (erosion) was evaluated by calculating the percent remaining mass as follows:
Remaining Mass, % = \frac{m_d}{m_i} \times 100 \tag{2}

Where \( m_i \) is the initial weight of the sample. Thermal properties (DSC), inherent viscosity (Cannon-Fenske), and molecular weight (GPC) were also investigated for the degraded samples.

**Differential Scanning Calorimetry**

Thermal measurements were performed using a heat flux DSC (Mettler-Toledo, 822e). Temperature, heat flow, and tau-lag calibrations were performed relative to indium and zinc standards. Approximately 10 mg of each sample was weighed into a 40 µL aluminum pan. Amorphous polymer samples were heated from -10 °C to 100 °C, then cooled to -30 °C and heated back to 100 °C. Semi-crystalline polymers were heated from 25 °C to 200 °C, then cooled to -30 °C and heated back to 200 °C. Heating and cooling rates of 10 °C min\(^{-1}\) and a nitrogen purge at a flow rate of 80 mL min\(^{-1}\) were used for all thermal scans. An empty aluminum pan was used as the reference.

**Dilute-Solution Viscometry**

Dilute-solution viscometry was performed using a Cannon-Fenske viscometer (Cannon Instrument Company, viscometer size: 25) in a constant temperature water bath at 30 °C. Samples were prepared at concentrations between 4 and 7 mg mL\(^{-1}\) depending on the amount of sample available from the degradation study. Viscosities were performed in chloroform at a single concentration for each sample. Each sample was allowed to equilibrate to the bath temperature for 10 minutes in the viscometer prior to
measuring the efflux time. Three runs were performed for each sample, the reported results are an average of the runs.

**Gel Permeation Chromatography**

Samples for GPC analysis were prepared in chloroform at 1 mg mL\(^{-1}\) then injected into the chloroform mobile phase (1 mL min\(^{-1}\)) using a Perkin Elmer instrument with two columns in series (Waters HR2 Styrigel and Waters HR5E Styrigel, respectively) and a Perkin Elmer Series 200a refractive index detector. The column oven and detector temperature were maintained at 40 °C. Molecular weight estimates were calculated relative to a peak position calibration curve generated using narrow-fraction poly(styrene) reference standards.

**Results and Discussion**

**Dynamic Mechanical Analysis**

Dynamic mechanical relaxation behaviors of the linear and branched polymers are shown in Figure 1 and 2. Storage modulus (\(E'\)) is a measure of elastic response indicating material strength and loss modulus (\(E''\)) is the viscous response indicating liquid-like characteristics. The loss tangent (\(\tan\delta\)) is the ratio of \(E''\) to \(E'\). The sample retains more deformation energy due to the elasticity when \(\tan\delta < 1\) and more deformation energy is dissipated as heat when \(\tan\delta > 1\). \(T_g\) is usually reported as the maximum of \(E''\) or \(\tan\delta\). Table 1 contains a summary of \(T_g\) by DSC and DMA as well as Log \(E'\) and \(E''\) at 25 and 37.5 °C.
Figure 1. Variation of storage modulus as a function of temperature by DMA tensile mode.
Figure 2. Variation of loss tangent as a function of temperature by DMA tensile mode.
<table>
<thead>
<tr>
<th>Polymer</th>
<th>$T_{g,DSC}$ [°C]</th>
<th>$T_{g,E''}$ [°C]</th>
<th>$T_{g,tan \delta}$ [°C]</th>
<th>$T_{g,G''}$ [°C]</th>
<th>Log $E'$ at 25 °C [Pa]</th>
<th>Log $E'$ at 37.5 °C [Pa]</th>
<th>Log $E''$ at 25 °C [Pa]</th>
<th>Log $E''$ at 37.5 °C [Pa]</th>
<th>$G$ cross-over [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLLA35</td>
<td>53</td>
<td>74</td>
<td>80</td>
<td>-</td>
<td>9.1</td>
<td>8.0</td>
<td>9.1</td>
<td>8.0</td>
<td>-</td>
</tr>
<tr>
<td>PLGA12</td>
<td>42</td>
<td>43</td>
<td>45</td>
<td>50</td>
<td>9.0</td>
<td>8.2</td>
<td>9.0</td>
<td>8.3</td>
<td>57</td>
</tr>
<tr>
<td>PLGA20</td>
<td>45</td>
<td>50</td>
<td>53</td>
<td>54</td>
<td>9.1</td>
<td>8.0</td>
<td>9.1</td>
<td>8.0</td>
<td>54</td>
</tr>
<tr>
<td>PEG-PLGA6</td>
<td>45</td>
<td>44</td>
<td>48</td>
<td>49</td>
<td>9.3</td>
<td>8.1</td>
<td>9.2</td>
<td>8.4</td>
<td>50</td>
</tr>
<tr>
<td>PEG-PLLA7</td>
<td>51</td>
<td>50</td>
<td>50</td>
<td>-</td>
<td>9.1</td>
<td>8.0</td>
<td>9.0</td>
<td>8.1</td>
<td>-</td>
</tr>
<tr>
<td>PG2-PLGA2</td>
<td>40</td>
<td>36</td>
<td>41</td>
<td>45</td>
<td>8.8</td>
<td>7.6</td>
<td>8.3</td>
<td>8.0</td>
<td>46</td>
</tr>
<tr>
<td>PG4-PLLA2</td>
<td>43</td>
<td>49</td>
<td>60</td>
<td>50</td>
<td>9.0</td>
<td>8.0</td>
<td>9.0</td>
<td>8.0</td>
<td>50, 94, 130</td>
</tr>
</tbody>
</table>
$T_g$ measured by DMA is often 10 °C higher than $T_g$ by DSC but can vary as much as 25 °C between $T_{g,E'}$, $T_{g,\tan \delta}$, and $T_{g,DSC}$ because $T_g$ is frequency dependent in DMA. $T_{g,E'}$, $T_{g,\tan \delta}$, and $T_{g,DSC}$ all agreed within 10 °C for PLGA12, PLGA20, PEG-PLGA6, PEG-PLLA7, and PG2-PLGA2 indicating a good correlation. However, the difference between $T_{g,E'}$, $T_{g,\tan \delta}$, and $T_{g,DSC}$ was larger than 10 °C in PLLA35 and PG4-PLLA2 which may be due to increased crystallinity from processing the polymers into bars. It is unclear why this larger difference in $T_g$ was not observed in PEG-PLLA7 except perhaps because the overall molecular weight was significantly lower than PLLA35 and PG4-PLLA2.

All of the polymers demonstrate $E'$ and $E''$ values of similar magnitudes. Values for Log $E'$ are larger than Log $E''$ at 25 and 37.5 °C indicating more solid-like characteristics at these temperatures. Log $E'$ and $E''$ did not change significantly between 25 and 37.5 °C for any of the polymers tested except PG2-PLGA2 which changed by half an order of magnitude.

**Melt Rheology**

Dynamic mechanical relaxation behaviors using melt rheology are expressed as shear storage modulus ($G'$) and shear loss modulus ($G''$). $G'$ and $G''$ have essentially the same meaning as $E'$ and $E''$ but are used when the deformation mode is shear instead of tensile. $G'$, $G''$, and η* decrease in the order PEG-PLGA6 < PLGA20 < PG2-PLGA2 ≈ PLGA12. Figure 3 shows the change in complex viscosity (η*) as a function of temperature. Branching has a dramatic effect on $G'$, $G''$, and η* as can be seen in Figure
Figure 3. Variation of complex viscosity as a function of temperature by melt rheometry.
3 by comparing PG2-PLGA2 ($\overline{M}_w = 54.2 \text{ kg mol}^{-1}$) and PLGA12 ($\overline{M}_w = 21.1 \text{ kg mol}^{-1}$).

In general, $G'$, $G''$, and $\eta^*$ decrease as a function of temperature for PG4-PLLA2 as in the other polymers tested but an increase is also observed for $G'$, $G''$, and $\eta^*$ between approximately 85 and 115 °C. The $G$ cross-over temperature is the point at which the sample becomes more liquid-like ($G'' > G'$) or solid-like ($G' > G''$). When the cross-over goes from $G'' > G'$ to $G' > G''$ it is often interpreted as gelation. Table 1 contains information for $T_{g,G''}$ and $G$ cross-over temperatures for each polymer. $G$ cross-over temperatures for PLGA12, PLGA20, PEG-PLGA6 and PG2-PLGA2 in all indicate a transition from solid-like to liquid-like and decrease in the order PLGA20 < PLGA12 < PG4-PLLA2 (1$^{\text{st}}$ cross-over temperature) $\approx$ PEG-PLGA6 < PG2-PLGA2. These results are expected due to the architectures and molecular weights of the different polymers. PG4-PLLA2 has three cross-over temperatures indicating transitions from solid to liquid (1$^{\text{st}}$ cross-over), liquid to solid (2$^{\text{nd}}$ cross-over), and solid to liquid (3$^{\text{rd}}$ cross-over). Although significant gelation is not expected for any of the polymers tested, a possible explanation for the 2$^{\text{nd}}$ $G$ cross-over in PG4-PLLA2 is crosslinking via the formation of a few small crystallites involving multiple chains. At higher temperature the crosslinks would be eliminated and the system would de-gel causing the 3$^{\text{rd}}$ $G$ cross-over. It is of note that there is an obvious change in slope for PEG-PLGA6 at approximately 110 °C.

This was observed in both runs indicating that it is likely due to the nature of the polymer and not an experimental anomaly. Glycolide is more reactive than lactide thus it is possible that the arms have characteristics of glycolide and lactide blocks. If lactide blocks in the arms are long enough, it is possible that small crystalline zones crosslinking
multiple chains may occur, as suggested above for PG4-PLLA2, although to a lesser extent.

**In Vitro Degradation**

Molecular Weight Loss during Sample Preparation

Thermal degradation of the polymers occurred while preparing the samples for the *in vitro* degradation study. Table 2 summarizes the molecular weights and $T_g$s prior to and after sample preparation. Previous studies\[^{26}\] have shown that these polymers start losing mass above 150 °C. Thermal degradation of PLLA35, PLGA20, and PLGA12 occurs in a single mass loss step while PEG-PLGA6, PEG-PLLA7, PG2-PLGA2, and PG4-PLLA2 occurs in two steps, mass loss of the polyester followed by polyether degradation. Mass loss in the amorphous polymers is not likely as samples were prepared well below 150 °C, however, scission of polymer chains can occur without the formation of small volatile fragments. PLLA35 and PEG-PLLA7 were heated to 190-200 °C and PG4-PLLA2 was heated to 170-180 °C during sample preparation. Some thermal degradation of the semi-crystalline polymers is expected to have occurred during sample preparation. Although more information is needed, the molecular weight loss mechanisms appear to be as follows: PLLA35 – unzipping depolymerization, PLGA12 and PLGA20 – random chain scission, PEG-PLGA6 and PEG-PLLA7 – nonrandom chain scission. Minimal molecular weight loss observed for PLLA35 is consistent with an unzipping depolymerization mechanism starting at the amorphous chain ends. A large drop in molecular weight for both PLGA12 and PLGA20 indicates a random chain
<table>
<thead>
<tr>
<th>Polymer</th>
<th>[LLA]/[Gly]/[PEG or PG]</th>
<th>$M_{n,\text{pre}}$ [kg mol$^{-1}$]</th>
<th>$M_{w,\text{pre}}$ [kg mol$^{-1}$]</th>
<th>$M_{n,\text{pre}}/M_{n,\text{pre}}$</th>
<th>$T_{g,\text{pre}}$ [°C]</th>
<th>$M_{n,\text{post}}$ [kg mol$^{-1}$]</th>
<th>$M_{w,\text{post}}$ [kg mol$^{-1}$]</th>
<th>$M_{w,\text{post}}/M_{n,\text{post}}$</th>
<th>$T_{g,\text{post}}$ [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLLA35</td>
<td>100/0/0</td>
<td>34.5</td>
<td>61.3</td>
<td>1.8</td>
<td>53</td>
<td>31.3</td>
<td>55.6</td>
<td>1.8</td>
<td>57</td>
</tr>
<tr>
<td>PLGA12</td>
<td>75/25/0</td>
<td>11.7</td>
<td>21.1</td>
<td>1.8</td>
<td>42</td>
<td>7.9</td>
<td>15.2</td>
<td>1.9</td>
<td>31</td>
</tr>
<tr>
<td>PLGA20</td>
<td>85/15/0</td>
<td>20.1</td>
<td>60.0</td>
<td>3.0</td>
<td>45</td>
<td>17.9</td>
<td>36.1</td>
<td>2.0</td>
<td>39</td>
</tr>
<tr>
<td>PEG-PLGA6</td>
<td>71/24/5</td>
<td>14.6</td>
<td>27.0</td>
<td>1.8</td>
<td>45</td>
<td>6.0</td>
<td>17.8</td>
<td>2.8</td>
<td>36</td>
</tr>
<tr>
<td>PEG-PLLA7</td>
<td>96/0/4</td>
<td>15.5</td>
<td>29.0</td>
<td>1.9</td>
<td>51</td>
<td>6.6</td>
<td>12.7</td>
<td>1.9</td>
<td>36</td>
</tr>
<tr>
<td>PG2-PLGA2</td>
<td>70/25/5</td>
<td>43.0</td>
<td>54.2</td>
<td>1.3</td>
<td>40</td>
<td>36.7</td>
<td>50.0</td>
<td>1.3</td>
<td>29</td>
</tr>
<tr>
<td>PG4-PLLA2</td>
<td>94/0/6</td>
<td>35.5</td>
<td>46.1</td>
<td>1.3</td>
<td>43</td>
<td>27.4</td>
<td>38.5</td>
<td>1.4</td>
<td>41</td>
</tr>
</tbody>
</table>
scission mechanism. The polyester arms for PEG-PLGA6 and PEG-PLLA7 had a $\bar{M}_n$ of approximately 7 kg mol$^{-1}$ each. After sample preparation the $\bar{M}_n$ for PEG-PLLA7 and PEG-PLGA6 was reduced to approximately 6 kg mol$^{-1}$, indicating that the polymer was cleaved at or near the branch point in accordance with a nonrandom mechanism. There are no good indicators of the molecular weight loss mechanism for PG2-PLGA2 or PG4-PLLA2. However, the high branching density of PG2-PLGA2 and PG4-PLLA2 makes chain scission at or near the backbone unlikely due to steric hindrance leaving the unzipping depolymerization mechanism as the most likely mechanism.

Molecular Weight and Mass Loss During In Vitro Studies

Kenley et al.$^{[28]}$ described 3 major features of PLGA degradation curves: (1) Induction period where mass and molecular weight values are unchanged, (2) Onset of molecular weight loss becoming exponential with time, and (3) Erosion onset. Several factors contribute to the hydrolytic degradation (molecular weight loss) of aliphatic polyesters. Among these are molecular weight, composition (monomer selection, ratios for copolymers), initiator selection, and morphology. Hydrolytic degradation of biodegradable polyesters occurs by random or nonrandom chain scission. Hydrolysis of linear PLLA and PLGA is generally considered to proceed by random cleavage of ester bonds. However, nonrandom ester cleavage of PLGA arms from a PEG block has been observed in 2-arm PEG-PLGA.$^{[29, 30]}$ The chain scission mechanism in multi-arm PLLA and PLGA has been shown to be dependent on the backbone material.$^{[20, 29]}$ Random chain scission of the PLLA and PLGA branches has been observed in polymers with a
backbone of diethyaminoethyl dextran chloride\textsuperscript{[20]} and nonrandom chain scission when the backbone was dextran sulfate sodium,\textsuperscript{[20]} 4-arm PEO, or 8-arm PEO\textsuperscript{[29]}. Cleavage of the branches from the core material was followed by degradation of the resulting linear polyester fragments via the random scission mechanism until the molecular weight was low enough for the fragments to be water-soluble. When the polymer fragments are small enough to be water soluble then erosion (mass loss) is observed. Polymer mass loss may occur via a surface or bulk erosion mechanism. Polymers that undergo bulk erosion absorb water into the polymer matrix and undergo hydrolysis uniformly throughout the sample. Surface eroding polymers do not absorb water into the matrix rather, erode from the outer layer in. Bulk erosion is considered to be the primary erosion mechanism for PLA and PLGA, however, it has been shown that PLA and PLGA erode in a nonuniform manner with faster degradation in the center of implants than at the surface.\textsuperscript{[31]} This heterogeneous bulk erosion is caused by autocatalysis, accelerated degradation inside the polymer matrix by trapped acidic degradation products. It is expected that the 2-arm PEG-polyesters and the multi-arm PG-polyesters in this study demonstrate similar degradation behavior to the 2-arm, 4-arm, and 8-arm PEG/PEO polymers discussed above.

Degradation and erosion behavior of linear and branched poly(L-lactide)s and poly(L-lactide-co-glycolide)s were investigated. Normalized molecular weight loss vs. time is reported in Figure 4 and follows the order PLLA35 < PG4-PLLA2 < PEG-PLLA7 < PG2-PLGA2 < PEG-PLGA6 < PLGA20 ≈ PLGA12. Figure 5 shows the normalized erosion vs. time for the polymers studied. Normalized erosion rates followed the order of
Figure 4. Hydrolytic degradation displayed as percent $\bar{M}_w$ remaining vs. time in phosphate buffer.
Figure 5. Erosion displayed as percent mass remaining vs. time in phosphate buffer.
PLLA35 < PEG-PLLA7 ≈ PG4-PLLA2 < PEG-PLGA6 ≈ PLGA20 < PG2-PLGA2 < PLGA12. Erosion and MW loss for the semi-crystalline polymers (PLLA35, PEG-PLLA7, and PG4-PLLA2) were significantly slower than that of the amorphous polymers (PLGA12, PLGA20, PEG-PLGA6, and PG2-PLGA2). This was expected as polymers containing PLLA are more hydrophobic than those containing PLGA. Hydrophobicity of PLLA slows the diffusion rate of water into the sample, and the crystallinity of PLLA reduces the amount of free volume in the sample. Therefore, less water is absorbed affecting the amount of water available for hydrolysis. Erosion lags behind MW loss for all of the polymers tested. The lag implies that hydrolysis proceeds throughout the polymer bulk. Degradation by the surface erosion mechanism requires mass loss precede MW loss.

Normalized hydrolysis and erosion rates of the semi-crystalline polymers followed the order PLLA35 < PG4-PLLA2 < PEG-PLLA7 and PLLA35 < PEG-PLLA7 ≈ PG4-PLLA2. PLLA35 is the most hydrophobic and crystalline of the polymers tested and did not undergo significant hydrolysis during this study, not unexpectedly, no erosion was observed. PEG-PLLA7 and PG4-PLLA2 both have crystalline PLLA arms but contain a hydrophilic core disrupting the crystallinity and increasing the hydrophilicity of the polymers causing them to degrade faster than PLLA35. It has been reported that polylactide degradation starts in the amorphous regions then occurs in the crystalline areas.\[32, 33\] In polymers with a PG or PEG core, the regions near the backbone would be amorphous. Also, with a hydrophilic backbone, it seems reasonable to assume there is more water near the branch points than surrounding the hydrophobic, crystalline arms. It
is expected that the amorphous regions and greater availability of water near the branch points increases the likelihood of chain scission near the branch points resulting in a nonrandom chain scission mechanism for PEG-PLLA7 and PG4-PLLA2. After the chain scission near the branch points, degradation of the resulting PLLA fragments is expected to proceed via the random chain scission mechanism.

Molecular weight analysis and mass loss results confirm this dual degradation mechanism. Faster MW loss was observed for the branched polymers due to preferential cleavage of PLLA from the PEG or PG core. Initially, hydrolysis occurred more rapidly in PEG-PLLA7 than PG4-PLLA2 even though PEG-PLLA7 is more crystalline, absorbed less water than PG4-PLLA2 (2% vs. 7%, respectively at 7 days), and has a lower molecular weight. Nonrandom scission at the branch points eliminates both branches on PEG-PLLA7 more quickly than the 51 branches on PG4-PLLA2 resulting in a faster initial rate of hydrolysis for PEG-PLLA7. MW loss slowed for PEG-PLLA7 after 7 days which indicates the degradation mechanism changing from nonrandom scission of the branches to random scission of the resulting polymer fragments. The change in degradation mechanism was not obvious from MW loss data for PG4-PLLA2 as the degradation rate remained constant throughout the study. However, the erosion rates of PG4-PLLA2 and PEG-PLLA7 were approximately the same even though the molecular weight of PG4-PLLA2 was significantly higher. This observation indicates the polyester branches in PG4-PLLA2 are eliminated in a nonrandom manner similar to PEG-PLLA7. Branches are removed from the backbone first, then, the linear polymer fragments continue to undergo hydrolysis to water soluble degradation products resulting in mass
loss. Degradation products such as PLLA oligomers or monomers are produced in fewer hydrolytic steps than in linear polymers of similar molecular weight leading to faster erosion.

Normalized hydrolysis and erosion rates of the amorphous polymers followed the order PG2-PLGA2 < PEG-PLGA6 < PLGA20 ≈ PLGA12 and PEG-PLGA6 ≈ PLGA20 < PG2-PLGA2 < PLGA12. PLGA12 and PLGA20 differed in initial molecular weight ($M_w = 15$ vs. 36 kg mol$^{-1}$) and lactide/glycolide (La:Gly) ratio (La:Gly = 75:25 vs. 85:15) but degraded at approximately the same normalized rate. This is unexpected since higher lactide content and greater MW increases the hydrophobicity of PLGA20 compared to PLGA12, and this is thought to reduce the degradation rate. There are several possible explanations for this: (1) the larger ratio of dodecanol to lactide and glycolide in PLGA12 has a larger effect on the hydrophobicity for low molecular weight PLGA slowing hydrolysis, (2) PLGA20 degrades faster than expected due to autocatalysis while PLGA12 is hydrophilic enough to have good diffusion of acidic degradation products out of the matrix thus does not experience autocatalysis, or (3) water-soluble oligomers and monomers are produced in fewer steps in PLGA12 due to the low molecular weight leading to faster erosion leaving only the larger fragments to be evaluated for molecular weight thereby skewing the degradation profile. MW and monomer ratio are observed to affect erosion rates as faster erosion was observed in PLGA12 than in PLGA20. Slower erosion rates for polymers with larger molecular weights are in agreement with the random chain scission mechanism because it takes more hydrolysis steps for a linear polymer with a larger molecular weight to degrade to
water soluble products. Monomer ratio may have also affected the erosion rate since Gly-Gly and La-Gly bonds hydrolyze faster than La-La bonds likely due to the methyl group of the lactide sterically hindering hydrogen bonding of the ester linkage by water.\textsuperscript{[34]} Statistically, PLGA20 should have more La-La bonds which would take longer to degrade to water soluble species. The slower degradation rates of PEG-PLA polymers relative to the linear PLA and PLGA polymers is not unexpected as this has been observed previously\textsuperscript{[30, 35]} and was attributed to a less acidic microenvironment due to the increased permeability of the polymer matrix to water and diffusion of the acidic degradation products.

Observed degradation rates for PLGA12, PLGA20, and PEG-PLGA6 were similar for approximately 7 days with PEG-PLGA6 lagging slightly. After the first 7 days the hydrolysis rate of PEG-PLGA6 slowed, indicating a change in degradation mechanism. Although the initial molecular weights are different, $\bar{M}_w = 18$ vs. 36 kg mol\textsuperscript{-1}, respectively for PEG-PLGA6 and PLGA20, the mass loss rates were approximately the same throughout the study. This observation is in agreement with the observed $\bar{M}_w$ losses and concentrations as both PLGA20 and PEG-PLGA6 reached water soluble molecular weights and similar concentrations ($1/\bar{M}_n$) at the same time. As discussed above, PEG-PLLA7 and PG4-PLLA2 degrade by nonrandom chain scission of the branches followed by random chain scission of the resulting linear polymer fragments, PEG-PLGA6 and PG2-PLGA2 are expected to degrade by the same mechanism. Initially, hydrolysis occurred more rapidly in PEG-PLGA6 than PG2-PLGA2 even though PEG-PLGA6 absorbed less water than PG2-PLGA2 (13% vs. 101%, respectively,
at 7 days), and has a lower molecular weight. Both branches on PEG-PLGA6 are eliminated from the backbone more quickly than the 51 branches on PG2-PLGA2 can be, resulting in a faster initial rate of hydrolysis for PEG-PLGA6. After 7 days, MW loss slowed for PEG-PLGA6 until the hydrolysis rate was approximately the same as PG2-PLGA2. The change in hydrolysis rate indicates degradation mechanism change from nonrandom chain scission to random chain scission. The degradation rate of PG2-PLGA2 remained constant throughout the study. Unlike PG4-PLLA2 and PEG-PLLA7, the erosion rates of PG2-PLGA2 and PEG-PLGA6 were different. Branches cleaved from the PG backbone of PG2-PLGA2 have smaller molecular weights than the branches from PEG-PLGA6 requiring fewer hydrolytic steps to produce water-soluble degradation products resulting in faster erosion of the PG2-PLGA2 matrix.

The molecular weight polydispersity is another indicator of the degradation mechanism. Random chain scission would result in an increase of polydispersity over time. No significant change in polydispersity was observed for PLLA35 or PEG-PLLA7. Elucidation of the degradation mechanism from the polydispersity for these polymers is inconclusive because of a lack of significant degradation during the study. The polydispersity of PLGA12 and PLGA20 increased from 2 to a maximum of 3 at 14 and 21 days respectively, then decreased below 2. An increase in polydispersity over several days indicates a random scission mechanism. After the maximum polydispersity is reached, further chain scission results in a decrease in polydispersity as the molecular weight of the chain fragments becomes more uniform. The maximum polydispersity of PEG-PLGA6 was observed at the beginning of the study then decreased. Nonrandom
cleavage of the PLGA arms on PEG-PLGA6 near the PEG core is in agreement with the observed polydispersity changes since the resulting fragments will have roughly equivalent molecular weights thus maintaining the polydispersity. Bimodal molecular weight distributions were observed throughout the degradation study for PG4-PLLA2 and PG2-PLGA2. There were no significant changes in the polydispersities of the major, minor, or combined peaks for either of these polymers. Over time, the percent of area under the minor peak increased and the minor peak changed from a large tail to a distinct peak indicating an increase in low molecular weight species. The major peak can be associated with the branched polymer and the minor peak can be associated with the polymer arms cleaved from the backbone. These results indicate a nonrandom chain scission mechanism for PG4-PLLA2 and PG2-PLGA2.

The water adsorption vs. time is shown in Figure 6. Two distinct behaviors are identified: semi-crystalline polymers absorbed small amounts of water and amorphous polymers absorbed larger amounts of water. The rate of water uptake followed the order PG2-PLGA2 > PLGA12 > PLGA20 >> PEG-PLGA6 > PG4-PLLA2 ≈ PEG-PLLA7 ≈ PLLA35. PG2-PLGA2 also had the greatest maximum absorption, absorbing enough water to increase the sample weight by nearly 200%. This high water uptake both in terms of rate and total amount can be attributed to the highly branched structure as well as the hydrophilic PG backbone. PLGA12 and PLGA20 also have significant water uptake with maximums of 58% and 74% weight increases. PLGA12 absorbs water
Figure 6. Water absorption vs. time in phosphate buffer.
more rapidly than PLGA20. This is likely due to the higher hydrophilicity of lower molecular weight PLGA12. PLGA12 and PLGA20 having a faster and larger water uptake than PEG-PLGA6 was unexpected and difficult to explain. However, if PEG-PLGA6 has PLLA blocks as hypothesized, the more hydrophobic La-La bonds may explain this phenomenon. The result was consistent for each time point and thus can be attributed to the nature of the polymer, such as La blocks, rather than an experimental issue. No correlation was found between water uptake and degradation or erosion kinetics. This result agrees with the results reported by Wiggins et al.\textsuperscript{[36]}

As the polymers degrade, the number of end groups increases with the number of short chains created by hydrolysis leading to an increase in free volume resulting in lower $T_g$s. The percent loss in $T_g$ vs. time follows the order PLGA20 $\gg$ PLGA12 $\gg$ PEG-PLGA6 $>$ PG2-PLGA2 $>$ PG4-PLGA2 $\approx$ PEG-PLLA7 $\approx$ PLLA35. Table 3 summarizes the initial and final $\bar{M}_w$, $T_g$, and crystallinity ($X_c$) for the samples in the degradation study. Along with rapid $\bar{M}_w$ loss a rapid decrease in $T_g$ is observed for PLGA12 and PLGA20. PG2-PLGA2 lost $\bar{M}_w$ at a lower rate than PLGA12 and PLGA20 for reasons discussed previously which resulted in a slower decrease in $T_g$. Final $T_g$s for PEG-PLGA6 and PG2-PLGA2 are approximately the same although $\bar{M}_w$ for PEG-PLGA6 is significantly lower than PG2-PLGA2. It is well known that branched architectures reduce molecular interactions thereby decreasing $T_g$ which explains why PG2-PLGA2, with a higher molecular weight, has a lower $T_g$ than PEG-PLGA6. PEG-PLLA7 lost approximately 44% $\bar{M}_w$ during the study but the $T_g$ did not change and the $X_c$ appears to be slightly higher. A similar result was observed for PG4-PLLA2 where it lost approximately 25%
Table 3. Molecular Weight, Crystallinity, and Glass Transition Beginning and End of *In Vitro* Study

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$\bar{M}_{w,0}$ [kg mol$^{-1}$]</th>
<th>$\eta_{inh,0}$ [dL g$^{-1}$]</th>
<th>$\bar{M}_{w,f}$ [kg mol$^{-1}$]</th>
<th>$\eta_{inh,f}$ [dL g$^{-1}$]</th>
<th>$X_{c,0}$</th>
<th>$X_{c,f}$</th>
<th>$T_{g,0}$ [°C]</th>
<th>$T_{g,f}$ [°C]</th>
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<tbody>
<tr>
<td>PLLA35</td>
<td>55.6</td>
<td>0.55</td>
<td>48.9</td>
<td>0.50</td>
<td>51</td>
<td>52</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>PLGA12</td>
<td>15.2</td>
<td>0.14</td>
<td>1.5</td>
<td>0.03</td>
<td>-</td>
<td>-</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>PLGA20</td>
<td>36.1</td>
<td>0.28</td>
<td>1.5</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>PEG-PLGA6</td>
<td>17.8</td>
<td>0.20</td>
<td>3.4</td>
<td>0.08</td>
<td>-</td>
<td>-</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>PEG-PLLA7</td>
<td>12.7</td>
<td>0.17</td>
<td>7.1</td>
<td>0.13</td>
<td>40</td>
<td>44</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>PG2-PLGA2</td>
<td>50.0</td>
<td>0.13</td>
<td>18.6</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>23</td>
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<tr>
<td>PG4-PLLA2</td>
<td>38.5</td>
<td>0.13</td>
<td>29.0</td>
<td>0.12</td>
<td>4</td>
<td>13</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>
but the $T_g$ did not change and the $X_c$ increased over time. These observations indicate the crystalline regions have more impact on $T_g$ than molecular weight for these polymers. With the incubation temperature at or above $T_{g, \text{onset}}$ and below $T_m$ for PEG-PLLA7 and PG4-PLLA2 conditions were favorable for crystal growth. PLLA35 did not undergo significant degradation therefore no change in $T_g$ was expected.

The results from dilute solution viscometry compliment the molecular weight results obtained by GPC. Initial and final inherent viscosities ($\eta_{\text{inh}}$) for the samples in the degradation study are shown in Table 3. Normalized $\eta_{\text{inh}}$ loss over time follows essentially the same trend as percent $M_w$ loss with the order PLLA35 < PG4-PLLA2 < PEG-PLLA7 < PG2-PLGA2 < PEG-PLGA6 < PLGA20 < PLGA12. Larger $M_w$ corresponds to larger $\eta_{\text{inh}}$ for the linear polymers PLLA35, PLGA20, PLGA12, and PEG-PLGA6. PEG-PLLA7 also follows this correlation for all time points except the first which appears to be experimental error. The lowest initial $\eta_{\text{inh}}$ observed were for the branched polymers PG2-PLGA2 and PG4-PLLA4. It is well known that branched polymers exhibit lower viscosities. The $M_w$ vs. $\eta_{\text{inh}}$ for PLGA12 and PLLA35 was plotted, linear regression performed, and theoretical $\eta_{\text{inh}}$ was calculated for the linear equivalents of PG2-PLGA2 and PG4-PLLA2. The actual $\eta_{\text{inh}}$ of the branched polymers was found to be 65-80 % lower than the theoretical values confirming a substantial difference in hydrodynamic volumes of linear and branched architectures.
Conclusion

The dynamic mechanical and hydrolytic degradation properties of linear and branched PLLA and PLGA were investigated. Melt rheology shows branched polymers have favorable processing temperatures compared to linear polymers while DMA demonstrates melt processed polymer samples have similar storage and loss modulus values at room temperature and body temperature. Molecular weight loss occurs during sample preparation by melt processing, although it is not as significant for the branched polymers. Clearly, branched polymers have processing advantages over linear polymers.

In vitro degradation was observed for linear and branched PLLA and PLGA. Linear PLLA and PLGA are found to degrade by a random chain scission mechanism and multi-arm PLLA and PLGA degrade by a dual mechanism, nonrandom chain scission mechanism at or near the branch points followed by random chain scission of the resulting PLLA or PLGA fragments. Erosion is found to lag behind MW loss indicating a bulk erosion mechanism. However, PG2-PLGA2 is found to have near constant degradation and erosion. The degradation profile of PG2-PLGA2 creates a uniform hydrophobic environment for drugs encapsulated in the polymer matrix throughout degradation of the delivery system which should result in a favorable environment for constant drug release and quick elimination of the remaining polymer after completion of drug release.
Acknowledgements

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References


CONCLUSIONS

This dissertation research has developed the synthesis methods for multi-arm PLLA or PLGA polymers with PG backbones, investigated the properties of these polymers, and compared these properties to those of linear and two-arm PLLA and PLGA. The thermal stability, mechanical properties, and hydrolytic degradation of polymers with a PG core were found to be favorable for use as polymeric drug delivery systems.

Thermal degradations of PG, PG-g-La, and PG-g-Gly were investigated to understand the thermal degradation of PG and simple branched systems with lactide and glycolide. Thermal degradation of PG was found to be similar to PEG with a single mass loss step, similar peak degradation temperature, and degradation products. PG thermal degradation was most likely a combination unzipping and random chain scission mechanism. PG-g-La and PG-g-Gly degraded in two steps, corresponding to the degradation of the lactide or glycolide pendant groups by chain scission at the alkyl-oxygen bond in the first step followed by the degradation of the PG backbone in the second step.

Single-arm (PLLA35, PLGA12, PLGA20), double-arm (PEG-PLLA7, PEG-PLGA6), and multi-arm (PG4-PLLA2, PG2-PLGA2) PLLA and PLGA were
synthesized, evaluated, and compared. It was demonstrated that highly branched polymers with a PG core could be produced with a high degree of substitution at the branch points on the PG. As expected, crystallinity and number of arms affected $T_g$. Single-arm PLLA and PLGA were found to degrade in a single mass loss step. Two mass loss steps were observed for the double- and multi-arm polymers. The first stage was attributed to the PLLA or PLGA arms depolymerizing via an unzipping mechanism catalyzed by Sn and the second stage was associated with the degradation of the PEG or PG core. $T_{\text{max}}$ for all the single-arm, double-arm, and multi-arm PLLA and PLGA were similar. The depolymerization reaction catalyzed by Sn was found to be the main thermal degradation pathway for PLLA and PLGA regardless of differences in the ratio of lactide, glycolide, coinitiator, number of branches or branch length.

The isoconversional analysis results indicated similarities in the $E_\alpha$ dependencies for the linear and branched polyesters. A plateau for $E_\alpha$ values was observed for PG-g-La and PG-g-Gly at $\approx 100$ kJ mol$^{-1}$ consistent with the degradation of lactide and glycolide before $E_\alpha$ rose to $\approx 150$ kJ mol$^{-1}$ indicating the degradation of PG. Initial $E_\alpha$ values for PLLA35, PLGA12, PLGA20, PEG-PLLA7, PEG-PLGA6, PG4-PLLA2, and PG2-PLGA2 were approximately 80-100 kJ mol$^{-1}$ indicating that the degradation initiation steps are similar. $E_\alpha$ dependencies for the double- and multi-arm polymers follow the same pattern as single-arm PLLA and PLGA. Degradation kinetics of these polymers is limited by the degradation of PLLA or PLGA without respect to polymer architecture.
Dynamic mechanical testing demonstrated processing advantages of multi-arm polymers. Molecular weight loss occurred during melt processing, however, the loss was not as significant for the multi-arm polymers as it was for the single- and double-arm polymers. Branched polymers may be processed at lower temperatures while maintaining similar storage and loss modulus values as the single- and double-arm polymers at room temperature and body temperature.

Hydrolytic degradation and erosion of linear and branched PLLA and PLGA were observed in a phosphate buffer system. Linear PLLA and PLGA were found to degrade by a random chain scission mechanism, double- and multi-arm PLLA and PLGA degraded by a dual mechanism, nonrandom chain scission mechanism at or near the branch points followed by random chain scission of the resulting PLLA or PLGA fragments. Erosion was observed to occur by a bulk erosion mechanism. The degradation profile of PG2-PLGA2 was found to have near constant degradation and erosion creating a uniform hydrophobic environment in the polymer matrix.

The properties of branched PLLA and PLGA with PG cores were found to be favorable for use as polymeric drug delivery systems. Thermal stability of branched PLLA and PLGA were equivalent to linear PLLA and PLGA. Melt processing of branched PLLA and PLGA can be performed with less molecular weight loss than linear and two-arm PLLA and PLGA. Storage and loss modulus values at room temperature and body temperature are similar for the branched and linear PLLA and PLGA. Branched PLGA with a PG core, in particular, shows promise for use in drug delivery systems due to the uniform hydrophobic environment in the polymer matrix throughout
degradation which should result in a favorable environment for constant drug release and quick elimination of the remaining polymer after completion of drug release. Additional research should be performed to further evaluate and determine structure-property relationships for branched PLGA and PLLA with PG backbones.
LIST OF REFERENCES


