



# Synthesis and Characterization of Novel Biodegradable Polymers from Renewable Resources: A Study on the Properties and Applications of Poly(lactic acid-co-glycolic acid) Copolymers

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## Abstract

The rise in demand for biodegradable plastic packaging with high barrier properties has spurred interest in poly(lactic acid-co-glycolic acid) (PLGA) copolymers with a relatively high glycolide content. In this work, we examined how reaction conditions affect the synthesis of PLGA25 (L:G 25:75) through the ring-opening polymerisation of D-L-lactide (L) and glycolide (G), using tin 2-ethylhexanoate ( $\text{Sn}(\text{Oct})_2$ ) as the catalyst and 1-dodecanol as the initiator. The effects of varying the initiator concentration, catalyst concentration, reaction time, and temperature on the molecular weight, monomer conversion, and thermal properties of PLGA25 were investigated. Increasing the reaction temperature from 130 to 205 °C significantly reduced the time required for high monomer conversions but caused greater polymer discolouration. Whilst increasing the  $[\text{M}]:[\text{C}]$  from 6500:1 to 50,000:1 reduced polymer discolouration, it also resulted in longer reaction times and higher reaction temperatures being required to achieve high conversions. High  $M_n$  and  $M_w$  values of 136,000 and 399,000  $\text{g mol}^{-1}$  were achieved when polymerisations were performed in the solid state at 150 °C using low initiator concentrations. These copolymers were analysed using high temperature SEC at 80 °C, employing DMSO instead of HFIP as the eluent.

## 1.Introduction

The use of biodegradable plastic packaging is regarded as an effective way to reduce the amount of plastic pollution in the natural environment. After starch blends, poly(lactic acid) (PLA) is the world's most widely used biodegradable plastic [1]. One factor limiting PLA's usage is its poor barrier properties in comparison to petroleum-based plastics, such as PET, PE, PP, or EVOH [2–6]. Additionally, PLA requires industrial composting facilities (>58 °C) to undergo biodegradation and is slow to degrade in the ocean and other natural environments [7–9]. Therefore, in order to expand the applications of biodegradable plastics, there is a need to develop high performance biodegradable plastics with more controlled hydrolytic degradation over a wider range of conditions [10]. Poly(glycolic acid) (PGA) is a biodegradable aliphatic polyester that has biodegradation rates comparable to cellulose. It possesses a higher tensile strength, superior barrier properties, and higher thermal stability than most currently used packaging plastics [11,12]. As a result of the increased demand for biodegradable packaging, interest in PGA-based packaging has risen due to its exceptional material properties. However,



PGA has some limitations, such as its brittleness, high degree of crystallinity (>40%), and high melting temperature (220–230 °C) making it difficult to process. Furthermore, PGA has a high susceptibility towards hydrolytic degradation, which aids biodegradation, but can also result in a short service life when used in packaging due to the concomitant deterioration of its mechanical and barrier properties. Copolymerisation of glycolide with other monomers can alter the properties of PGA based materials and overcome the above issues. Poly(lactic acid-co-glycolic acid) (PLGA) is a common copolymer that has found widespread commercial use in biomedical devices. PLGAs with high glycolide contents possess PGA's high barrier properties and tensile strength, whilst having lower melting temperatures so they can be processed at lower temperatures [13]. Due to their reduced hydrophobicity and crystallinity in comparison to PLA, PLGAs display much faster biodegradation, whilst maintaining similar mechanical properties to PLA [7]. This has encouraged research into the development of high barrier PLGA based biodegradable packaging. PLGA is currently a relatively high cost material and so suited to high value applications, such as medical devices. Similarly, the price of medical grade PLA is high in comparison to packaging grade PLA [14]. By adapting PLGA production processes towards those used for packaging grade PLA, high barrier biodegradable PLGA packaging materials may be produced. Furthermore, the cost of PLGA may decline as a result of the development of new synthetic routes towards glycolic acid [13,15,16].

High molecular weight PLGA is typically synthesised through the ring-opening polymerisation (ROP) of lactide and glycolide. Whilst a wide variety of organometallic and organic catalysts have proved to be effective in ROP, tin catalysts are preferred in industry due to their low cost and high activity at the elevated temperatures required for melt polymerisation [17–19]. For biomedical uses, the residual tin content in the final polymer must be below 20 ppm, meaning that either a low catalyst concentration must be used during synthesis or that excess catalyst is removed from the polymer through a solvent based purification step. Since high glycolide PLGAs are insoluble in common organic solvents, they are typically synthesised using very low catalyst concentrations. Vicryl is an absorbable suture made of PLGA containing 90 mol% of glycolide. Examples in the patent literature state that it is synthesised using low Sn(Oct)<sub>2</sub> concentrations ([M]:[C] = 50,000:1 to 250,000:1) at high reaction temperatures (≥200 °C) for at least 5 h [20,21]. However, polymer degradation and transesterification under these conditions make it difficult to obtain high molecular weights. Most commercial PLGA produced for biomedical applications contains at least 50 mol% of lactide. Despite the fact that PLGA is a well-established polymer that has been used for decades in biomedical applications, little has been published examining the synthesis conditions of PLGAs with high glycolide contents. Gilding and Reed published the first major work regarding the ROP of PLGA in 1979, in which some high glycolide PLGAs were synthesised at 200 °C for 4 h [22]. Since then, various authors have examined how the reaction temperature, reaction time, catalyst concentration, and initiator concentration affect the molecular weight (typically inferred from intrinsic viscosity) and conversion of PLGAs



with high lactide contents synthesised by ROP [23–28]. Many authors have also evaluated the reaction kinetics and the effects of altering reaction parameters on the ROP of PLAs [29–32].

However, there are wide disparities between the reported synthetic conditions for PLGAs throughout the literature. The faster rate of propagation ( $k_p$ ) of glycolide relative to lactide and PGA's higher  $T_m$  are contributing factors to this, resulting in the optimum conditions varying depending upon the composition of the PLGA. Therefore, we carried out an extensive study examining how varying the reaction conditions affects the synthesis of PLGAs containing high percentages of glycolide. In order to be commercially viable, high glycolide content PLGAs need to have a high molecular weight, as this increases their thermomechanical properties, hydrolytic stability, and retention of strength during degradation [24,33–35]. Due to its low melt viscosity, low molecular weight PLA is only suitable for injection moulding, whereas high molecular weight PLA can be thermoformed, fibre-spun, and film extruded, allowing for a wide variety of additional applications [35,36].

This suggests that in order to be melt-processed using a wide range of techniques, high molecular weight PLGAs would also be required. In this work, our aim was to synthesise high molecular weight PLGA25 (L:G 25:75) at high conversions ( $\geq 96\%$ ) and at relatively low reaction temperatures. Therefore, we examined how the initiator concentration, catalyst concentration, reaction temperature, and reaction time affect the molecular weight, monomer conversion, colour, and thermal properties of PLGA25. This L:G composition was selected as it is high in glycolide content whilst still being an amorphous material, which results in transparent products. Once the lactide percentage falls below 15%, the copolymer becomes semicrystalline and has a  $T_m$  of about  $190^\circ\text{C}$  [13]. All PLGAs in this study were synthesised by the ROP of glycolide and D-L-lactide using tin 2-ethylhexanoate ( $\text{Sn}(\text{Oct})_2$ ) as the catalyst and 1-dodecanol as the initiator.

## 2. Materials and Methods

### 2.1. Materials

D-L-lactide was purchased from Arcos Organics (Leicestershire, UK). Glycolide was provided by Pujing Chemicals Ltd. (Shanghai, China) Both were recrystallized from ethyl acetate three times before use.  $\text{Sn}(\text{Oct})_2$  ( $>96\%$ ) and acetone (analytical grade) was purchased from VWR, Alfa Aesar (Leicestershire, UK). Anhydrous toluene, 1-dodecanol (ACS reagent,  $\geq 98.0\%$ ), ethyl acetate (HPLC grade,  $\geq 99.7\%$ ), HFIP, DMSO- $d_6$  and DMSO (dry puriss) were purchased from Sigma-Aldrich (Gillingham, UK).

### 2.2. Synthesis of PLGA

For the reactions varying the monomer to 1-dodecanol ( $[\text{M}]:[\text{I}]$ ) ratio, 0.015 mol (1.74 g) of glycolide, and 0.005 mol (0.72 g) of D-L-lactide were added to a dried Schlenk flask. This was sealed, attached to a Schlenk line, and purged with  $\text{N}_2$ . Solutions containing 1-dodecanol and



tin(II) 2-ethylhexanoate in anhydrous toluene were then injected and a vacuum was applied to remove the toluene. The reaction mixture was put under a flow of N<sub>2</sub>, placed in an oil bath at 150 °C and magnetically stirred at 300 rpm for 2.5 h. After 2.5 h, the flask was removed from the oil bath, and the polymer was removed whilst still hot. The polymer was ground using a freezer mill before being analysed. For the conversion optimisation experiments, a reaction mixture containing 0.04 mol (4.92 g) of monomer and the desired amounts of catalyst and initiator was made. A total of 0.8 g of this mixture was then added to a 15 mL sample vial, sealed, and purged with N<sub>2</sub>. The vial was then added to an oil bath at a set temperature. After the desired time, the vial was removed, placed in liquid N<sub>2</sub>, and smashed to remove the sample.

### 2.3. Nuclear Magnetic Resonance Spectroscopy (NMR Spectroscopy)

The 400 MHz <sup>1</sup>H NMR spectra were recorded at 80 °C on an AV400 Bruker Avance III 400 MHz spectrometer (Coventry, UK) using DMSO-d<sub>6</sub> as the solvent. For sample preparation, 15 mg of PLGA25 was added to 0.7 mL DMSO-d<sub>6</sub> and stirred at 80 °C for 30 min.

## 3. Results and Discussion

### 3.1. Initiator Concentration

The ROP of cyclic esters is often initiated by hydroxyl compounds, where a reduction in the concentration of the initiator relative to the monomer increases the molecular weight of the product. 1-Dodecanol is frequently used as an initiator in the ROP of PLGA, as its high boiling point prevents evaporation during polymerisation and its relatively high LogP value reduces the ingress of water into the reaction. When synthesising PLGA75, Wang et al. varied the monomer to the 1-dodecanol ratio ([M]:[I]) from 20:1 to 300:1 and observed that the M<sub>n</sub> increased from 3400 to 99,000 g mol<sup>-1</sup> [24]. Elsewhere in the literature, researchers have used even lower 1-dodecanol concentrations to target higher molecular weights (>100,000 g mol<sup>-1</sup>) for PGA, PLA, and PLGA [16,23,27–29,37]. When performing the ROP of lactide and glycolide in bulk at high temperatures, the obtained molecular weights are not always reflective of the [M]:[I] due to side reactions, such as transesterification, occurring alongside chain propagation. Therefore, in order to examine the relationship between the initiator concentration and molecular weight in PLGA25, a series of PLGA25s were synthesised in which the [M]:[I] was varied from 30:1 to 30,000:1. These experiments were all performed at 150 °C over 2.5 h using a monomer to catalyst ratio ([M]:[C]) of 6500:1.

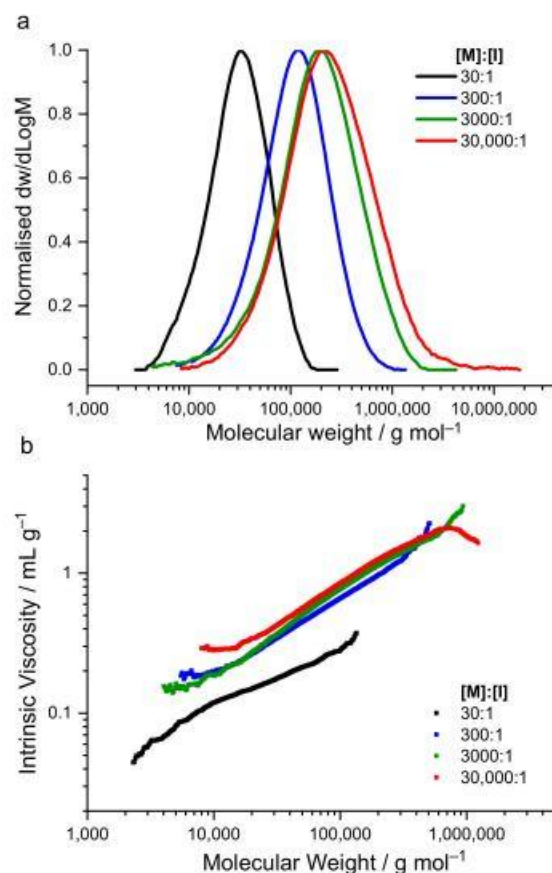


Figure 1 .(a) SEC traces and (b) Mark–Houwink–Sakurada (MHS) plots for PLGA25 synthesised

Unexpectedly, greater discolouration occurred as the 1-dodecanol concentration was reduced (Figure S2). The PLGA25 turned from white to orange/brown as the  $M_n$  increased from 23,400 to 136,000  $g\ mol^{-1}$ . Discolouration is a common problem encountered in the synthesis of polyesters by both polycondensation and ROP and has been reported to be influenced by the catalyst used [39,40]. During PLA synthesis, discolouration is frequently observed at higher reaction temperatures ( $>180\ ^\circ C$ ) and longer reaction times and is generally attributed to side reactions and polymer degradation [41]. However, these experiments were performed at relatively low temperatures ( $150\ ^\circ C$ ) and the only variable changed was the 1-dodecanol concentration, which led to an increase in molecular weight and discolouration.

Mark–Houwink–Sakurada (MHS) measurements were also obtained to observe whether any changes in structure occurred with the change in molecular weight. The MHS plots for the three high molecular weight PLGA25s synthesised using  $[M]:[I] = 3000:1$ – $30,000:1$  show good linearity over a wide molecular weight range with  $\alpha$  values of 0.55–0.59, suggesting linear polymers (Figure 1b and Table S2). The low molecular weight PLGA25 synthesised using an  $[M]:[I] = 30:1$  had a much lower intrinsic viscosity and  $\alpha$  value = 0.37. This lower intrinsic viscosity suggests this sample contains some cyclic polymers formed from back-biting reactions. Previous



researchers have shown cyclic PLA's to have lower intrinsic viscosities than their linear counterparts [41,42]. The  $^1\text{H}$  NMR spectra revealed that as the  $[\text{M}]:[\text{I}]$  increased, the total monomer conversion (CLD+GD) decreased from 98.8 to 94.0%. For each polymerisation, the glycolide conversion (CGD) was high, however, the lactide conversion (CLD) decreased from 98.0% to 76.9%, indicating that the decrease in total monomer conversion was due to a decrease in the lactide conversion. It is known that glycolide has a faster rate of propagation than lactide often resulting in PLGA having a lower L:G ratio than the monomer feed [22]. This drop in lactide conversion resulted in a lower lactide content in the final PLGA. It has been reported that increasing the 1-dodecanol concentration increases the reaction rate, leading to shorter reaction times being required to achieve high conversions [18,29,32]. Therefore, longer reaction times are needed to achieve higher lactide conversions at lower 1-dodecanol concentrations.

### 3.2. Reaction Temperature, Time, and Catalyst Concentration

As the lactide conversion for the high molecular weight PLGA25 synthesised using an  $[\text{M}]:[\text{I}] = 30,000:1$  was relatively low, further reaction optimisation was required. Aside from causing a poor yield, a low conversion is undesirable as it results in higher traces of a residual monomer in the polymer product. Residual lactide and glycolide increase the rate of hydrolytic degradation and result in poorer mechanical properties, decreasing the product life-time. Additionally, they cause degradation during melt-processing [35,43]. Therefore, they require removal after synthesis, increasing production costs. Reaction conversions above 96% are generally considered high in polylactides synthesised by ROP [22,44]. A series of experiments were performed to examine the effects of reaction time and temperature on monomer conversion. To begin, PLGA25 was polymerised at  $150\text{ }^\circ\text{C}$  using an  $[\text{M}]:[\text{C}] = 6500:1$  and  $[\text{M}]:[\text{I}] = 30,000:1$  at times ranging from 15 min to 8 h. The  $^1\text{H}$  NMR spectra of these polymers revealed how conversion changed with time, Figure 2. Conversion initially increased, reaching a peak (CLD+GD = 97.6%) at 4 h, and then fell to 92.5% after 8 h due to thermal depolymerisation. Similarly, both  $M_n$  and  $M_w$  initially increased, but then started to decrease after 1 h, most likely due to random chain scission during the reaction. However, the conversion improved significantly during this time, increasing from 93.8% to 97.6% when the reaction time was increased from 1 to 4 h. Similar observations of reductions in molecular weight and conversion after certain periods of time have been reported previously for PLA and PLGA synthesised using  $\text{Sn}(\text{Oct})_2$  [23,29–31].

### 4. Conclusions

When synthesising PLGA25 by ROP at  $150\text{ }^\circ\text{C}$ , increasing the ratio of the monomer to 1-dodecanol ( $[\text{M}]:[\text{I}]$ ) from 30:1 to 30,000:1 increased the  $M_n$  from 23,400 to 136,000  $\text{g mol}^{-1}$ . This increase in  $M_n$  was accompanied by increases in dispersity and discolouration. When using a monomer to catalyst ratio ( $[\text{M}]:[\text{C}]$ ) of 6500:1, increasing the reaction temperature reduced the time required to achieve high monomer conversions (>96%), such that reactions for 8 h at  $130\text{ }^\circ\text{C}$ , 4 h at  $150\text{ }^\circ\text{C}$  and 2 h at  $180\text{ }^\circ\text{C}$  yielded similar conversion and  $M_n$  values. However,



increasing the reaction temperature resulted in greater polymer discolouration, causing the PLGA25 to turn from beige to dark brown. Increasing the [M]:[C] from 6500:1 to 50,000:1 decreased polymer discolouration, but resulted in longer reaction times (8–16 h) and higher temperatures (150–170 °C) being required to achieve high conversions. Thermal analysis showed that increasing the molecular weight increased the  $T_g$  from 31.1 to 41.6 °C and improved the  $T_d$  (5%) from 238 to 267 °C. An increase in the thermal stability was also found upon reducing the catalyst concentration. These results demonstrate how reaction variables can be altered in order to achieve high molecular weights and conversions in the synthesis of high glycolide PLGAs for packaging applications.

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