SYNTHESIS AND CHARACTERIZATION OF POLY(PROPYLENE FUMARATE) OLIGOMERS VIA A CHAIN-GROWTH MECHANISM FOR CONTINUOUS DIGITAL LIGHT PROCESSING (CDLP)

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SYNTHESIS AND CHARACTERIZATION OF POLY(PROPYLENE FUMARATE) OLIGOMERS VIA A CHAIN-GROWTH MECHANISM FOR CONTINUOUS DIGITAL LIGHT PROCESSING (CDLP)

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Thesis

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ABSTRACT

There is an unmet demand in bone-tissue engineering to find new materials for the treatment of orthopedic injuries. More than 6.3 million fractures occurred in the United States in 2003 and around 1 million needed hospitalizations.\(^1\) More than 36 million Americans suffer from arthritis.\(^2\) Biodegradable synthetic polymers have many advantages over other materials for bone-tissue engineering. One of the most important advantages is that the mechanical properties and degradation kinetics can be tailored to meet different clinical requirements.\(^3\) Poly(lactic acid), poly(glycolic acid) and their copolymers have been used extensively in surgical sutures.\(^3\) Polyesters are also used in tissue-engineering applications because their non-toxic degradation products generated through hydrolytic degradation are absorbed readily through metabolic pathways.\(^4\) Poly(propylene fumarate) (PPF) is an unsaturated linear, biodegradable, synthetic polyester that can be crosslinked through its double bond. Three dimensional (3D) printed PPF is an attractive candidate for bone tissue engineering due to high mechanical strength and controlled porosity of the scaffold for bone in-growth.\(^5\) During the last three decades, there have been many studies on PPF as a biodegradable bone cement.\(^6\) However, the traditional method to synthesize PPF using a step-growth polymerization requires high energy input, long reaction time with high molecular mass distribution, uncontrolled isomerization or cross-linking.\(^7-8\) These factors greatly influence the resulting mechanical properties and degradation rates of the final product, which further
hinder studies of PPF-based 3D printed scaffolds on large animal models and pilot human clinical trials. To further improve the properties of PPF, a mild catalytic chain-growth mechanism was used in this study.\textsuperscript{9,10} The goal of this project is to synthesize PPF oligomers with well-defined properties to improve applications of PPF in bone tissue engineering. Kinetics studies on PPF oligomer synthesis by the copolymerization of maleic anhydride and propylene oxide with magnesium ethoxide as initiator were performed. Then, PPF oligomers at five number-average molecular weights ($M_n$) (700 Da, 1270 Da, 1860 Da, 2450 Da, 3160 Da) were synthesized. The chemical structures and molecular mass properties of these PPF oligomers were characterized and confirmed by nuclear magnetic resonance proton spectroscopy ($^1$H NMR), nuclear magnetic resonance carbon spectroscopy ($^{13}$C NMR), matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer, Fourier transform infrared spectroscopy (FTIR) and ultraviolet–visible spectrophotometer (UV-Vis). Differential scanning calorimetry (DSC) was used to detect the glass transition temperature of PPF samples. Intrinsic viscosities of PPF samples at five molecular mass levels were obtained in THF using an Ubbelohde viscometer.

\textit{Keywords:} Poly(propylene fumarate), ring-opening polymerization, unsaturated polyester, low molecular mass, biodegradability, bone tissue engineering, cross-linkable property
DEDICATION

This master thesis is dedicated to my parents, my advisor and all my friends who have supported me through my entire life.
ACKNOWLEDGEMENTS

First of all, I would like to express my appreciation to my advisor, Dr. Matthew L. Becker, for his patient direction, continuous support and warm encouragement. It is my great honor to work with such an optimistic, humorous and intelligent advisor during my graduate study. This is an important period in my life and will set the foundation of my career and influence the character of me.

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Last, I would like to express my special thanks and love to my parents who have moved our home address to achieve a better education for me three times during my childhood. Thanks for their understanding, trust, support, inspiration and sacrifice. They told me the importance of education by practical action and formed my personality of persistence, optimism and responsibility.
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CHAPTER I

INTRODUCTION

There is an unmet demand in bone-tissue engineering to find new materials for the treatment of orthopedic injuries. For example, more than 6.3 million fractures occurred in the United States in 2003 and around 1 million needed hospitalizations.\(^1\) An ideal material for the replacement of a defective or diseased bone should have the following properties. First, the material should be non-toxic and not lead to significant systemic inflammation. Second, the material should have similar mechanical properties to the host bone the surgeon is seeking to replace to provide structure stability. Third, the material should have the ability to be fabricated into various shapes and sizes for a range of clinical needs. Lastly, the material should be sterilized with existing technology.\(^{11}\)

There are two kinds of bone grafts currently in use, natural bone grafts (autograft, allograft) and synthetic bone grafts.\(^{12-13}\) However, none of these satisfy all of the ideal properties outlined above. Autografts are currently preferred because of the transplantation of bone from the host with vascular fragments and a resident cell population which prevents immune rejection.\(^{14}\) However, there is a limited amount of autograft material available for transplant and any remaining would result in a secondary wound site with the potential for additional pain or surgical complications. With regard to allografts, the possibility for rejection and disease transfer cannot be ignored. In addition,
natural bone grafts do not meet the requirement to be fabricated into various shapes or sizes for specific surgical sites. When it comes to synthetic bone grafts, a variety of metallic, polymeric and ceramic materials have been studied for use as bone substitutes. However, when compared with autografts, each kind of synthetic bone graft has its own limitations. Metallic bone grafts are permanent biomaterials which often possess mechanical strength far in excess of natural bone. This greater strength often leads to stress shielding and eventually to bone resorption around the implant. Ceramic grafts have been used since 1892 as bone cements having the osteoinductivity, moldability and nontoxicity. The primary disadvantages of ceramic grafts are their brittleness and slow degradation properties which limit the formation of new bone. Recently discovered biodegradable synthetic materials have attracted the attention of scientists as a result of the mechanical and degradation properties that can be tailored by composition and processing conditions. Furthermore, some of these synthetic biodegradable materials, which can be polymerized in situ by thermal crosslinking or photo-crosslinking, have the potential to be fabricated into different shapes or sizes for specific applications. In addition they can be injected with growth factors or antibiotics, and eliminate the need for secondary removal surgeries resulting from their biodegradability.

Poly(propylene fumarate) (PPF), an unsaturated polyester, is one such injectable biodegradable synthetic material which has the potential to meet the market needs for bone-tissue engineered grafts. PPF and PPF-based biomaterials have been investigated in a number of orthopaedic and regenerative medicine applications over the last three decades. There are significant barriers to moving PPF into mainstream clinical trials. The first challenge is inherent to the step growth polymerization process in the
traditional synthetic method.23 Previously reported methods to synthesize PPF require high energy input, high vacuum, long reaction times, and result in low conversion with uncontrolled molecular mass distribution, conjugate-addition side reactions, and unwanted cross-linking, all of which greatly influence the mechanical properties and degradation rates of the final product.10, 23 It is very difficult to reliably and reproducibly synthesize well-defined, low-molecular-mass oligomers of any material using a step-growth polymerization method.10

Recently, Coates and coworkers have successfully synthesized PPF using a ring-opening copolymerization of maleic anhydride and propylene oxide with chromium salen as a catalyst at 45 °C. The resulting poly(propylene maleate) was isomerized using diethyl amine at room temperature for 16 hours to yield poly(propylene fumarate). The solid PPF material possessed molecular masses $M_n$ around 17 kDa, molecular mass distribution of 1.6 and less than 1% ether linkage less with 99% conversion.8b Compared with traditional synthesis methods, the chain growth mechanism provides PPF with better molecular properties, and the reaction is more reproducible, making it possible to produce PPF with controlled properties for further mechanical, toxicity and degradation tests, and for large-scale production in manufacturing.

This thesis summarizes our efforts to synthesize PPF oligomers through a chain-growth mechanism. We hypothesize that PPF polymerized using a chain-growth mechanism will have well-defined properties including molecular mass, narrow molecular mass distribution, and predictable degradation kinetics. It also should have more consistent reproducibility characteristics in vitro and in vivo than those polymers synthesized by the traditional step-growth synthetic mechanism.
In Chapter II, the unmet medical needs of biodegradable polymers and opportunities for unsaturated biodegradable synthetic polymers like PPF are briefly analyzed. Meanwhile, the traditional methods of step-growth polymerization of PPF and a novel chain-growth polymerization of PPF are provided and discussed, which inspires my master thesis objective and hypothesis.

In Chapter III, the synthesis and characterization methods are described.

Chapter IV includes the results and discussion of my work.

In Chapter V, the conclusion of my current study and future work plan are listed.

Chapter VI shows the summary of this project.
CHAPTER II
BACKGROUND

2.1 Introduction to biodegradable polymers and unmet medical needs

There is an unmet need in bone-tissue engineering to find new materials to treat orthopedic injuries. More than 6.3 million fractures occurred in the United States in 2003 of which around 1 million needed hospitalizations.\textsuperscript{1} Around 36 million Americans suffer from arthritis.\textsuperscript{2} In 2004 alone, more than 1,100,000 surgical procedures involving partial excision of bone, bone grafting and inpatient fracture repair were performed with an estimated total cost of more than $5 billion.\textsuperscript{18} The worldwide incidence of bone disorders and conditions is estimated to double by 2020.\textsuperscript{24} However, the current treatment for critical-sized and non-union bone defects still remains to be autograft or allograft repairs, which are limited in availability, are difficult to shape, and require additional surgeries and operative time in order to harvest the graft, which highlights the urgent necessity to find alternative substitutes that can enhance the quality of patients’ lives.\textsuperscript{25}

The bone substitute material should have the ability to promote differentiation of immature progenitor cells toward an osteoblastic lineage (osteoinduction), encourage the ingrowth of surrounding bone (osteocoduction), and integrate into the surrounding tissue (osseointegration).\textsuperscript{18,24} Compared with the limitations of currently used autograft or allograft bone, synthetic biodegradable polymers have attracted increased attention in
tissue-engineering applications as a result of their many advantages including non-toxic degradation products, tunable mechanical properties, controllable microstructure and precise degradation kinetics that can be tailored through varied composition and fabrication techniques.\textsuperscript{26-28}

2.2 Introduction to unsaturated biodegradable synthetic polymers such as PPF

Unsaturated biodegradable synthetic polymers are used to fill cavities with complex geometries since they bond well with tissue, can be injected with growth factors to promote cell growth, and can be precisely pre-fabricated into complex shapes containing appropriate pore structures designed from micro-CT images of patient’s defect.\textsuperscript{29} Poly(propylene fumarate), an unsaturated linear polyester, is a biodegradable synthetic polymer in the polyester family. The degradation products of PPF are fumaric acid and 1,2-propanediol, which are both resorbable in the human body,\textsuperscript{3} and PPF has been widely studied during the three decades to promote its application in bone-tissue engineering. At low molecular mass, PPF is a viscous liquid at room temperature and can be radically cured thermally or photo-crosslinked with precursor monomer or other vinyl monomers.\textsuperscript{30-31} In comparison with poly(methyl methacrylate) (PMMA) cement with a maximum release temperature of 94 °C during curing, the maximum temperature of curing PPF varies from 38 to 48 °C with curing times ranging from 1 to 121 min.\textsuperscript{4} PPF undergoes bulk degradation and the degradation time is found to be dependent on polymer structure and compositions with no deleterious long-term inflammatory response when implanted subcutaneously in rats.\textsuperscript{4} Based on the above analysis, PPF has the potential to be tailored to specific applications in bone-tissue engineering.
2.3 Introduction to the difference between a step growth polymerization and chain growth polymerization mechanism

The distinction between "step-growth polymerization" and "chain-growth polymerization" was introduced by Paul Flory in 1953, and refers to the reaction mechanism, respectively.

![Schemes of step growth and chain growth polymerization](image)

As shown in Figure 1, step-growth polymerizations proceed by the only one elementary reaction between the functional groups of reactants. The length of the polymer molecules increases at a relatively slow pace in such polymerizations. That reaction can happen between any of the different-sized species, which makes it difficult to control the molecular mass distribution in such reactions.

In a chain-growth polymerization method, an initiator is used to generate an initiator species R* with a reactive center, which is called the initiation step. The reactive center could be either a radical or an ion depending on the type of initiators. Only monomers can react with the reactive centers, in the chain propagation step, which enables the control of molecular mass distribution.
2.4 Introduction to traditional methods for polymerization of PPF

A number of pathways have been used to prepare PPF, and each has resulted in different polymer properties.\textsuperscript{3} In 1988, Sanderson produced PPF by transesterification of diethyl fumarate and propylene glycol with para-toluene sulfonic acid as the initiator at 250 °C (Scheme 1). The yield in this process was approximately 35%. In 1989, Gerhart and Hayes prepared PPF through a condensation reaction of propylene glycol and fumaric acid, heated gradually from 145 °C to 180 °C (Scheme 2).\textsuperscript{23} Poly(propylene fumarate) diol with $M_n$ in the range of 500 Da to 1200 Da and molecular mass distributions from 3 to 4 are typically prepared by this method.\textsuperscript{3,4} Also in 1989, Domb prepared PPF through several reaction methods. The first method included preparing the bis-(hydroxylpropyl) fumarate trimer and propylene bis(hydrogen maleate) trimer by reacting propylene glycol/fumaric acid, and maleic anhydride/propylene glycol, respectively.\textsuperscript{3,4} The two trimers were then reacted at 180 °C to produce PPF. The bis-(hydroxypropyl) fumarate trimer can also be prepared at ambient temperature by reacting fumaryl chloride and propylene glycol. The purified trimer is reacted at 160 °C in the presence of the transesterification initiator antimony trioxide to produce PPF (Scheme 3). PPF with $M_n$ in the range of 750 Da to 1500 Da is prepared by this method and its molecular mass distribution ranged from 1.7 to 3. In 1994, Yaszemski synthesized PPF through an initial reaction of fumaryl chloride and propylene glycol at room temperature to produce bis(hydroxypropyl fumarate). This product underwent transesterification at 160 °C under vacuum with antimony trioxide as a initiator to yield PPF (Scheme 4). By varying polymerization time from 4 to 24 hours, $M_n$ of PPF in the range of 850 Da to 1500 Da and molecular mass distribution ranging from 1.6 to 3 were synthesized.\textsuperscript{3,4}
Clearly, traditional methods to synthesize PPF require high energy input, high vacuum and long reaction times, and they generally result in low yield with uncontrolled molecular mass distribution, conjugate-addition side reactions, and unwanted cross-linking, all of which greatly influence the mechanical properties and degradation rates of the final product.\textsuperscript{10,32}

\begin{center}
\begin{tabular}{c}
\includegraphics[width=\textwidth]{polypropylene_fumarate_synthesis}
\end{tabular}
\end{center}

Scheme 1. Poly(propylene fumarate) synthesis method by Sanderson
Scheme 2. Poly(propylene fumarate) synthesis method by Gerhart and Hayes

Scheme 3. Poly(propylene fumarate) synthesis method by Domb
2.5 Introduction to a novel chain-growth polymerization of PPM and PPF

Based on the above-listed limitations of traditional PPF synthetic routes, there is an obvious need to develop a versatile and mild synthetic route to functionalize unsaturated PPF in order to enhance the properties of the polymer and expand its applications in bone-tissue engineering.

Recently, DiCiccio and Coates have successfully synthesized PPF with a high $M_n$ above 17 kDa, narrow molecular mass distribution around 1.6 and low ether linkage ($< 1\%$) using a chain-growth mechanism with mild reaction conditions. In their method, maleate anhydride and epoxide are polymerized through a ring-opening copolymerization using chromium Salen as a initiator at 45 °C, and the poly(propylene maleate) produced

Scheme 4. Poly(propylene fumarate) synthesis method by Yaszemski
is isomerized using diethyl amine at room temperature for 16 hours to yield poly(propylene fumarate).

Compared with traditional synthetic methods, the chain-growth mechanism provides PPF with better molecular properties (like a narrower molecular mass distribution), and the reaction is more reproducible, making it possible to synthesize PPF with controlled properties for further mechanical, toxicity and degradation tests and for large-scale production in manufacturing.

2.6 Introduction to three dimensional (3D) printing

Additive manufacturing, dating back to the middle 1980s, has the potential to revolutionalize regenerative medicine and fundamentally alter how surgeons approach complicated reconstructive efforts in craniomaxillofacial, orthopaedic trauma and cancer, because of the faster processing of products. Bone tissue engineering has taken the advantage of additive manufacturing in scaffolds fabrication in recent years. Among those additive manufacturing methods, three dimensional (3D) printing has gained more and more popularity because scaffolds can be directly printed with designed shapes, geometries and porous structure (such as porosity, pore size, and pore volume). Those parameters, which cannot be controlled through traditional porous bone scaffolds fabrication methods (such as extrusion, solvent casting, chemical/gas foaming, particle/salt leaching, and so on), are crucial in cell-material interactions for bone repair and regeneration. While numerous 3D printing methods have been reported, photochemical-based printing methods in particular have shown potential in producing reliable, high-fidelity scaffolds from medical imaging reconstructions. Advances in
image projecting in continuous digital light processing (cDLP) based methods have enabled complicated geometric design coupled with very fine features. 24, 39-41

2.7 Objectives, motivation, innovation and hypothesis

This thesis summarizes our efforts to synthesize PPF oligomers through a chain-growth mechanism. We hypothesize that the chain-growth polymerization will provide PPF with well-controlled properties including molecular mass, narrow molecular mass distribution, consistent degradation kinetics, and reproducibility over the traditional PPF synthetic methods. This would advance and accelerate the application of PPF as a 3D-printable biodegradable synthetic polymer for clinical bone tissue engineering applications.
3.1 Materials and analytical methods

Unless otherwise set forth herein, the materials used are those set forth in Table 1, below.

Table 1. Materials/reagents used

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
<th>Purity</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maleic Anhydride (MAn)</td>
<td>( \text{C}_4\text{H}_2\text{O}_3 )</td>
<td>99%</td>
<td>Fluka</td>
</tr>
<tr>
<td>Propylene Oxide (PO)</td>
<td>( \text{C}_3\text{H}_6\text{O} )</td>
<td>99.5%</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Magnesium Ethoxide</td>
<td>( \text{Mg(OEt)}_2 )</td>
<td>98%</td>
<td>Aldrich</td>
</tr>
<tr>
<td>Diethylamine</td>
<td>( \text{C}<em>4\text{H}</em>{10}\text{N} )</td>
<td>99%, extra pure</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>HCl</td>
<td>ACS, 37%</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Toluene (Tol)</td>
<td>( \text{C}_7\text{H}_8 )</td>
<td>anhydrous, 99.8%</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Tetrahydrofuran (THF)</td>
<td>( \text{C}_4\text{H}_8\text{O} )</td>
<td>GR ACS</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Chloroform</td>
<td>( \text{CHCl}_3 )</td>
<td>GR ACS</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Hexane</td>
<td>( \text{C}<em>6\text{H}</em>{12} )</td>
<td>98.5%</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Sodium Phosphate Dibasic</td>
<td>( \text{Na}_2\text{HPO}_4 )</td>
<td>BioXtra, ( \geq )99.0%</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Sodium Phosphate Monobasic</td>
<td>( \text{NaH}_2\text{PO}_4 )</td>
<td>BioXtra, ( \geq )99.0%</td>
<td>Sigma-Aldrich</td>
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Unless otherwise set forth herein, the analytical methods described herein were performed using the equipment and conditions set forth in Table 2, below.

### Table 2. Analytical methods/equipment used

<table>
<thead>
<tr>
<th>Analytical Methods</th>
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<tbody>
<tr>
<td>$^1$H NMR spectroscopy</td>
<td>Varian Mercury 300 Spectra</td>
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<tr>
<td>$^{13}$C NMR spectroscopy</td>
<td>Varian Mercury 300 Spectra</td>
</tr>
<tr>
<td>Ubbeohde viscometer</td>
<td>Cannon State College, PA, 16804, 0016, USA, 50 L79</td>
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<tr>
<td>UV-Visible spectrophotometry</td>
<td>HP Hewlett Packard 8453 UV-Vis Instrument</td>
</tr>
<tr>
<td>FTIR (Fourier Transform Infrared Spectroscopy)</td>
<td>Excalibur Spectrometer Manual (FTS 3000 and FTS 4000 Series)</td>
</tr>
<tr>
<td>DSC (Differential Scanning Calorimetry)</td>
<td>TA instrument DSC Q2000</td>
</tr>
<tr>
<td>SEC (Size Exclusion Chromatography)</td>
<td>GPCmax VE 2011 (with Waters 2414 Reflective Index Detector)</td>
</tr>
<tr>
<td>MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization Time-of-Flight)</td>
<td>Bruker UltraFlex III MALDI tandem Time-of-Flight (TOF/TOF) mass spectrometer (Bruker Daltonics, Billerica, MA, USA) equipped with a Nd: YAG laser emitting at 355 nm</td>
</tr>
</tbody>
</table>

3.2 Synthesis

We aim to achieve low molecular mass PPF with well-defined properties for 3D printing (such as continuous dynamic light processing) to improve the feasibility for using of PPF in bone tissue engineering by utilizing a chain-growth ring-opening and varying the conditions including: time, monomer-to-initiator ratio, and temperature.
The synthesis contains two steps as shown in Scheme 5 and Scheme 6 below.

**Scheme 5.** Polymerization of poly(maleic anhydride-co-propylene oxide).

**Scheme 6.** Isomerization of poly(maleic anhydride-co-propylene oxide).

3.2.1 Representative synthesis of flowable PPM

MAAn (7.00 g, 71.4 mmol) and PO (5.00 mL, 71.4 mmol) were dissolved in 10.0 mL toluene in a 100 mL round-bottom flask at room temperature under nitrogen atmosphere. After all monomers were dissolved in toluene by magnetic stirring, 67 mg (0.585 mmol) Mg(OEt)$_2$ were added to the mixture and the flask was moved into a silicone oil bath equipped with a water reflux condenser to start polymerization at 80 °C for each study time (45h, 18h, 6h, 3h and 2h). After polymerization, the system was cooled to room temperature under nitrogen protection and then diluted with CHCl$_3$ or ethyl acetate, followed by several washes with 1.2 mmol HCl solution to quench the organic compound completely. The organic layer was dripped into hexane, and the precipitated polymer mixture was re-dissolved in a minimal amount of CHCl$_3$, then evaporated by rotary
evaporation. Poly(maleic anhydride-co-propylene oxide) was obtained after drying the product under vacuum overnight at room temperature to remove all volatiles.

3.2.2 Representative isomerization of flowable PPM

Diethylamine (0.1 equivalent) was added to poly(maleic anhydride-co-propylene oxide) after dissolving the polymer in CHCl₃ in a round-bottom flask at 55 °C for about 20 hours under a nitrogen atmosphere. The mixture was then concentrated by rotary evaporation and washed with phosphate buffer saline solution (0.5 M, pH = 4.0) to remove the diethylamine. The organic layer was then precipitated into hexane several times to remove impurities. The precipitate was collected and kept in vacuum overnight at room temperature to remove all volatiles.

3.2.3 Representative synthesis of PPM in kinetic study to generate higher molecular mass PPF for 3D printing

MA n (70.1 g, 714 mmol) and PO (50.0 mL, 714 mmol) were dissolved in 100 mL of toluene in a 500 mL round-bottom flask at room temperature under a nitrogen atmosphere. After all of the monomers were dissolved in toluene with constant magnetic stirring, 0.272 g (2.38 mmol, molar ratio of MAn/Mg(OEt)₂ = 300:1, Mg(OEt)₂ was added to the mixture and the flask was moved into a silicone oil bath equipped with a reflux condenser to initiate the polymerization at 80 °C. The polymerization was allowed to proceed and aliquots were taken at defined time points (3 h, 6 h, 18 h, 24 h and 48 h). Similar studies incorporating molar ratio of MAn/Mg(OEt)₂ = 200:1, 100:1 were also
conducted. After the designated polymerization time, the system was cooled to ambient temperature under nitrogen, and subjected to reduced pressure conditions to remove all volatile materials. The residue was diluted with chloroform (CHCl₃), and washed with water containing trace amount of hydrochloric acid (HCl) to remove the inorganic Mg(OEt)₂ compound. The organic layer was dripped into hexane followed by rotary evaporation, and the precipitated polymer mixture was re-dissolved in a minimal amount of CHCl₃. The residue was then concentrated by rotary evaporation. Poly(maleic anhydride-co-propylene oxide) was obtained after drying the product under vacuum overnight at ambient temperature to remove all volatiles, and then the molecular mass and mass distribution properties were characterized by SEC at each time point after ¹H NMR characterization.

3.2.4 Large batch PPF synthesis (Mₙ=1.27 kDa)

Several large batches of PPF were synthesized based on the following procedures for 3D printing tests.

3.2.4.1 Representative large batch synthesis of PPM

MAn (2.856 mol) and PO (2.856 mol) were dissolved in toluene (400 mL) in a 2 L round-bottom flask at ambient temperature under nitrogen. After all monomers were dissolved in toluene with magnetic stirring, Mg(OEt)₂ (119 mmol; molar ratio of MAn/Mg(OEt)₂ = 24:1) was added to the mixture and the flask was moved into a silicone oil bath equipped with a water reflux condenser to start polymerization at 80 °C for 40 h. After the designated polymerization time, the system was cooled to room temperature
under nitrogen, evaporated to remove all volatiles and then was diluted with CHCl₃, washed with water containing trace amount of HCl to remove the inorganic compound. The organic layer was dripped into hexane after rotary evaporation, and the precipitated polymer mixture was re-dissolved in a minimal amount of CHCl₃ then concentrated by rotary evaporation. Poly(maleic anhydride-co-propylene oxide) was obtained after drying the product under vacuum overnight at room temperature to remove all volatiles, and the molecular mass and mass distribution properties were characterized by SEC after ¹H NMR characterization (SEC: Mₙ: 1200 Da, Mₚ: 1600 Da; ¹H NMR please see Figure 2).

3.2.4.2 Representative large batch isomerization of PPM

Diethylamine (0.15 equivalent) was added to poly(maleic anhydride-co-propylene oxide) after dissolving the polymer in CHCl₃ (1 mol/L) in 2 L a round-bottomed flask equipped with a water reflux condenser to start isomerization at 55 °C for 20 h under nitrogen. The mixture was then concentrated by rotary evaporation and washed with phosphate buffer saline solution (0.5 M, pH = 6) to remove the diethylamine. The organic layer was collected after separation and sodium sulfate was added into the organic layer to remove water. The concentrated organic layer was then precipitated into hexane several times to remove impurities. The precipitate was collected and kept in vacuum overnight at room temperature to remove all volatiles (Characterization in Figure 2 for ¹H NMR; SEC: Mₙ : 1270 Da, Mₚ: 1710 Da).
3.2.4.3 Large batch synthesis of PPF polymers at 5 Mₙ levels (Mₙ=0.7 kDa, 1.27 kDa, 1.86 kDa, 2.45 kDa, and 3.16 kDa)

Table 3. Large batch synthesis of PPF polymers at 5 Mₙ levels

<table>
<thead>
<tr>
<th>PPF #</th>
<th>MAn or PO (mol)</th>
<th>Monomer/Toluene (mol/L)</th>
<th>Molar ratio of Monomer/Mg(OEt)₂</th>
<th>t (h)</th>
<th>T (°C)</th>
<th>Molar ratio of PPM/DEA</th>
<th>PPM/CHCl₃ (mol/L)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.962</td>
<td>7.14</td>
<td>5.7</td>
<td>~6</td>
<td>r.t.</td>
<td>6.67</td>
<td>1</td>
<td>50</td>
<td>16</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>2.856</td>
<td>7.14</td>
<td>24</td>
<td>40</td>
<td>80</td>
<td>6.67</td>
<td>1</td>
<td>60</td>
<td>16</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>2.856</td>
<td>7.14</td>
<td>48</td>
<td>40</td>
<td>80</td>
<td>10</td>
<td>1</td>
<td>60</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>2.856</td>
<td>7.14</td>
<td>200</td>
<td>42</td>
<td>80</td>
<td>10</td>
<td>1</td>
<td>60</td>
<td>22</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>0.714</td>
<td>7.14</td>
<td>200</td>
<td>138</td>
<td>80</td>
<td>6.67</td>
<td>1</td>
<td>55</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>

PPF polymers having Mₙ of 0.7 kDa, 1.27 kDa, 1.86 kDa, 2.45 kDa, and 3.16 kDa were synthesized using the large batch PPF procedures described above in 3.2.4 using the polymerization parameters set forth in Table 3.

3.3 Characterization

The positions and relative intensities of each characteristic peak or band in nuclear magnetic resonance proton spectra (¹H NMR), nuclear magnetic resonance carbon spectra (¹³C NMR), matrix-assisted laser desorption/ionization time-of-flight, FTIR and UV-Vis spectra were used to prove the chemical structures of the products. ¹H NMR and ¹³C NMR were recorded with a Varian NMRS 300 MHz instrument. Deuterated chloroform (CDCl₃) was used as solvent. Chemical shifts, δ (ppm), were referenced to the residual proton signal of the solvent. Chemical structures of PPF samples were further analyzed by a Bruker Ultraflex III MALDI-ToF/ToF mass spectrometer. The samples
were dissolved in CHCl₃ at a final concentration of 10 mg/mL. The sandwich method was used with trans-2-[3-(4-tert-Butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) as matrix and NaTFA as salt 10:1. FTIR spectra were recorded for film samples cast on potassium bromide (KBr) disks from CHCl₃ solution by an Excalibur Spectrometer (FTS 3000 and FTS 4000 Series) with a wavenumber range from 400 cm⁻¹ to 4000 cm⁻¹. UV-visible spectra were obtained by dilute solutions of polymers in acetonitrile using a HP Hewlett Packard 8453 UV-Vis instrument with a wavelength range from 190 nm to 700 nm.

The molecular mass and molecular mass distribution of each polymer was determined by SEC. SEC analysis in THF at 35 °C was performed on a Viscotek GPCmax VE 2011 GPC Solvent Sample Module with a Waters 2414 Reflective Index Detector, with polystyrene standards of narrow molecular mass distributions (with Mₘ (g/mol): 580, 1280, 3180, 4910, 10440, 21810, 51150, 96000, 230900).

The thermal properties of PPF were characterized by DSC using TA Q2000 Differential Scanning Calorimeter from -100 °C to 100 °C at a scanning rate of 10 °C /min in order to obtain the glass transition temperature (T_g).

The intrinsic viscosity of PPF samples at five molecular mass levels were tested in THF using an Ubbelohde viscometer at 35 °C.
CHAPTER IV
RESULTS AND DISCUSSION

4.1 $^1$H NMR of PPM and PPF

$^1$H NMR of poly(maleic anhydride-co-propylene oxide):

$^1$H NMR (300 MHz, Chloroform-$d$ $\delta$ ppm 1.13 - 1.41 (d, 3H, OCH$_2$CH(CH$_3$)O), 2.05 (s, 1H, solvent), 4.04 - 4.36 (m, 2H, OCH$_2$CH(CH$_3$)O),
5.23 - 5.30 (m, 1H, OCH\textsubscript{2}CH(CH\textsubscript{3})O), 6.24 - 6.42 (m, 2H, CH=CH (cis-configuration)).

From the characteristic signals of each peak of the orange spectrum in Figure 4.1, it was determined that the synthesis of PPM was successful. The residual solvent used in the purification step can be further removed with longer vacuum time or in vacuum oven.

\textsuperscript{1}H NMR of poly(propylene fumarate):
\textsuperscript{1}H NMR (300 MHz, Chloroform-\textit{d}) \( \delta \) ppm 1.11-1.43 (d, 3H, OCH\textsubscript{2}CH(CH\textsubscript{3})O), 4.09-4.39 (m, 2H, OCH\textsubscript{2}CH(CH\textsubscript{3})O), 5.21-5.35 (m, 1H, OCH\textsubscript{2}CH(CH\textsubscript{3})O), 6.83-6.91 (m, 2H, CH=CH (trans-configuration)).

From the characteristic signals of each proton in the blue spectrum in Figure 2, it was clear that PPM was successfully isomerized to PPF since almost all the \textit{cis}-configuration protons (peaks labeled with orange a, a’) on C=C bonds had been transferred into the \textit{trans}-configuration protons (peaks labeled with blue a, a’) on C=C bonds.
4.2 $^{13}$C NMR of PPM and PPF

$^{13}$C NMR of poly(maleic anhydride-co-propylene oxide):

$^{13}$C NMR (300 MHz, Chloroform-$d$) $\delta$ ppm 164.64, 164.63, 164.35; 130.42, 129.92, 129.78, 129.25; 69.15; 66.37; 16.19.

$^{13}$C NMR of poly(propylene fumarate):

$^{13}$C NMR (300 MHz, Chloroform-$d$) $\delta$ ppm 164.36, 164.35, 164.04, 163.98; 134.01, 133.27; 69.26; 66.58; 16.34.

The spectra in Figure 3 showed characteristic signals of each carbon on PPM and PPF polymer backbones that further demonstrated the successful synthesis of PPM and PPF.

Figure 3. $^{13}$C NMR of PPM and PPF
4.3 Size exclusion chromatography

SEC was used to obtain the number molecular mass ($M_n$), peak molecular mass ($M_p$), molecular mass distribution ($D_m$) of PPM and PPF.

4.3.1 Relationship between polymerization time, number average molecular mass ($M_n$), and molecular mass distribution ($D_m$) in flowable PPM synthesis

![Graph showing the relationship between polymerization time, number average molecular mass ($M_n$), and molecular mass distribution ($D_m$) in flowable PPM synthesis.]

Figure 4. The relationship between polymerization time, number average molecular mass ($M_n$), and molecular mass distribution ($D_m$) in flowable PPM synthesis

As shown in Figure 4, when polymerization time decreased, $M_n$ decreased and the state of the polymer at room temperature changed from solid to liquid. At the same time, when the polymerization time decreased, the molecular mass distribution increased slightly; a result attributed to the fact that at a lower $M_n$ level, adding or removing one repeat unit had a significant influence on the molecular mass distribution. In short, a polymerization time of 2h produced PPM with $M_n = 570$ Da, which demonstrated flowability at room temperature.
4.3.2 Relationship between yield and $M_n$ in flowable PPM synthesis

![Graph showing the relationship between yield and $M_n$](image)

Figure 5. Relationship between yield and $M_n$ in flowable PPM synthesis

As shown in Figure 5, shorter polymerization time lowered yield and also the $M_n$ of PPM. On the other hand, the relationship between yield and $M_n$ followed the expected relationship for a chain-growth mechanism because of the fact that in a chain-growth polymerization mechanism, longer reaction time contributed to higher yield with a slight increase in molecular mass. From the blue dots, after 18h, the yield increased slower as polymerization time increased. This indicated a slower relative polymerization rate resulting from higher viscosity, because competition between chain propagation and depropagation occurred at higher yield.
4.3.3 Relationship between monomer-to-initiator molar ratio and $M_n$, peak molecular $M_p$ and yield in flowable PPM synthesis

Table 4. Relationship between monomer-to-initiator molar ratio and $M_n$, $M_p$ and yield in flowable PPM synthesis

<table>
<thead>
<tr>
<th>Monomer-to-initiator molar ratio</th>
<th>122:1</th>
<th>12.2:1</th>
<th>5.8:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_n$ (Da)</td>
<td>630</td>
<td>560</td>
<td>550</td>
</tr>
<tr>
<td>$M_p$ (Da)</td>
<td>890</td>
<td>670</td>
<td>650</td>
</tr>
<tr>
<td>$D_m$</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>3</td>
<td>26</td>
<td>59</td>
</tr>
</tbody>
</table>

As shown in Table 4, to obtain PPM with similar molecular mass, a lower monomer-to-initiator ratio (e.g. 5.8:1) resulted in higher yield. This indicated more monomers can be initiated at the same time at a lower monomer-to-initiator feed ratio when other synthesis conditions were kept the same. As such, a ratio of 5.8 was used for further study since a lower the molecular mass distribution gives better control of mechanical properties and degradation kinetics in the resulting materials.

4.3.4 Relationship between polymerization temperature and molecular mass properties in flowable PPM synthesis

Table 5. Relationship between polymerization temperature and molecular mass (with molecular mass distribution) in flowable PPM synthesis

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_n$ (Da)</td>
<td>550</td>
<td>650</td>
<td>770</td>
</tr>
<tr>
<td>$M_p$ (Da)</td>
<td>650</td>
<td>900</td>
<td>910</td>
</tr>
<tr>
<td>$D_m$</td>
<td>1.2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>
As shown in Table 5, when the polymerization temperature increased, $M_n$ increased with a broader molecular mass distribution. The $M_n$ increased when polymerization time increased because, at higher temperature, the propagation rate was larger and generated longer growing polymer chains. The molecular mass distribution increased because there was a rapid exchange reaction of active species to monomers at higher temperature and caused a competition between chain propagation reaction and exchange reaction of active species into monomers. Since a narrower distribution was desired to achieve better control of polymer properties like mechanical property and degradation rate, a polymerization temperature of 80 °C was used for further study.

However, the flowable PPF with $M_n$ around 500 Da to 700 Da could not be 3D printed into solid scaffolds within a specific printing time range. It was assumed this resulted from the relatively low molecular mass; thus, a new kinetic study was performed to increase the molecular mass of PPF by increasing the monomer-to-initiator ratio as discussed below to target the ideal 3D printing requirement.
4.3.5 \( M_n, M_p, \) PDI or \( D_m \) as a function of reaction time for PPM intermediates using molar ratios of monomer-to-initiator of 100:1, 200:1, and 300:1.

In Figure 6, clearly, \( M_n \) and \( M_p \) increased and the state of the polymer at room temperature changed from flowable liquid to sticky solid as the polymerization time increased from 3 h to 48 h. The narrow error bars for \( M_n, M_p \) and \( D_m \) demonstrated the reproducibility of this reaction. At the same time, the molecular mass distribution of all reactions was around 1.6, showing more precise control over molecular mass distribution compared to a step-growth mechanism where \( D_m \) is usually 2 or higher. In the future, this kinetic study can be used for large batch PPF synthesis to target specific molecular mass properties.

PPF with \( M_n \) range from 1200 Da to 1900 Da have been 3D printed successfully. (Figures of scaffolds are shown in Figure 14)
4.4 FTIR of PPM and PPF

In the PPM spectra, the peak at 1715-1740 cm\(^{-1}\) represented the unsaturated C=O (ester) stretch, which demonstrated the formation of the ester bond in the PPM synthesis process. Peaks at 2988 cm\(^{-1}\), 1642 cm\(^{-1}\), 1162 cm\(^{-1}\), 814 cm\(^{-1}\) showed C-H stretch, C=C (alkene) stretch, O-C (alkoxy) stretch, and C-H (cis alkene) bend (broad) patterns separately. In the spectra of PPF, the peak at 1715-1740 cm\(^{-1}\) represented the unsaturated C=O (ester) stretch peak. Peaks at 2986 cm\(^{-1}\), 1646 cm\(^{-1}\), 1156 cm\(^{-1}\), 984 cm\(^{-1}\) were C-H stretch, C=C (alkene) stretch, O-C (alkoxy) stretch and C-H (trans alkene) bend patterns respectively. The appearance of C-H (trans alkene) bending at 960-990 cm\(^{-1}\) in the blue curve demonstrated the isomerization process. These characteristic signals supported the successful synthesis of PPM and isomerization of PPM to PPF.
4.5 UV-Vis of PPM and PPF

In the UV-Vis spectrum of PPM, there was a strong absorbance at the wavelength of 192 nm, which corresponded to the $\pi - \pi^*$ transition of cis-configuration C=C bonds in PPM. In the spectrum of PPF, there was a strong absorbance at a wavelength of 210 nm, which was the $\pi - \pi^*$ transition of trans-configuration C=C bond in PPF. The shift may be a result of the higher steric hindrance in the cis-configuration C=C bonds, because higher steric hindrance caused lower conjugation and an increasing amount of energy was required for the $\pi - \pi^*$ transition to occur. This resulted in a shorter absorption wavelength, as seen in the UV-Vis spectra (Figure 8).
4.6 DSC characterization of PPM and PPF

DSC was used to obtain the glass transition temperature of PPM and PPF (PPM : $M_n$ 410 Da, $D_m$ 1.3; Corresponding PPF: $M_n$ 490 Da, $D_m$ 1.3). As shown in Figure 9, the $T_g$ of cis-configuration PPM was -28.1 °C and the $T_g$ of trans-configuration PPF was -19.1 °C. The difference in $T_g$ may be the result of the loose packing of molecules in the cis-configuration PPM, because of the steric bulk contributed by C=O groups on the same side of the C=C bond. This circumstance increased the free volume of molecular chains, resulting less energy to make a transition from the glass phase to the rubbery phase. The $T_g$ of cis-configuration PPM is lower than that of trans-configuration PPF, which also helped to prove the isomerization process from cis-configuration PPM to trans-configuration PPF.

Figure 9. DSC characterization of PPM and PPF
4.7 MALDI-TOF mass spectrograph of representative PPF samples in Table 6

Despite the above characterizations, Matrix-Assisted Laser Desorption/Ionization Time-of-Flight approach was used to further prove the possible molecular structures of PPF samples as discussed below.

4.7.1 MALDI-TOF mass spectrograph of representative PPF (sample 2 in Table 6)

![Mass spectrograph of PPF sample 2 in Table 6](image)

Figure 10. Mass spectrograph of PPF sample 2 in Table 6

There were three distributions which corresponded to a variety of end groups in the mass spectrograph of PPF sample 2 in Figure 10. These chemical structures were shown in Figure 11 after analysis.
The repeat unit for PPF sample 2 in Table 6 also showed the possible end group chemistries which corresponded to the individual peaks in the distribution depicted in Figure 11. The mass spectra data confirmed the successful synthesis of PPF.

Figure 11. Zoomed-in mass spectrograph of PPF sample 2 in Table 6
4.7.2 MALDI-TOF mass spectrograph of representative PPF (sample 3 in Table 6)

In Figure 12, there were three distributions which corresponded to a variety of end groups in the mass spectrograph of PPF sample 3. These chemical structures were shown in Figure 13 after analysis.

Figure 12. Mass spectrograph of PPF sample 3 in Table 6
The repeat unit for PPF sample 3 in Table 6 also showed the possible end group chemistries which corresponded to the individual peaks in the distribution depicted in and Figure 13. The mass spectra data confirmed the successful synthesis of PPF.

Figure 13. Zoomed-in Mass spectrograph of PPF sample 3 in Table 6

4.8 Physical properties of representative PPF samples at 5 Mₙ levels

As shown in Table 6, when the number molecular mass of PPF increased from 700 Da to 3160 Da, the glass transition temperature of PPF increased from -25 °C to 12 °C and the intrinsic viscosity of PPF at 35 °C increases from 0.00288±0.00009 dL/g to
0.00780±0.00022 dL/g. This suggested that the smaller molecular mass, the more flexible the molecular chain was, and the lower the glass transition temperature and the lower the intrinsic viscosity. At room temperature, PPF sample 1 had flow property, PPF sample 2 and PPF sample 3 were sticky liquids, and PPF sample 4 and PPF sample 5 were sticky solids.

Table 6. Physical properties of representative PPF samples at 5 M_n levels

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>M_n (Da)</th>
<th>M_p (Da)</th>
<th>D_m</th>
<th>T_g (°C)</th>
<th>[η] (dL/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>700</td>
<td>980</td>
<td>1.6</td>
<td>-25</td>
<td>0.00288±0.00009</td>
</tr>
<tr>
<td>2</td>
<td>1270</td>
<td>1710</td>
<td>1.5</td>
<td>-3</td>
<td>0.00490±0.00001</td>
</tr>
<tr>
<td>3</td>
<td>1860</td>
<td>2570</td>
<td>1.6</td>
<td>0</td>
<td>0.00529±0.00013</td>
</tr>
<tr>
<td>4</td>
<td>2450</td>
<td>3190</td>
<td>1.6</td>
<td>6</td>
<td>0.00622±0.00006</td>
</tr>
<tr>
<td>5</td>
<td>3160</td>
<td>5970</td>
<td>1.7</td>
<td>12</td>
<td>0.00780±0.00022</td>
</tr>
</tbody>
</table>
4.9 3D printed PPF scaffold (collaborator)

As shown in Figure 14, the PPF sample 2 and PPF sample 3 have been successfully 3D printed with the helical sleeve structure (2.75 mm OD, 2.5 mm ID, 6 mm height, 350 micron pore size) using a continuous Digital Light Processing (cDLP) method.

Figure 14. 3D printed PPF Scaffold
In this work, poly(propylene fumarate) (PPF), an unsaturated biodegradable synthetic material, with naturally occurring degradation products, has been reproducibly synthesized through a ring-opening copolymerization method using a chain-growth mechanism. $^1$H NMR and $^{13}$C NMR characterization showed the successful synthesis of PPM and PPF. UV-Vis spectrophotometry and FTIR were also used to support the conversion of PPM to PPF. The confirmed repeat unit of PPF and the end-groups analysis performed using MALDI-TOF mass spectrometer characterization further indicated the successful synthesis of PPF. SEC was used to target the molecular mass of flowable PPF at the initial stage of this project and to set up the molecular mass properties as a function of polymerization time in kinetic studies. The narrow molecular mass distribution and reproducible molecular mass properties of PPM showed in SEC characterization demonstrated that the goal of precise control in molecular mass properties of PPF was achieved via a chain-growth ring opening polymerization method. It was also demonstrated PPF with number molecular mass ($M_n$) above 1 kDa, can be 3D printed. PPF samples at five individual $M_n$ levels (from 700 Da to 3160 Da) were synthesized and characterized by DSC to obtain the glass transition temperature and characterized by Ubbelohde viscometer to get the intrinsic viscosity.
To demonstrate the potential of PPF oligomers to be tailored to specific applications in bone tissue engineering, future work will be focused on 3D printing PPF oligomers at different molecular mass levels with subsequent mechanical tests, degradation kinetic studies *in vitro*, and cellular toxicity tests. Further functionalization of PPF oligomers with bioactive molecules to optimize *in vivo* bone repair and regeneration should also be considered.
CHAPTER VI
SUMMARY

This thesis outlined our efforts to synthesize poly(propylene fumarate) (PPF) oligomers, an unsaturated biodegradable synthetic material with naturally occurring degradation products, through a ring-opening copolymerization. The use of a chain-growth mechanism allowed for the production of PPF with well-defined molecular mass properties that meet the scaffold market demands in bone tissue engineering.

By adjusting the polymerization time, monomer-to-initiator ratio, and polymerization temperature, flowable PPF was synthesized in high yield with low molecular weight and narrow molecular mass distribution. Large batch synthesis of PPF at five molecular mass levels (0.7 kDa, 1.27 kDa, 1.86 kDa, 2.45 kDa, and 3.16 kDa) was performed and several of those materials have been successfully 3D printed. The chemical structures were characterized by $^1$H NMR, $^{13}$C NMR, FTIR and UV-Vis. MALDI-TOF mass spectrometer confirmed the repeat unit and the possible end-groups in PPF backbone. These characterization data have shown that PPF with controlled molecular mass and molecular mass distribution have been successfully synthesized.

Thermal properties of the PPF at different molecular mass level were studied by DSC and the corresponding intrinsic viscosity was tested in THF by Ubbelohde viscometer at 35 °C. Those physical properties are important to guide the PPF blend studies.
In short, using a chain-growth mechanism, PPF oligomers with well-controlled properties including molecular mass, molecular mass distribution, and reproducibility have been synthesized and characterized in this thesis. Rather than the traditional PPF synthesis methods, methods used in this project would advance and accelerate the application of PPF as 3D printable biodegradable synthetic polymer for clinical bone tissue engineering applications.
REFERENCES


