SYNTHESIS AND CHARACTERIZATION OF PHOTORESPONSIVE POLYESTERS
FOR IMPROVED MECHANICAL PROPERTIES AND EROSION PROPERTIES

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Master of Science

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SYNTHESIS AND CHARACTERIZATION OF PHOTORESPONSIVE POLYESTERS
FOR IMPROVED MECHANICAL PROPERTIES AND EROSION PROPERTIES

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Thesis

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ABSTRACT

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable copolymer with a tailored degradation rate, which has been widely used in biomaterials, such as screws, sutures and as the matrix of drug release devices. However, PLGA has slow a hydrolytic degradation rate and relatively low modulus, which might hamper its applications. In this study, photo-responsive molecule 2-(4-(2-hydroxyacetyl) phenoxy)acetic acid was introduced into PLGA, which can provide spatial and temporal control of degradation under UV irradiation. The rigid structure of the photo-responsive molecule can be utilized to enhance the thermal properties and mechanical properties of PLGA. On the other hand, the photodegradable nature of the polymer may enable the degradation product to be recycled into useful products.

Another work involves 2-hydroxy-1-(4-(3-hydroxypropoxy)phenyl)ethanone based photo-degradable copolymers for controlled drug release. In this work, the photo-responsive molecule was incorporated into polymers. Surface erosion of polymeric matrixes is advantageous for controlled drug delivery. The erosion property of this polymer will be tested by ellipsometry.
ACKNOWLEDGEMENTS

First of all, I would like to thank my advisor Dr. Abraham Joy for his help on my research work, including picking up the interesting research topic and giving the valuable advices for experiments. Besides, thank him for the encouragement on my courses.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF SCHEMES</td>
<td>xi</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Need for biodegradable polymers</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Common biodegradable polymers</td>
<td>1</td>
</tr>
<tr>
<td>1.3 Poly(lactic-co-glycolic acid) (PLGA)</td>
<td>7</td>
</tr>
<tr>
<td>1.4 Photoresponsive polymers</td>
<td>8</td>
</tr>
<tr>
<td>1.5 Stress-strain diagram</td>
<td>9</td>
</tr>
<tr>
<td>1.6 Abbreviations in the project</td>
<td>10</td>
</tr>
<tr>
<td>II. EXPERIMENTAL</td>
<td>12</td>
</tr>
<tr>
<td>2.1 Chemicals</td>
<td>12</td>
</tr>
<tr>
<td>2.2 Equipment</td>
<td>12</td>
</tr>
</tbody>
</table>
2.3 Synthesis of photoresponsive monomers and polymers ........................................ 13
  2.3.1 Introduction of DP9 and AJ5 .................................................................................. 13
  2.3.2 Synthesis of DP2 .................................................................................................. 14
  2.3.3 Synthesis of DP4 .................................................................................................. 15
  2.3.4 Synthesis of DP8 .................................................................................................. 15
  2.3.5 Synthesis of DP9 .................................................................................................. 16
  2.4 Synthesis of Photodegradable PLGA ....................................................................... 17
    2.4.1 Synthesis of pre-PLGA ......................................................................................... 17
    2.4.2 Synthesis of pre-PLGA under room temperature .................................................. 18
    2.4.3 Synthesis of photoresponsive PLGA0505 .......................................................... 19
    2.4.4 Synthesis of photoresponsive PLGA0703 .......................................................... 21
  III. CHARACTERIZATION .......................................................................................... 23
    3.1 Glass transition temperature and decomposition temperatures of polymers.......... 23
    3.2 Photoresponsive properties of photoresponsive PLGA in liquid phase ................. 23
    3.3 Fabrication of thin films ......................................................................................... 24
    3.4 Irradiation of thin films for different time periods ................................................... 24
    3.5 Stress-strain curves of photoresponsive PLGA ....................................................... 24
  IV. RESULTS AND DISCUSSION ............................................................................... 25
    4.1 Pre-polymer of PLGA .............................................................................................. 25
    4.2 Photodegradable PLGA ......................................................................................... 26
4.3 One-step synthesis of photodegradable PLGA ................................................................. 28
4.4 Glass transition temperature and decomposition temperatures of polymers ............29
4.5 Photoresponsive properties of photoresponsive PLGA in liquid phase ................. 30
4.6 Irradiation of thin films for different time periods ....................................................... 31
4.7 Stress-strain curves of photoresponsive PLGA ......................................................... 31

V. CONCLUSIONS ........................................................................................................... 35

VI. INTRODUCTION ......................................................................................................... 37

6.1 Controlled Drug Release Systems ........................................................................... 37
   6.1.1 Need for Controlled Drug Release systems ............................................................ 37
6.1.2 Methods to release drug ....................................................................................... 38
   6.1.3 Zero-order Release and Non zero-order Release ................................................... 40
6.2 Polymer Matrixes for Controlled Drug Release ....................................................... 41
   6.2.1 Common Biodegradable Polymers ..................................................................... 41
   6.2.2 Degradation Mechanism of Biodegradable polymers ....................................... 41
6.3 Photoresponsive polymers ....................................................................................... 42
6.4 Mimic of surface erosion with UV irradiation ......................................................... 42
6.5 Spin Coating ............................................................................................................. 43
6.6 Abbreviations in the project ..................................................................................... 43

VII. EXPERIMENTAL ....................................................................................................... 45

7.1 Chemicals .................................................................................................................... 45
7.2 Equipment ........................................................................................................ 45

7.3 Synthesis of photoresponsive monomers and polymerization ............................. 45

7.3.1 Synthesis of AJ2 .......................................................................................... 46

7.3.2 Synthesis of AJ3 .......................................................................................... 46

7.3.3 Synthesis of AJ4 .......................................................................................... 48

7.3.4 Synthesis of AJ5 .......................................................................................... 48

7.3.5 Synthesis of N,N-bis(2-hydroxyethyl)propionamide ...................................... 49

7.3.6 Synthesis of photoresponsive AJ5 copolymer .............................................. 50

7.4 Fabrication of thin films with spin coating ..................................................... 51

VIII. RESULTS AND DISCUSSION ......................................................................... 52

IX. CONCLUSIONS ................................................................................................. 54

REFERENCES ......................................................................................................... 55

APPENDIX ............................................................................................................... 57
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Summary of degradable polymers’ applications, advantages, disadvantages, degradation rate, and structure</td>
<td>2</td>
</tr>
<tr>
<td>1.2 Summary of enzymatically degradable polymers</td>
<td>4</td>
</tr>
<tr>
<td>1.3 RESOMER® Biodegradable Polymers: Poly(D,L-lactide-co-glycolide)</td>
<td>7</td>
</tr>
<tr>
<td>4.1 The relationship of reaction times and molecular weights of pre-polymers</td>
<td>26</td>
</tr>
<tr>
<td>4.2 Analysis of $^1$H NMR data of photodegradable PLGA from two-step method</td>
<td>27</td>
</tr>
<tr>
<td>4.3 Analysis of GPC data of photodegradable PLGA from two-step method</td>
<td>27</td>
</tr>
<tr>
<td>4.4 Analysis of $^1$H NMR data of two polymers</td>
<td>28</td>
</tr>
<tr>
<td>4.5 Analysis of GPC data of two polymers</td>
<td>28</td>
</tr>
<tr>
<td>4.6 Analysis of $^1$H NMR data of photodegradable PLGA from one-step synthesis</td>
<td>28</td>
</tr>
<tr>
<td>4.7 Analysis of GPC data of photodegradable PLGA from one-step synthesis</td>
<td>29</td>
</tr>
<tr>
<td>4.8 Glass transition temperatures and decomposition temperatures of polymers</td>
<td>29</td>
</tr>
<tr>
<td>4.9 The molecular weights of PLGA0703DP902 2g after different irradiation times</td>
<td>30</td>
</tr>
<tr>
<td>8.1 GPC data of AJ5 copolymer</td>
<td>52</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Water molecule breaks the hydrolytically labile bond to produce the products</td>
<td>2</td>
</tr>
<tr>
<td>1.2 Stress-strain curve for a brittle material</td>
<td>10</td>
</tr>
<tr>
<td>1.3 Stress-strain curves for ductile materials</td>
<td>10</td>
</tr>
<tr>
<td>4.1 Photoresponsive properties of photoresponsive PLGA in liquid phase</td>
<td>30</td>
</tr>
<tr>
<td>4.2 Photos of samples after irradiation</td>
<td>31</td>
</tr>
<tr>
<td>4.3 Stress-strain curve of PLGA0703DP902 2g after 0 minutes of irradiation</td>
<td>32</td>
</tr>
<tr>
<td>4.4 Stress-strain curve of PLGA0703DP902 2g after 10 minutes of irradiation</td>
<td>32</td>
</tr>
<tr>
<td>4.5 Stress-strain curve of PLGA0703DP902 2g after 20 minutes of irradiation</td>
<td>33</td>
</tr>
<tr>
<td>4.6 Stress-strain curve of PLGA0703DP902 2g</td>
<td>33</td>
</tr>
<tr>
<td>6.1 The impact of burst release, pulsatile release and controlled release on the therapeutic range</td>
<td>38</td>
</tr>
<tr>
<td>6.2 Coumarin-modified silica MCM-41 particles works as a photoswitched storage-release controlled release system</td>
<td>39</td>
</tr>
<tr>
<td>6.3 The two different mechanisms of degradation</td>
<td>42</td>
</tr>
<tr>
<td>6.4 Procedure of spin coating</td>
<td>43</td>
</tr>
<tr>
<td>8.1 GPC trace of AJ5 copolymer</td>
<td>52</td>
</tr>
</tbody>
</table>
## LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Rearrangement mechanism of DP9 or AJ5</td>
<td>13</td>
</tr>
<tr>
<td>2.2 Synthesis of DP2</td>
<td>14</td>
</tr>
<tr>
<td>2.3 Synthesis of DP4</td>
<td>15</td>
</tr>
<tr>
<td>2.4 Synthesis of DP8</td>
<td>16</td>
</tr>
<tr>
<td>2.5 Synthesis of DP9</td>
<td>17</td>
</tr>
<tr>
<td>2.6 Synthesis of pre-PLGA with refluxing</td>
<td>18</td>
</tr>
<tr>
<td>2.7 Synthesis of pre-PLGA with DIC/DPTS</td>
<td>19</td>
</tr>
<tr>
<td>2.8 Synthesis of PLGA0505(24h)DP9</td>
<td>20</td>
</tr>
<tr>
<td>2.9 Synthesis of PLGA0505(6.5h)DP9</td>
<td>20</td>
</tr>
<tr>
<td>2.10 Synthesis of photoresponsive PLGA with one-step method</td>
<td>21</td>
</tr>
<tr>
<td>7.1 Synthesis of AJ2</td>
<td>46</td>
</tr>
<tr>
<td>7.2 Synthesis of AJ3</td>
<td>47</td>
</tr>
<tr>
<td>7.3 Synthesis of AJ4</td>
<td>48</td>
</tr>
<tr>
<td>7.4 Synthesis of AJ5</td>
<td>49</td>
</tr>
<tr>
<td>7.5 Synthesis of N,N-bis(2-hydroxyethyl)propionamide</td>
<td>50</td>
</tr>
<tr>
<td>7.6 Synthesis of AJ5 copolymer</td>
<td>51</td>
</tr>
</tbody>
</table>
CHAPTER I
INTRODUCTION

1.1 Need for biodegradable polymers

As environmental consideration becomes more important, a significant increase in the worldwide usage of biodegradable polymers has occurred; from 14 million kg to 68 million kg in 5 years. Compared with the persistence of conventional polymers including polyethylene and polypropylene, biodegradable polymers can degrade with chemical hydrolysis or the help of bioactivities, such as bacteria, fungi and algae, after disposing in the environment. Biodegradable polymers can be applied for fabrication of packaging materials and consumer goods, including trash bags, food containers, toys, egg cartons and so on. With consideration of the need for biodegradable polymers, in this research, a biodegradable and photodegradable material with improved mechanical properties was studied. The designed features for this material include a high glass transition temperature (higher than 60 °C), high molecular weight and if it is possible, photodegradation products can be recycled for new polymerization.

1.2 Common biodegradable polymers

Biodegradable polymers can be broadly sorted as hydrolytically and enzymatically degradable polymers.

Hydrolytically degradable polymers are those whose backbones have labile chemical bonds and these chemical bonds can be broken by water without secondary influence to
generate two products. As shown in Figure 1.1, one product has a hydroxyl group and the other gets a hydrogen atom. Examples of hydrolytically degradable polymers include anhydrides, esters, acetals, amides, carbonates, phosphates and urethanes. One of the important characteristics for these polymers is their erosion mechanisms and relative rates of degradation. The degradation rate difference between very hydrolytically unstable polymers (polyphosphazenes) and very hydrolytically stable polymers (polyamides) can be 12-fold which is shown in Table 1.1. Additionally, the degradation rate of these certain polymers (polyphosphazenes and polyanhydrides) can be significantly affected by water diffusion, polymer diffusion, monomer solubility and size, and device geometry.\(^5\)

![Figure 1.1. Water molecule breaks the hydrolytically labile bond to produce the products.](image)

Table 1.1 Summary of degradable polymers’ applications, advantages, disadvantages, and structure\(^5\)

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Applications</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyphosphazenes</td>
<td>Tissue engineering</td>
<td>Tunable properties</td>
<td>Complicated synthesis</td>
<td><img src="image" alt="Polyphosphazene structure" /></td>
</tr>
<tr>
<td>Polyanhydrides</td>
<td>Drug delivery; Tissue engineering</td>
<td>Flexibility in monomer; Tailored rates of degradation</td>
<td>Limited molecular weights; Poor mechanical properties</td>
<td><img src="image" alt="Polyanhydride structure" /></td>
</tr>
</tbody>
</table>
Enzymatically degradable polymers contain hydrolytic bonds that will degrade, but this process requires catalysis under physiological conditions. The structures of these polymers mostly contain amide or ether bonds. Table 1.2 shows the major enzymatically degradable polymers.\textsuperscript{5,6}

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Applications</th>
<th>Properties</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyacetals</td>
<td>Drug delivery</td>
<td>pH response resulting in degradation products who are mild pH</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Poly(orthoesters)</td>
<td>Drug delivery</td>
<td>Tailored rates of degradation; pH response</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Polyphosphoesters</td>
<td>Drug delivery; Tissue engineering</td>
<td>Biocompatibility</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Polycaprolactone</td>
<td>Tissue engineering</td>
<td>Available in market</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Polyurethanes</td>
<td>Prostheses; Tissue engineering</td>
<td>Good mechanical properties</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Polylactide</td>
<td>Tissue engineering; Drug delivery</td>
<td>Available in market</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Polycarbonates</td>
<td>Drug delivery; Tissue engineering;</td>
<td>Tunable properties; Surface Erosion</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Polyamides</td>
<td>Drug delivery</td>
<td>Modifiable pendant groups; Biocompatibility</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
Table 1.2. Summary of enzymatically degradable polymers\textsuperscript{5,6}

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Application</th>
<th>Structure</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteins</td>
<td>Sutures, Scaffolds in tissue engineering; Drug delivery</td>
<td>A three-dimensional folded structure arranged by amino acid polymers</td>
<td>Synthesized by the human body with four major stages</td>
</tr>
<tr>
<td>Collagen</td>
<td>Primary initiators of the coagulation cascade; Natural substrate for cell attachment; Haemostatic agent; Tissue engineering; Wound dressing application; Carriers for drug delivery</td>
<td>A rod-type polymer with length of about 300 nm; Molecular weight of 300,000;</td>
<td>The major component of extracellular matrix, skin and other musculoskeletal tissues; Sorted as Type I–IV; Good solubility in acidic aqueous solutions; High thrombogenicity; Crosslink easily</td>
</tr>
<tr>
<td>Type I Collagen</td>
<td></td>
<td>Three polypeptide subunits, everyone has 1050 amino acids, containing about 33% glycine, 25% proline and hydroxyproline, separately, with lysine</td>
<td></td>
</tr>
<tr>
<td>Poly-(\gamma)-glutamic acid ((\gamma)-PGA)</td>
<td>Drug delivery vehicles; Scaffolds for tissue engineering; Thermosensitive polymers</td>
<td></td>
<td>High functionality; Thermosensitive</td>
</tr>
<tr>
<td>Poly((\varepsilon)-L-lysine)</td>
<td>Scaffolds for tissue engineering; Drug delivery vehicles</td>
<td></td>
<td>Biocompatible; Antibacterial, antiviral and antitumor activity; Cytotoxicity high positive charge</td>
</tr>
<tr>
<td>Material</td>
<td>Application</td>
<td>Properties</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cyanophycin</td>
<td>Limited application</td>
<td>Highly polydisperse polymer</td>
<td></td>
</tr>
<tr>
<td>Poly(L-glutamic acid) (L-PGA)</td>
<td>Biodegradable materials; Gene/plasmid delivery vehicle; Polymeric drugs;</td>
<td>L-glutamic acid residues were linked by amide bonds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adhesive and hemostatic</td>
<td>Highly sensitivity in degradation with lysosomal enzymes resulting in L-glutamic acid; Under physiological pH, highly charged</td>
<td></td>
</tr>
<tr>
<td>Poly(aspartic acid)</td>
<td>Smart drug delivery vehicles</td>
<td>biodegradation with lysosomal enzymes</td>
<td></td>
</tr>
<tr>
<td>Elastin</td>
<td>Biological coatings for synthetic vascular grafts</td>
<td>Highly cross-linked polymer formed by covalently bond from tropoelastin molecules.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insoluble; Interaction with platelets</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>Intravenous drug/gene delivery carrier vehicle; Coating materials for</td>
<td>A water soluble-protein (66 kDa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cardiovascular devices</td>
<td>Water soluble; blood compatibility</td>
<td></td>
</tr>
<tr>
<td>Polymers</td>
<td>Applications</td>
<td>Properties</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Fibrin</td>
<td>Hemostasis; Tissue sealing; Carrier vehicle</td>
<td>Derived from a 360 kDa protein, fibrinogen, formed by three pairs of polypeptide chains</td>
<td>Excellent biocompatibility; Injectability; Biodegradability</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Metastasis; Wound healing; Inflammation; Tissue engineering; Drug delivery</td>
<td>Water soluble; Degraded by free radicals in body; Immunoneutrality</td>
<td></td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Wound healing; Tissue engineered implant</td>
<td>Non-immunogenicity; Biocompatibility</td>
<td></td>
</tr>
<tr>
<td>Chitosan</td>
<td>Food additive; Wound healing; Drug delivery device; Scaffolds in tissue engineering; Permeation enhancer; Injectable thermosensitive carrier</td>
<td>Degraded by chitosanase, lysozyme and papain; Inflammatory response; Soluble in solution which is weakly acidic; Strong positive charges; Biocompatibility; Biodegradability</td>
<td></td>
</tr>
<tr>
<td>Alginic acid</td>
<td>Food additive; Scaffold for bone regeneration; Drug delivery Device</td>
<td>Non-toxicity; Poor degradability; Poor cell adhesion</td>
<td></td>
</tr>
</tbody>
</table>

From the above tables, most of the biodegradable polymers have the application of drug release. In the controlled drug release area, the most commonly used biodegradable polymer is poly(lactic-co-glycolic acid) (PLGA). For this reason PLGA was chosen as the new material in this study.
1.3 Poly(lactic-co-glycolic acid) (PLGA)

The reasons PLGA has been widely applied as the base material in biomedical area fall into these categories. First, PLGA is a biocompatible polymer; second, the biodegradation rate can be modified by the ratio of lactic acid and glycolic acid and molecular weight; third, the surface of the material made from PLGA can be modify.¹

Besides the above features, the physical properties will also be tailored by the copolymer ratio. It also makes PLGA a good choice as the new material in this research. The information on the physical properties of commercial PLGA is in Table 1.3. This information was found on the website of Aldrich® Materials Science and PLA/PGA RESOMER® polymers were synthesized by Evonik Röhm Pharma GmbH.

Table 1.3. RESOMER® Biodegradable Polymers: Poly(D,L-lactide-co-glycolide)

<table>
<thead>
<tr>
<th>Prod. No.</th>
<th>RESOMER® Type</th>
<th>Ratio of Lactic acid and glycolic acid</th>
<th>Molecular Weight Range</th>
<th>T_g /°C</th>
<th>T_m /°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>719897</td>
<td>RESOMER® RG 502 H</td>
<td>50: 50</td>
<td>7,000-17,000</td>
<td>42-46</td>
<td>Amorphous</td>
</tr>
<tr>
<td>719870</td>
<td>RESOMER® RG 503 H</td>
<td>50: 50</td>
<td>24,000 - 38,000</td>
<td>44-48</td>
<td>Amorphous</td>
</tr>
<tr>
<td>719900</td>
<td>RESOMER® RG 504 H</td>
<td>50: 50</td>
<td>38,000 - 54,000</td>
<td>46-50</td>
<td>Amorphous</td>
</tr>
<tr>
<td>739960</td>
<td>RESOMER® RG 505</td>
<td>50: 50</td>
<td>54,000 - 69,000</td>
<td>48-52</td>
<td>Amorphous</td>
</tr>
<tr>
<td>719862</td>
<td>RESOMER® RG 653 H</td>
<td>65: 35</td>
<td>24,000-38,000</td>
<td>46-50</td>
<td>Amorphous</td>
</tr>
<tr>
<td>719919</td>
<td>RESOMER® RG 752 H</td>
<td>75: 25</td>
<td>4,000-15,000</td>
<td>42-46</td>
<td>Amorphous</td>
</tr>
<tr>
<td>739979</td>
<td>RESOMER® RG 858 S</td>
<td>85: 15</td>
<td>190,000 - 240,000</td>
<td>-</td>
<td>Amorphous</td>
</tr>
</tbody>
</table>

See more information at the website <http://www.sigmaaldrich.com/materials-science/polymer-science/resomer.html>
From the above table, features can be found and they can be applied for designing the new copolymer. When the ratio of lactic acid and glycolic acid was the same, as the molecular weight increases, $T_g$ will also increase. While the molecular weight of PLGA was the same, increasing of the lactic acid in the copolymer will result in the increasing of $T_g$. So for the new polymer in this study, the high $T_g$ can be obtained from the high molecular weight and the high content of lactic acid.

1.4 Photoresponsive polymers

Photoresponsive polymers, which are similar to enzymatically degradable polymers, contain hydrolytic bonds that will degrade under UV, visible and near-infrared light. Compared to other stimuli responsive polymers, photoresponsive polymers exhibit excellent spacial and temporal control of degradation, so the photoresponsive property will be introduced into the new copolymer in this study.\textsuperscript{8,9}

For applications of photoactivation, photodegradable polymers have been used for reducing the pollution from plastics throughout history. With the development of photoresponsive polymers, there are two major applications now. On one hand, photoactivation can cause polymer backbone scission; on the other hand, it can control properties of the polymer, such as bending, release or capture of drugs or other fillers, and phase behavior.

For biological applications of this kind of polymer, a strong need arises currently. As materials in biological applications, photoresponsive polymers can be biodegradable and photodegradable in the biological environment. So with these advantages, these polymers are designed as drug delivery vehicles and platforms which have phototunable properties.\textsuperscript{8,9}
Ma, L., et al. designed nanoparticles loaded with Nile Red in which Nile Red was triggered burst released. Nile Red was released by a degradable UV-responsive polymer synthesized via condensation polymerization of azalaic acid dichloride and 2-nitrobenzyl (4-(1, 2-dihydroxyethyl) phenyl) carbamate. After irradiation, aniline was deprotected by removing nitrobenzyl urethane protecting group and 1, 6-elimination reactions of aniline happened spontaneously, which led to degradation of the polymer. Pieroni, O., et al. reviewed the current work on the photoresponsive effects of polypeptides, azobenzene and spiropyran units from polypeptides attached to macromolecules giving reversible change of their structure responding to dark or light conditions.

1.5 Stress-strain diagram

Different materials will provide the various stress-strain diagrams, even the different results may be achieved by the same material, which are influenced by the temperature of testing and the loading speed. However, according to the common features of the stress-strain diagrams, materials can be divided into two categories: brittle materials and ductile materials. The stress-strain curves can be applied to analyze what kind of materials are tested and the young’s modulus can be calculated.

Figure 1.2 shows the stress-strain curve of brittle materials. The rupture of brittle materials will occur within a very small strain. While for ductile materials, as the load increases, the length initially grows linearly at a very slow rate. Then a critical value of stress is reached, and a large deformation in the sample will occur with a small increase of the load. After reaching a maximum load, the size of the sample decreases because of necking, which was shown in the Figure 1.3.
1.6 Abbreviations in the project

DP1: 4’-hydroxyacetophenone

DP2: 2-bromo-1-(4-hydroxyphenyl)ethan-1-one

DP4: 2-(4-hydroxyphenyl)-2-oxoethyl acetate

DP8: Methyl 2-(4-(2-acetoxyacetyl)phenoxy)acetate

DP9: 2-(4-(2-hydroxyacetyl)phenoxy)acetic acid

PLGA: Poly(lactic-co-glycolic acid)
p-TSA: p-Toluenesulfonic acid

DPTS: 4-(N,N’-Dimethylamino)pyridinium-4-toluenesulfonate

DIC: N,N'-Diisopropylcarbodiimide
CHAPTER II

EXPERIMENTAL

2.1 Chemicals

Potassium carbonate was bought from Fisher and dried in an oven at 70 °C overnight before use. Sodium bisulfate, 18-crown-6, sodium hydroxide, p-toluene sulfonic acid (PTSA) methyl 2-bromoacetate, lactic acid, glycolic acid and chloroform were used as received from Fisher. Anhydrous sodium sulfate, 4-hydroxyacetophenone, cupric bromide and sodium acetate trihydrate were used as received from Acros Organics. Activated 4 Å molecular sieves purchased from Fisher were used to dry acetone. Other solvents, such as ethanol, methanol and so on were purchased from Fisher and Acros Organics. Dichloromethane (DIC) was bought from Oakwood.

2.2 Equipment

A Varian Mercury 300 MHz NMR spectrometer was performed to record the \(^1\)H NMR. Molecular weights of polymers were analyzed on a TOSOH EcoSEC HLC-8320 GPC, which has two TSK-GEL® Super H 3000 columns and one TSK-GEL® Super H 4000 column in series, and chloroform was used as the mobile phase. Irradiation was performed in a Rayonet® RPR-200 reactor at 300 nm (1.98. mW/cm²). An OPHIR AN/2 light power meter was applied to measure the irradiation intensity. DMA Q800 V20.26 Build 45 was applied to obtain the strain-stress curves.
2.3 Synthesis of photoresponsive monomers and polymers

The photoresponsive properties of polymers were introduced by the unique monomers called DP9 and AJ5, separately. The synthesis routes of these monomers and polymers were shown in the following sections.

2.3.1 Introduction of DP9 and AJ5

The photoresponsive monomers, DP9 and AJ5, were degraded under UV irradiation. As one kind of hydroxyphenacyl esters, the photo-Favorski type rearrangement will occur during this process. As the phenacyl chromophore was excited initially to obtain the singlet excited state, the quick intersystem crossing of singlet–triplet led to the generation of the triplet state (2). Then an intermediate spirodienedione (3) was generated by the rearrangement of the phenacyle triplet. In the end, hydroxyphenylacetic acid (4) was formed by intermediate spirodienedione (3) or the reduced acetophenone product (5) was achieved after fragmentation.

Degradation of copolymers under UV light can be finished by the introduction of DP9 or AJ5 into the backbones of copolymers. The degradation mechanism of photoresponsive monomers is shown in Scheme 2.1.8

Scheme 2.1. Rearrangement mechanism of DP9 or AJ58
2.3.2 Synthesis of DP2

The synthesis route of DP2 is shown in Scheme 2.2.

DP1 (10.0 g, 73.4 mmol, 1 eq) was dissolved in CHCl₃ (70 ml) in a 100 mL round bottom flask. Meanwhile, cupric bromide (34.3 g, 146.9 mmol, 2 eq) was added to methanol (50 ml) in a 250 mL round bottom flask to obtain a suspension. Then the solution of DP1 was added into the suspension while vigorously stirring. After refluxing for 3.5 hours, the white CuBr was formed from the black CuBr₂ and the solution was filtered. The solvent from filtrate was removed on the rotary evaporator resulting in a violet solid. Extraction of the solid was performed with water and ethyl acetate. During the extraction, some white cream was formed occasionally in the interphase of the green water layer and light green/yellow organic layer. It could be removed by filtration. The ethyl acetate layers were collected and dried by sodium acetate. After removing the solvent, a dark green solid was obtained. The dark green or purple color was removed by recrystallization or column chromatography and the white solid (15.7 g), which was the mixture of DP2 and DP1, could be used for the next reaction. Column chromatography (25% ethyl acetate -75% hexane) can be applied for further purification of DP2 to obtain a white solid.¹³¹H NMR (300 MHz, CHLOROFORM-d) δ 4.39 (s, 2H), 6.91 (d, J = 8.78 Hz, 2H), 7.95 (d, J = 8.78 Hz, 2H).

Scheme 2.2. Synthesis of DP2¹³
2.3.3 Synthesis of DP4

The synthesis route of DP4 is shown in Scheme 2.3.

The white solid (14.6 g, 67.7 mmol, 1 eq), which was the mixture of DP1 and DP2, was dissolved in methanol (68 mL) and sodium acetate trihydrate (11.06 g, 81.3 mmol, 1.2 eq) was dissolved in water (34 mL). Then the two solutions were mixed in a 250 mL round bottom flask. After adding acetic acid (3.4 ml) into the mixture, the mixture was refluxed with stirring for 3.5 hours. Solvent was removed on the rotary evaporator and a little amount of ethyl acetate was added to dissolve the solid. Water was added to increase the volume of solution to 60 mL. Ethyl acetate (60 mL × 3) was applied to extract the water. Sodium sulfate was used to dry the collected organic layers and the solvent was removed resulting in the crude product, which was a light yellow solid. Purification was performed by column chromatography (28% ethyl acetate - 72% hexane) to give a white solid (10.5 g).13 $^1{H}$ NMR (300 MHz, DMSO- $d_6$) $\delta$ 2.11 (s, 3H), 5.33 (s, 2H), 6.86 (d, J = 8.78 Hz, 2H), 7.82 (d, J = 8.49 Hz, 2H).

![Scheme 2.3. Synthesis of DP4](image)

2.3.4 Synthesis of DP8

The synthesis route of DP8 is shown in Scheme 2.4.

To a 250 mL one neck round bottom flask, dry potassium carbonate (5.6 g, 40.6 mmol, 1.25 eq), which was dried in the oven, and DP4 (6.31 g, 32.5 mmol, 1 eq) were added. After vacuuming and backfilling the flask with nitrogen twice, anhydrous acetone (48 ml)
was added through a syringe and needle. The mixture was stirred for 30 minutes and methyl bromoacetate (3.40 ml, 5.47 g, 35.8 mmol, 1.1 eq) was added into the above mixture, then the reaction was refluxed with stirring for 3 hours. The solvent from the filtrate, which was obtained from filtering the mixture, was removed on the rotary evaporator to yield a white/light yellow solid. Column chromatography (30% ethyl acetate - 70% hexane) was performed, resulting in a white solid. (8.3 g).\(^{13}\)\(^{1}\)H NMR (300 MHz, DMSO-\(_d_6\)) \(\delta\) 2.12 (s, 3H), 3.69 (s, 3H), 4.92 (s, 2H), 5.38 (s, 2H), 7.06 (d, \(J = 8.78\) Hz, 2H), 7.91 (d, \(J = 8.78\) Hz, 2H).

\[
\text{Scheme 2.4. Synthesis of DP8}\(^{13}\)
\]

2.3.5 Synthesis of DP9

The synthesis route of DP9 is shown in Scheme 2.5.

DP8 (8.30 g, 31.2 mmol, 1 eq) and p-TSA (1.1860 g, 6.2 mmol, 0.2 eq) were added to a 250 mL round bottom flask, then acetonitrile (93 mL) and water (62 mL) were added to the above flask. The solution was refluxed with stirring for 24 hours. After removing all solvent from solution on a rotary evaporator, 20 mL water was applied to wash the solid to remove p-TSA. The suspension of water was filtered, resulting in a white/light yellow solid. After drying the solid, further purification was performed by recrystallization from acetonitrile and methanol to obtain the white pure powder. (5.3 g).\(^{13}\)\(^{1}\)H NMR (300 MHz, DMSO-\(_d_6\)) \(\delta\) ppm 4.71 (s, 2H), 4.76 (s, 2H), 7.00 (d, \(J = 9.08\) Hz, 2H), 7.89 (d, \(J = 8.78\) Hz, 2H).
2.4 Synthesis of Photodegradable PLGA

Two methods were applied to fabricate photoresponsive PLGA. One approach was a two-step synthesis, that is, the pre-polymer of PLGA was synthesized first, then the DP9 was added to the pre-polymer to produce the photoresponsive PLGA. Another method was a one-step synthesis in which lactic acid, glycolic acid and DP9 were added together to produce the photoresponsive PLGA.

2.4.1 Synthesis of pre-PLGA

The synthesis route is shown in Scheme 2.6. Lactic acid (85%, 1.18 g, 13.1 mmol, 1 eq), glycolic acid (1.00 g, 13.1 mmol, 1 eq) and p-TSA (0.0375 g, 0.20 mmol, 0.015 eq) were added to a 250 mL round bottom flask. After adding toluene (150 mL) to the flask, the solution was refluxed with stirring for 48 hours. Meanwhile, the water formed from polymerization was removed on a Dean-Stark apparatus. A viscous liquid was yielded as pre-polymer after removing the toluene from solution on the rotary evaporator. For purification, precipitation in different solvents was performed to remove p-TSA. It turned out that pre-polymer cannot be precipitated in methanol, ethanol, isopropanol or cold hexane, so the alternative method that was carried out was that pre-polymer was dissolved in a mixture solution of dichloromethane and methanol and added to a dialysis tube with 10 kDa molecular-weight cutoffs. After one day, all pre-polymer was found in the dialysate,
which showed the molecular weight of pre-polymer was lower than 10 kDa and p-TSA was not removed. $^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ 1.58 (d, $J = 7.32$ Hz, 3H) which was overlapped with water, 4.81 (s, 2H), 5.22-5.28 (m, 1H). Because the p-TSA was not removed, the $^1$H NMR was not clear.

![Scheme 2.6. Synthesis of pre-PLGA with refluxing](image)

2.4.2 Synthesis of pre-PLGA under room temperature

The synthesis route is shown in Scheme 2.7.

Lactic acid (0.7107 g, 7.89 mmol, 1 eq), which was dried on the lyophilizer to remove water, glycolic acid (0.6000 g, 7.89 mmol, 1 eq) and DPTS (0.9224 g, 3.16 mmol, 0.4 eq) were added to a 25 mL round bottom flask. After adding anhydrous dichloromethane to the above flask, the solution was set on cryogenic condition and vacuumed twice to remove water. Isotherm was achieved by placement in an ice bath for 10 minutes, then the DIC (3.7 mL, 2.9870 g, 23.67 mmol, 3 eq) was added dropwise to the solution. After another 20 minutes in the ice bath, the reaction was purged with nitrogen under room temperature for different times (6 h, 12 h, 24 h and 48 h) to obtain pre-polymer with differing molecular weights. Precipitation in methanol was performed to obtain the pre-polymer as white fibers. For the 6-hour reaction, $^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ 1.58 (d, $J = 6.73$ Hz, 3H) which was overlapped with water, 4.81 (s, 2H), 5.16-5.23 (m, 1H); For the 12-hour reaction, the influence of a cryogenic condition was studied. Two reactions were set up and the only difference was whether or not the cryogenic condition applied. When the
cryogenic condition was performed, $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.18-5.24 (m, 1H); When there was no cryogenic condition, $^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ 1.58 (d, $J$ = 7.03 Hz, 3H), 4.81 (s, 2H), 5.16-5.28 (m, 1H); For the 24-hour reaction, $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.18-5.24 (m, 1H); For the 48-hour reaction, $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.18-5.24 (m, 1H).

Scheme 2.7. Synthesis of pre-PLGA with DIC/DPTS

2.4.3 Synthesis of photoresponsive PLGA0505

In the two-step approach, the first step was synthesis of pre PLGA. The procedure has already been described above. Lactic acid (0.7107 g, 7.89 mmol, 1 eq), which was dried on the lyophilizer to remove water, glycolic acid (0.6000 g, 7.89 mmol, 1 eq) and DPTS (0.9224 g, 3.16 mmol, 0.4 eq) were applied.

After polymerizing for 24 hours, DP9 (0.4974 g, 2.58 mmol, 0.3 eq of PLGA), DPTS (0.2767 g, 0.95 mmol, 0.4 eq) and DIC (1.1 mL, 0.90 g, 7.1 mmol, 3 eq) were added to the solution of pre-polymer and the reaction time for the whole two-step was set as 3 days. After precipitating the polymer into methanol, the photoresponsive PLGA, which was named PLGA0505(24h)DP9, was obtained as white fibers. $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.09 (s, 0.4H), 5.18-5.24 (m, 1H), 5.57 (s, 0.4H), 7.13 (d, $J$ = 8.78 Hz, 0.4H), 7.95 (d, $J$ = 8.20 Hz, 0.4H). The synthesis route is shown in Scheme 2.8.
After polymerizing for 6.5 hours, DP9 (0.3316 g, 1.58 mmol, 0.2 eq of PLGA), DPTS (0.1845 g, 0.63 mmol, 0.4 eq) and DIC (0.74 mL, 0.5973 g, 4.73 mmol, 3 eq) were added to the solution of pre-polymer and the whole two-step reaction time was set as 3 days. Precipitation in methanol resulted in photoresponsive PLGA, which was named PLGA0505(6.5h)DP9, and appeared as white fibers. $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.09 (s, 0.2H), 5.15-5.27 (m, 1H), 5.57 (s, 0.2H), 7.13 (d, $J = 8.49$ Hz, 0.2H), 7.95 (d, $J = 8.49$ Hz, 0.2H). The synthesis route is shown in Scheme 2.9.
In the one step method, lactic acid (0.7107 g, 7.89 mmol, 1 eq), which was dried on the lyophilizer to remove water, glycolic acid (0.6000 g, 7.89 mmol, 1 eq), DP9 (0.3316 g, 1.58 mmol, 0.2 eq of PLGA) and DPTS (0.9224 g, 3.16 mmol, 0.4 eq) were added to a 25 mL round bottom flask. Then anhydrous dichloromethane was added to the above flask. The solution was set to cryogenic conditions and vacuumed twice. Ice bath was applied to reach isotherm. After 10 minutes, DIC (3.7 mL, 2.9870 g, 23.67 mmol, 3 eq) was added dropwise to the solution. The mixture was kept in the ice bath for an additional 20 minutes, and nitrogen was purged into the reaction under room temperature for 48 h to obtain the photoresponsive PLGA named PLGA0505DP902. The polymer was purified by precipitating in methanol resulting in white fibers. $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.47 (d, 3H), 4.89 (s, 2H), 5.05 (s, 0.4H), 5.18-5.24 (m, 1H), 5.53 (s, 0.4H), 7.09 (d, J = 8.30 Hz, 0.4H), 7.91 (d, J = 7.61 Hz, 0.4H). The synthesis route is shown in Scheme 2.10.

![Scheme 2.10. Synthesis of photoresponsive PLGA with one-step method](image)

2.4.4 Synthesis of photoresponsive PLGA0703

The photoresponsive PLGA, whose ratio of lactic acid and glycolic acid was 0.7: 0.3, was synthesized by the one step method. To a 25 mL round bottom flask, lactic acid (0.8291 g, 9.20 mmol, 0.7 eq), which was dried on the lyophilizer to remove water, glycolic acid
(0.3000 g, 3.94 mmol, 0.3 eq), DP9 (0.3869 g, 1.84 mmol, 0.2 eq of PLGA) and DPTS (0.9347 g, 3.20 mmol, 0.4 eq) were added. After adding anhydrous dichloromethane to dissolve all monomers and catalyst, the reaction was set to cryogenic conditions and vacuumed twice. The reaction was subjected to isotherm for 10 minutes in an ice bath. Then DIC (3.8 mL, 3.0268 g, 23.98 mmol, 3 eq) was added dropwisely. After 20-minute in the ice bath, the reaction was purged with nitrogen at room temperature for 48 hours. Purification was achieved by precipitation in methanol resulting in white fibers, and the product was named PLGA0703DP902. 1H NMR (300 MHz, DMSO- d6) δ 1.46 (d, 3H), 4.88 (s, 0.86H), 5.04 (s, 0.4H), 5.18-5.28 (m, 1H), 5.54 (s, 0.4H), 7.07 (d, J = 8.20 Hz, 0.4H), 7.91 (d, J = 7.90 Hz, 0.4H).

The same reaction was performed on a large scale to make sure that there were enough materials for the testing of mechanical properties. The procedure was the same and lactic acid (2.0452 g, 22.70 mmol, 0.7 eq), which was dried on the lyophilizer to remove water, glycolic acid (0.7400 g, 9.73 mmol, 0.3 eq), DP9 (0.9544 g, 4.54 mmol, 0.2 eq of PLGA), DPTS (2.3057 g, 7.89 mmol, 0.4 eq) and DIC (9.26 mL, 7.2661 g, 59.16 mmol, 3 eq) were applied. After purification, the polymer was white fibers and named PLGA0703DP902 2g. 1H NMR (300 MHz, DMSO- d6) δ 1.46 (d, 3H), 4.88 (s, 0.86H), 5.04 (s, 0.4H), 5.18-5.28 (m, 1H), 5.54 (s, 0.4H), 7.07 (d, J = 8.20 Hz, 0.4H), 7.91 (d, J = 7.90 Hz, 0.4H).
CHAPTER III
CHARACTERIZATION

3.1 Glass transition temperature and decomposition temperatures of polymers

TGA was performed to test the $T_d$ of the polymers. Polymers (3-4 mg) were loaded onto platinum plates and the temperature was increased from room temperature to 500 °C with the rate of heating set to 10 °C/min in the nitrogen atmosphere.

DSC was applied to test the $T_g$ of polymers. Polymers (2-3 mg) were loaded in the pans and sealed with lids. The rate of heating and cooling was set as 10 °C/min. Temperature was increased to 160 °C and held constant for 3 minutes, then cooled to -20 °C and held constant for 3 minutes. After reheating the sample to 160 °C, the test was finished. When the $T_g$’s (46-66 °C) of polymers were obtained, they were close to the starting temperature (40 °C) in DSC. To make sure the $T_g$ was accurate, a cooling process was added before the test. The temperature was decreased to 20 °C at a rate of 10 °C/min, then procedure outlined above was performed.

3.2 Photoresponsive properties of photoresponsive PLGA in liquid phase

PLGA0703DP902 2g was used for the test of photodegradable properties, because it had the highest $T_g$ among the polymers. PLGA0703DP902 2g (36 mg) was dissolved in 18 mL of GPC-grade chloroform to obtain a solution with a concentration of 2 mg/mL. The solution was added to six quartz cuvettes separately and every cuvette contained 3 mL solution. The cuvettes were set up in the Rayonet® RPR-200 reactor at 300 nm (1.98
mW/cm²) at different times (0 minutes, 5 minutes, 10 minutes, 20 minutes, 40 minutes and 100 minutes). After different times of irradiation, the solution was filtered and GPC samples were prepared. At last, the molecular weights of polymers under irradiation for different times were analyzed.

3.3 Fabrication of thin films

Panpan Lin from Dr. Wang’s research group helped to obtain these films. Compression molding was applied to yield the thin films with the thicknesses around 100 μm. The films were transparent and brittle.

3.4 Irradiation of thin films for different time periods

Thin film was cut into small samples (around 2 cm × 5 mm × 0.1 mm) and placed into a group of samples. Every group contained six samples. Different groups of samples were set up in the Rayonet® RPR-200 reactor at 300 nm (1.98 mW/cm²) for different times (0 minute, 10 minutes and 20 minutes). During the test, methanol was added on top of the samples. After irradiation, samples were dried in the vacuum oven at 40 °C over night to remove methanol.

3.5 Stress-strain curves of photoresponsive PLGA

PLGA0703DP902 2g was used in this test. Instron was performed to test the polymer initially, but there were only two data points obtained from this method, because of the brittle polymer. Then DMA was used to produce the stress-strain curves of polymers, but the sample slipped in the clamp due to the brittle nature and thinness of the polymer. Because of this, temperature controlled DMA was performed to test the polymer. By remaining at 40 °C during the test, the polymer became a little soft to help hold the sample in the clamp. Strain was ramped at a rate of 2.50 % per minute up to 200.000 %.
CHAPTER IV
RESULTS AND DISCUSSION

4.1 Pre-polymer of PLGA

Because p-TSA cannot be removed from the pre-polymer, it was harmful for GPC analysis and to the DIC/DPTS catalysts in the following step. For this reason the acid catalyst was replaced by a DIC/DPTS catalyst system. After applying this catalyst system, clean $^1$H NMR plots could be obtained and the structures of all of the pre-polymers were matched with the $^1$H NMR plots.

The relationship of reaction time and molecular weight of pre-polymer were analyzed to set the maximum reaction time for the polymerization of pre-polymer. The relationship is shown in the following table. As the reaction time increased, the molecular weights also increased. However, after 24 hours, the molecular weights started to decrease, which showed that the pre-polymer began to degrade. So the maximum reaction time for the polymerization of pre-polymer should be 24 hours. The influence of a cryogenic condition on the molecular weight was also analyzed. For the 12-hour reactions, two polymerization reactions were set up and the only difference was the application or absence of a cryogenic condition. The reaction with the cryogenic condition had a higher molecular weight than the reaction without the cryogenic condition. So the cryogenic condition will be applied to all future polymerizations of PLGA copolymers.
Table 4.1. The relationship of reaction times and molecular weights of pre-polymers

<table>
<thead>
<tr>
<th>Reaction Time (h)</th>
<th>Mn (kDa)</th>
<th>Mw (kDa)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>36</td>
<td>65</td>
<td>1.803</td>
</tr>
<tr>
<td>12 without cryogenic condition</td>
<td>42</td>
<td>70</td>
<td>1.663</td>
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<tr>
<td>12</td>
<td>49</td>
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<td>1.430</td>
</tr>
<tr>
<td>48</td>
<td>53</td>
<td>78</td>
<td>1.458</td>
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</tbody>
</table>

4.2 Photodegradable PLGA

Two-step synthesis of photodegradable PLGA

Polymers produced using this method were hard to fully dissolve in common solvents, including dichloromethane, chloroform, dimethylformamide and tetrahydrofuran. The polymer solutions were filtered to obtain the $^1$H NMR and GPC data. These data are listed in the Table 4.2 and Table 4.3, respectively.

From Table 4.2, it showed that DP9 did not fully react with the pre-polymers. In the Table 4.3, the molecular weight of PLGA0505(24h)DP9 is shown and there are two peaks shown on the GPC trace. It shows that there might be two different polymers formed in two-step method.
Table 4.2. Analysis of $^1$H NMR data of photodegradable PLGA from two-step method

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Feed ratio</th>
<th>Composition shown in $^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactic acid</td>
<td>Glycolic acid</td>
</tr>
<tr>
<td>PLGA0505(24h)DP9</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>PLGA0505(6.5h)DP9</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 4.3. Analysis of GPC data of photodegradable PLGA from two-step method

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak 1</td>
</tr>
<tr>
<td></td>
<td>Mn (kDa)</td>
</tr>
<tr>
<td>PLGA0505(24h)DP9</td>
<td>30</td>
</tr>
</tbody>
</table>

The separation of the two possible polymers was performed. There were interesting phenomena that occurred during the precipitation. Firstly, parts of polymer were very easy to obtain a suspension of and the rest of the polymer was hard to suspend. Secondly, when the easy-to-dissolve polymer was added to methanol, the long white fibers were formed. $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.10 (s, 0.2H), 5.18-5.24 (m, 1H), 5.58 (s, 0.2H), 7.13 (d, $J = 8.49$ Hz, 0.2H), 7.95 (d, $J = 8.20$ Hz, 0.2H); While the hard-to-dissolve polymer gave a short white fiber or powder in methanol. $^1$H NMR (300 MHz, DMSO- $d_6$) $\delta$ 1.46 (d, 3H), 4.89 (s, 2H), 5.10 (s, 0.2H), 5.18-5.24 (m, 1H), 5.58 (s, 0.2H), 7.13 (d, $J = 8.78$ Hz, 0.2H), 7.95 (d, $J = 8.49$ Hz, 0.2H); According to these phenomena, two polymers were collected and analyzed, separately. Here are the $^1$H NMR and GPC data of two polymers.
Table 4.4. Analysis of $^1$H NMR data of two polymers

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Composition shown in $^1$H NMR</th>
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<tr>
<td></td>
<td>Lactic acid</td>
</tr>
<tr>
<td>Easy-to-dissolve polymer</td>
<td>0.5</td>
</tr>
<tr>
<td>Hard-to-dissolve polymer</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 4.5. Analysis of GPC data of two polymers

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Molecular Weight</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak 1</td>
<td>Peak 2</td>
</tr>
<tr>
<td></td>
<td>Mn (kDa)</td>
<td>Mw (kDa)</td>
</tr>
<tr>
<td>Easy-to-dissolve polymer</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>Hard-to-dissolve polymer</td>
<td>28</td>
<td>43</td>
</tr>
</tbody>
</table>

From the above data, the two polymers were actually the same. So the separation failed and the one-step method was applied to obtain better polymers.

4.3 One-step synthesis of photodegradable PLGA

From the $^1$H NMR and GPC data shown in Table 4.6 and Table 4.7, the structures of polymers were matched with the $^1$H NMR plots and the GPC data showed there was only one single peak in every trace. These data showed that this method was good for synthesizing the photodegradable PLGA.

Table 4.6. Analysis of $^1$H NMR data of photodegradable PLGA from one-step synthesis

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Feed ratio</th>
<th>Composition shown in $^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactic acid</td>
<td>Glycolic acid</td>
</tr>
<tr>
<td>PLGA0505DP902</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>PLGA0703DP902</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>PLGA0703DP902 2g</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Table 4.7. Analysis of GPC data of photodegradable PLGA from one-step synthesis

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Molecular Weight</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mn (kDa)</td>
<td>Mw (kDa)</td>
<td>PDI</td>
</tr>
<tr>
<td>PLGA0505DP902</td>
<td></td>
<td>26</td>
<td>43</td>
<td>1.640</td>
</tr>
<tr>
<td>PLGA0703DP902</td>
<td></td>
<td>17</td>
<td>56</td>
<td>3.373</td>
</tr>
<tr>
<td>PLGA0703DP902 2g</td>
<td></td>
<td>16</td>
<td>41</td>
<td>2.631</td>
</tr>
</tbody>
</table>

4.4 Glass transition temperature and decomposition temperatures of polymers

The $T_g$ of polymers should be varied with the different compositions, because of the rigid structure of DP9 and crystallinity of lactic acid. Here are the $T_g$ of polymers shown in the table.

Table 4.8. Glass transition temperatures and decomposition temperatures of polymers

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$T_g$ (°C)</th>
<th>$T_d$ (°C)</th>
<th>Molecular Weight</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mn (kDa)</td>
<td>Mw (kDa)</td>
<td>PDI</td>
</tr>
<tr>
<td>PLGA0505(24h)DP9</td>
<td>50.02</td>
<td>303.99</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>PLGA0505(6.5h)DP9</td>
<td>46.71</td>
<td>310.29</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>PLGA0505DP902</td>
<td>59.80</td>
<td>311.23</td>
<td>26</td>
<td>43</td>
<td>1.640</td>
<td></td>
</tr>
<tr>
<td>PLGA0703DP902</td>
<td>66.60</td>
<td>351.92</td>
<td>17</td>
<td>56</td>
<td>3.373</td>
<td></td>
</tr>
<tr>
<td>PLGA0703DP902 2g</td>
<td>66.27</td>
<td>314.20</td>
<td>16</td>
<td>41</td>
<td>2.631</td>
<td></td>
</tr>
<tr>
<td>Pre PLGA0505 (24h)</td>
<td>47.10</td>
<td>297.04</td>
<td>55</td>
<td>79</td>
<td>1.430</td>
<td></td>
</tr>
</tbody>
</table>

From the above Table 11, the following conclusions can be summarized. First, comparing the $T_g$ of pre-polymer with the highest molecular weight and copolymer with DP9, introduction of DP9 will increase the $T_g$. Second, as the ratio of lactic acid increases, $T_g$ will be increased. These conclusions were matched with the feature of common PLGA and hypothesis in the introduction of this thesis.
4.5 Photoresponsive properties of photoresponsive PLGA in liquid phase

Figure 4.1 shows the GPC traces of PLGA0703DP902 2g under different times of irradiation in liquid phase. The molecular weights of polymers for different irradiation times are also shown in the Table 4.9.

Table 4.9. The molecular weights of PLGA0703DP902 2g after different irradiation times

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mn (kDa)</td>
</tr>
<tr>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 4.1. Photoresponsive properties of photoresponsive PLGA in liquid phase
As irradiation time increased, the molecular weight of PLGA0703DP902 2g rapidly decreased. After 20 minutes of irradiation the decrease of molecular weight became slower.

4.6 Irradiation of thin films for different time periods

Samples after the irradiation were shown in Figure 4.2. After 20 minutes of irradiation, the samples became opaque and white.

![Figure 4.2. Photos of samples after irradiation](image1)

4.7 Stress-strain curves of photoresponsive PLGA

Stress-strain curves of PLGA0703DP902 2g are shown in the Figure 4.3, Figure 4.4, Figure 4.5 and the overall plots of all samples under different irradiation times was shown in Figure 4.6.
Figure 4.3. Stress-strain curve of PLGA0703DP902 2g after 0 minutes of irradiation

Figure 4.4. Stress-strain curve of PLGA0703DP902 2g after 10 minutes of irradiation
Figure 4.5. Stress-strain curve of PLGA0703DP902 2g after 20 minutes of irradiation

Figure 4.6. Stress-strain curve of PLGA0703DP902 2g
An interesting phenomenon was found here. After irradiation, the films had a higher young's modulus. Because the samples were white and opaque after irradiation, the higher modulus might be from crystallization or crosslinking during irradiation. To analyze this phenomenon, two experiments were performed. First, DSC was applied to test the $T_g$ and crystallization peak of PLGA0702DP902 2g (20 min). It turned out that the $T_g = 63 \, ^\circ C$ which was lower than the original $T_g (66 \, ^\circ C)$ and there was no crystallization peak. So there was no crystal formation during irradiation. Second, PLGA0702DP902 2g (20 min) was easy to dissolved in dimethyl sulfoxide, meaning crosslinking did not occur.
CHAPTER V
CONCLUSIONS

The following conclusions can be summarized:

First, introduction of DP9 will increase the $T_g$ of PLGA copolymer, because of its rigid structure. Second, as the ratio of lactic acid in the PLGA increases, $T_g$ of PLGA copolymer will also increase. Third, photodegradable property was introduced into PLGA with DP9.

For the synthesis of photoresponsive PLGA, two-step method did not yield an ideal polymer. From the research on the relationship between reaction time and molecular weight of PLGA, the maximum reaction for the whole two-step should be 24 hours, or the PLGA will begin to degrade. The reaction time as 3 days for the whole reaction might be the reason for the small peak shown on the GPC trace of photoresponsive PLGA from two-step approach.

For the increasing of young's modulus after irradiation in solid phase, from DSC and solubility tests, there was no crystal formation or crosslinking. A hypothesis for this phenomenon is that the degradation products inside the films work as fillers to enhance the modulus. More tests need to be performed to prove this hypothesis. After irradiation, more methanol will be used to wash the films to remove the degradation product as much as possible. The irradiation time will be increased to 40 minutes, or even 80 minutes to check the modulus. At certain time points, the modulus might decrease. If the degradation product can work as filler to strengthen the material, it will be attractive for applications.
Less DP9 might still be good for increasing the $T_g$ of the copolymer. The more important feature that might be obtained is that the material might be softer, so the polymer might be good for other mechanical properties. For example, Instron might be applied for the test, which will much better illustrate the mechanical properties of the materials.
CHAPTER VI
INTRODUCTION

6.1 Controlled Drug Release Systems

Controlled drug release involves releasing a drug at a predetermined rate over a suitable time period. Generally speaking, the design of the system determines the rate of release and the time period can be days or years. In this research, a photoresponsive polymer matrix was synthesized which can degrade under UV irradiation. Because of the limited penetration of UV light, the surface erosion might be achieved.

6.1.1 Need for Controlled Drug Release systems

Compared with conventional drug therapies that depend on eye drops, pills, intravenous solutions and ointments, controlled release systems have unique advantages. For example, after injecting the drug with standard dosage, the concentration of drug in blood rises and then decreases. The standard dosage should be within a therapeutic range, that is, the drug concentration should be below minimum toxic concentration and above the median effective concentration. In the case of conventional drug therapies, injecting once will display a burst release and injecting repeatedly will show a pulsatile release. If injecting only once, there is a limited time period which drug concentration is within the effective range while injecting repeatedly has a risk that the drug concentration may be out of the therapeutic range.¹⁴
The impact of burst release, pulsatile release and controlled release on the therapeutic range is shown in Figure 1.1. For controlled release systems, the drug concentration is in the therapeutic range during a reasonable time period and it will be finished just by a single operation or injection. As a rapidly developing area, controlled drug release systems focus on enhancing the effectiveness of drug therapy, including reduced toxicity, improved patient convenience and compliance.

6.1.2 Methods to release drug

There are several stimuli-responsive ways to release drug, including pH, light, temperature and redox microenvironment. Different stimuli-responsive systems are suited for a variety of uses based on unique features of each system and environmental conditions. pH sensitive systems are based on the fact that illnesses affect the extracellular and intracellular pH greatly and that the extracellular pH (~6.5) in solid tumor is different from the pH (7.4) of the blood in normal tissue at 37 °C. In addition, endosome and lysosome have even lower pH values (5.0~5.5) than the values mentioned above. Light
responsive systems release the drug under innocuous electromagnetic radiations which are mainly in range of UV, visible and near-infrared light. For example, this system based on coumarin crosslinking forms and breaks under light with different wavelengths, shown in Figure 1.2.\textsuperscript{20}

![Figure 6.2. Coumarin-modified silica MCM-41 particles works as a photoswitched storage-release controlled release system.\textsuperscript{20}](image)

For temperature sensitive systems, solubility of some polymers display a lower critical solution temperature (LCST) and will undergo a change in hydrophilicity with increasing environmental temperature. The phenomenon of phase separation is controlled by two aspects: the balance of hydrophilic and hydrophobic groups on the polymer chain and the free energy of mixing. The free energy has a relationship with enthalpy, entropy and temperature ($\Delta G = \Delta H - T\Delta S$): When $\Delta H$ is smaller than $\Delta S$, increasing temperature will lead to a large $T\Delta S$ and negative $\Delta G$. In this situation, the polymer chain will associate. Phase separation occurs from the molecular interactions which are temperature dependent, including hydrogen bonding and hydrophobic effects. Above the LCST, the hydrogen bonds between the polymer and water break and polymer-polymer interactions become more favorable.\textsuperscript{21}
Stimuli-responsive systems based on redox response are mainly used in gene delivery systems. Because the oxidizing extracellular space and reducing intracellular space have a great redox potential difference which is about 100–1000 fold.\textsuperscript{18}

6.1.3 Zero-order Release and Non zero-order Release

In Zero-order kinetics, the rate of diffusion is equal to a constant. That is

\[ rate = k \] \hspace{1cm} (1)

Where \( k \) is a constant that depends on environmental conditions and properties of the matrix and drug. From equation (1), the rate has no relationship with the concentration of drug. Zero-order release is hard to accomplish but it is an important goal for all controlled-release systems.

In a first-order process, the rate of diffusion has a linear relationship with concentration of drug. It is shown as

\[ rate = k' \times C_{drug} \] \hspace{1cm} (2)

Where \( k' \) is a rate constant which is similar to \( k \) and \( C_{drug} \) is the concentration of drug. Equation (2) indicates the diffusion rate will decrease with the decrease of the drug’s concentration.

In the situation of second-order release, the rate of diffusion has a linear relationship with the squared concentration of drug. It was shown in the following equation:

\[ rate = k'' \times C_{drug}^2 \] \hspace{1cm} (3)

Where \( k'' \) is a rate constant and \( C_{drug} \) is the concentration of drug. From equation (3), the rate decreases more rapidly with decreasing concentration of drug than that in equation (2). There also exists other kinds of release kinetics which are more complex than these three, for example, the combinations of these basic release kinetics.\textsuperscript{22}
6.2 Polymer Matrixes for Controlled Drug Release

Polymers used for the controlled drug release can be categorized as biodegradable polymers or non-degradable polymers. When using non-degradable polymers as polymer matrixes, an operation may be needed to remove the polymer after a given time, bringing inconvenience to the patients. Because of this, biodegradable polymers are preferred over non-degradable polymers in the field of controlled drug release.\(^3\)

6.2.1 Common Biodegradable Polymers

Common Biodegradable polymers have been already introduced in the introduction section of the development of photodegradable poly(lactic-co-glycolic acid) (PLGA) copolymers with improved mechanical properties.

6.2.2 Degradation Mechanism of Biodegradable polymers

The degradation mechanism of biodegradable polymers can be classified into surface erosion and bulk erosion. For surface eroding polymers, the rate of erosion is constant with the time period during erosion. In the case of bulk erosion, the rate is more complicated than surface erosion because the rate of erosion is not a constant. Both mechanisms will be found in most biodegradable polymers, but the relative ratio of bulk or surface erosion can be changed by the polymer backbone with different chemical structures. Two major processes during erosion affect the erosion kinetics. The rate of the polymer backbone degradation and the diffusion rate of water into the polymer. If the diffusion rate is faster than the degradation rate, bulk erosion will occur. Because there is water inside the polymer, degradation can happen not only on the surface of polymer, but also inside of polymer. However, if the diffusion rate is slower than the degradation rate, it means the hydrolysis
of bonds happens on the polymer surface. After the surface erodes, water can enter into the bulk. Figure 1.3 illustrates the two different mechanisms of degradation.

![Figure 1.3 illustrating the two different mechanisms of degradation](image)

6.3 Photoresponsive polymers

Photoresponsive polymers were also introduced in the introduction section of the development of photodegradable poly(lactic-co-glycolic acid) (PLGA) copolymers with improved mechanical properties.

6.4 Mimic of surface erosion with UV irradiation

Surface erosion means the polymer matrix will be degraded layer by layer. If the drug can be distributed well in the polymer matrix, which can degrade under surface erosion, when the polymer is degraded, every layer will have the almost same amount of drug and controlled drug release can be achieved.

Not every polymer can undergo surface erosion, which limits the development of controlled drug release. In this study, the UV irradiation will be applied to achieve surface erosion. Because the UV light has a weak penetration distance and photoresponsive polymer will degrade only under UV irradiation, when the top layer of photoresponsive polymer matrix is under irradiation, this layer will be eroded, while the rest of the materials
will be stable. After the top layer disappears, the irradiation reaches the next layer and the degradation of the next layer will happen. This process will mimic surface erosion.

6.5 Spin Coating

Spin coating is a procedure in which a uniform thin film is deposited on a flat substrate, especially for small flat disks. A small amount of polymer solution is added to the surface of the substrate, then the substrate is rotated at a high speed. While rotating, the solution is removed from the edges of the substrate by centrifugal force. The solution is distributed uniformly on the substrate and the solvent is evaporated simultaneously, resulting in a uniform thin film. Because of the volatile solvent, thinner film is achieved with the higher speed of spinning. Different viscosity and concentration of the solution can change the thickness of the film. In this work, polymer film will be made by spin coating in order to study the degradation mechanism of the photoresponsive polymer.

![Procedure of spin coating](image)

Figure 6.4. Procedure of spin coating.

6.6 Abbreviations in the project

AJ1: 1-(4-hydroxyphenyl)ethan-1-one or 4-hydroxyacetophenone
AJ2: 1-(4-(3-hydroxypropoxy)phenyl)ethanone
AJ3: 2-bromo-1-(4-(3-hydroxypropoxy)phenyl)ethanone
AJ4: 2-(acetyloxy)-1-(4-(3-hydroxypropoxy)phenyl)ethanone
AJ5: 2-hydroxy-1-(4-(3-hydroxypropoxy)phenyl)ethanone

DPTS: 4-(N,N’-Dimethylamino)pyridinium-4-toluenesulfonate

DIC: N,N'-Diisopropylcarbodiimide
CHAPTER VII
EXPERIMENTAL

7.1 Chemicals

Potassium carbonate was bought from Fisher and dried in the oven at 70 °C overnight before use. Sodium bisulfate, sodium hydroxide, 3-bromo-1-propanol, adipic acid and chloroform were purchased from Fisher and were used as received. Anhydrous sodium sulfate, 4-hydroxyacetophenone, cupric bromide and sodium acetate trihydrate were purchased from Acros Organics and were used as received. Activated 4 Å molecular sieves purchased from Fisher were used to dry acetone. Other solvents, such as ethanol, methanol and so on were purchased from Fisher and Acros.

7.2 Equipment

A Varian Mercury 300 MHz NMR spectrometer was used to record the $^1$H NMR. Molecular weights of polymers were analyzed on a TOSOH EcoSEC HLC-8320 GPC, which has one PSS GRAM analytical 1000Å column and one PSS GRAM analytical 100 Å column in series, and DMF was used as the mobile phase. Irradiation was performed in a Rayonet® RPR-200 reactor at 300 nm (1.98. mW/cm²).

7.3 Synthesis of photoresponsive monomers and polymerization

In this project, the photodegradable monomer, a diol named AJ5, was applied for synthesis of the photoresponsive polymer. The polymer will be degraded under UV light with wavelength of 300 nm.
7.3.1 Synthesis of AJ2

The synthesis route of AJ2 is shown in Scheme 2.1. AJ1 (20.0 g, 146.9 mmol, 1 eq), dry potassium carbonate (26.4 g, 191.0 mmol, 1.3 eq), which was kept in oven overnight, and 18-crown-6 (0.5824 g, 2.2 mmol, 1.5% eq) were added to a 250 mL one neck round bottom flask, then the flask was vacuumed and backfilled with nitrogen two times. A syringe and a needle were used to add anhydrous acetone (35 mL) into the flask. To mix the chemicals well, the mixture was stirred for 20 minutes at room temperature. After adding 1-bromo-3-propanol (15.6 mL, 176.3 mmol, 1.2 eq) to the flask, the mixture was refluxed for 24 hours. The crude product was obtained by removing acetone from filtrate, which was from filtering the mixture, on a rotary evaporator as much as possible. The purification of the crude product can be performed by column chromatography (28% ethyl acetate and 72% hexane).\(^8\)

\[^1\text{H} \text{NMR (300 MHz, DMSO-} \text{d} _6) \delta 1.82-1.91 \text{ (m, 2H), 2.49 (s, 3H, overlap with DMSO), 3.55 \text{ (m, 2H), 4.11 \text{ (t, J = 6.44 Hz, 2H), 4.53 \text{ (t, J = 4.98 Hz, 1H), 7.02 (d, J = 8.78 Hz, 2H), 7.91 (d, J = 8.78 Hz, 2H).} \]

The crude product can also be used directly for the next reaction.

![Scheme 7.1. Synthesis of AJ2](image)

7.3.2 Synthesis of AJ3

The synthesis route of AJ3 is shown in Scheme 2.2. The crude product (28.0 g, 144.2 mmol, 1 eq) was dissolved in CHCl\(_3\) (216 mL), then the solution was mixed with a suspension of cupric bromide (64.4 g, 288.4 mmol, 2 eq) and ethanol (144 mL) in a 500
mL one neck round bottom flask. The mixture was refluxed with vigorous stirring for 4 hours. During the reaction, white CuBr was formed from black CuBr$_2$. When the refluxing was finished, a violet solid was achieved by removing the solvent from filtrate, which was obtained by filtering the mixture, on rotary evaporator. Extraction of the solid was performed in a separatory funnel with water and ethyl acetate. The color of the organic phase was light green/light yellow, while the water phase was green. Some white cream came out in the interphase of two layers, which was removed by suction filtration. Anhydrous sodium sulfate was used to remove water from the organic layer. At last, the solvent in the organic layer was removed resulting in a dark green or purple solid. Column chromatography (25% ethyl acetate-75% hexane) was applied to purify the solid resulting in AJ3 which was a white solid (2.60 g).$^8$\textsuperscript{1}$^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ 2.04-2.12 (m, 2H), 3.88 (t, $J = 4.68$ Hz, 2H), 4.20 (t, $J = 6.01$ Hz, 2H), 4.39 (s, 2H), 6.97 (d, $J = 9.08$ Hz, 2H), 7.97 (d, $J = 9.08$ Hz, 2H).

The yield was pretty low, which was caused by the hood not working when the column was set up. No experiment could be performed until the hood was repaired. So the column could not be finished in a reasonable time. After one week, all compounds were almost degraded.

\begin{center}
\begin{tikzpicture}

\node (aj2) [draw, align=center] {AJ2};
\node (aj3) [draw, align=center, right=2cm] {AJ3};
\node (cubr) [right=0.5cm, above=0.5cm] {CuBr$_2$, EtOH, CHCl$_3$};
\node (reflux) [below=0.5cm] {reflux};

\draw[->] (aj2) -- (cubr);
\draw[->] (cubr) -- (reflux);
\draw[->] (reflux) -- (aj3);

\end{tikzpicture}
\end{center}

Scheme 7.2. Synthesis of AJ3$^8$
7.3.3 Synthesis of AJ4

The synthesis route of AJ4 is shown in Scheme 2.3. AJ3 (2.60 g, 9.5 mmol, 1 eq) was dissolved in ethanol (19.0 mL) and sodium acetate trihydrate (2.59 g, 19.0 mmol, 2 eq) was dissolved in water (9.5 mL), separately. Into a 100 mL one neck round bottom flask, both solutions were mixed, followed by adding acetic acid (0.95 mL) slowly to the solution. The solution was refluxed for 3.5 hours with stirring. When the refluxing was finished, rotary evaporator was applied to remove the solvent. After adding water to achieve a 60 mL solution, extraction was performed with ethyl acetate (60 mL × 3). All organic layers were collected and solvent was removed to yield the crude product (2.4 g). From thin layer chromatography (TLC), the yield was 100%. So the crude product could be used directly for the synthesis of AJ5. If there was a little yellow color in the crude product, purification could be performed by column chromatography (40% ethyl acetate - 60% hexane) resulting in a pure white product.\(^8\) \(^1\)H NMR (300 MHz, CHLOROFORM-d) \(\delta\) 2.04-2.08 (m, 2H), 2.22 (s, 3H), 3.87 (t, J = 5.86 Hz, 2H), 4.20 (t, J = 6.01 Hz, 2H), 5.29 (s, 2H), 6.96 (d, J = 8.78 Hz, 2H), 7.89 (d, J = 8.78 Hz, 2H).

![Scheme 7.3. Synthesis of AJ4\(^8\)](image)

7.3.4 Synthesis of AJ5

The synthesis route of AJ5 is shown in Scheme 2.4. To a 50 mL one neck round bottom flask, sodium hydroxide (0.4560 g, 11.4 mmol, 1.2 eq) was added in water (5 mL). Meanwhile, in another 50 mL one neck round bottom flask, AJ4 (2.4 g, 9.5 mmol, 1 eq)
was dissolved in methanol (14 mL). Then the solution of AJ4 was added to the base solution and it was stirred at room temperature. After 2 hour of reaction, neutralization of the solution was performed by sodium bisulfate (0.3426 g, 2.9 mmol, 0.3 eq) to set the value of pH to 6.5. After removing methanol on a rotary evaporator, a water suspension with white solid was obtained. Ethyl acetate was added to the suspension to dissolve the white solid and water was added to the above solution to obtain a 60 mL solution. Extraction was performed with ethyl acetate (60 mL × 3). At last, sodium sulfate was added to the collected organic layers. After removing solvent, a crude product was yielded and it was purified by column chromatography (50% ethyl acetate - 50% hexane) resulting in a white product (1.2 g).\(^8\) \(^1\)H NMR (300 MHz, CHLOROFORM-d) \(\delta\) 2.05-2.13 (m, 2H), 3.88 (t, \(J = 5.85\) Hz, 2H), 4.21 (t, \(J = 6.01\) Hz, 2H), 4.83 (s, 2H), 6.99 (d, \(J = 8.78\) Hz, 2H), 7.91 (d, \(J = 8.78\) Hz, 2H).

![Scheme 7.4. Synthesis of AJ5](image)

7.3.5 Synthesis of N,N-bis(2-hydroxyethyl)propionamide

The synthesis route of N,N-bis(2-hydroxyethyl)propionamide is shown in Scheme 2.5.

Diethanolamine (22.08 g, 200 mmol, 2 eq) and ethyl propionate (10.22 g, 100 mmol, 1 eq) were added to a 250 mL round bottom flask with a stir bar. After heating the mixture at 80 °C for 24 hours, the mixture was set on a high vacuum line to remove byproduct. Further purification was performed by column chromatography (10% methanol -90% dichloromethane) resulting in a viscous liquid which was set up on the high vacuum line
with stirring. Crystallization occurred yielding a white crystal as the pure product. (6 g).\(^2^7\)

\(^1\)H NMR (300 MHz, CHLOROFORM-d) \(\delta\) 1.15 (t, \(J = 7.47\), 3H), 2.39-2.47 (m, 2H), 3.53 (t, \(J = 5.05\) Hz, 4H), 3.83 (t, \(J = 4.68\) Hz, 4H).

Scheme 7.5. Synthesis of \(\text{N,N-bis(2-hydroxyethyl)propionamide}^2^7\)

7.3.6 Synthesis of photoresponsive AJ5 copolymer

AJ5 (0.3000 g, 1.43 mmol, 0.5 eq), adipic acid (0.4171 g, 2.85 mmol, 1 eq), \(\text{N,N-bis(2-hydroxyethyl)propionamide}^2\) (0.2300 g, 1.43 mmol, 0.5 eq) and DPTS (0.3337 g, 1.14 mmol, 0.4 eq) were added to a 25 mL round bottom flask, then the anhydrous dichloromethane was added to the flask through a needle and syringe. The reaction was set up under cryogenic conditions and vacuumed twice. After reaching constant temperature in an ice bath for 10 minutes, DIC (1.34 mL, 1.0805 g, 8.56 mmol, 3 eq) was added to the reaction dropwise and the solution was held at a constant temperature for 20 minutes in an ice bath. Nitrogen was purged into the reaction for 48 hours under room temperature. Further purification was performed by precipitation in methanol. After drying in the vacuum oven or on the high vacuum line, the polymer that was yielded was a light yellow sphere (545 mg). \(^1\)H NMR (300 MHz, CHLOROFORM-d) \(\delta\) 1.13 (t, \(J = 7.32\) Hz, 3H), 1.59-1.81 (m, 8H), 2.12-2.16 (m, 2H), 2.36 (t, \(J = 8.49\) Hz, 8H), 2.50 (m, 2H), 3.59 (t, 2H), 4.11 (t, 2H), 4.20 (t, \(J = 4.39\) Hz, 4H), 4.26 (t, \(J = 6.44\) Hz, 2H), 5.29 (s, 2H), 8.93 (d, \(J = 8.49\) Hz, 2H), 7.07 (d, \(J = 7.61\) Hz, 2H).
7.4 Fabrication of thin films with spin coating

Before spin coating was performed, silica wafers were cleaned. They were immersed in soap solution for 30 minutes, then deionized water was used to wash the wafers four times. After immersing wafers in acetone for 30 minutes, they were washed with acetone three times and dried with air. All wafers were kept in the hood overnight to make sure that acetone was evaporated.

AJ5 copolymer (160 mg) was dissolved in chloroform (8 mL) to obtain a 2% solution. 2000 RPM were applied to coat the polymer, then the films were dried at room temperature overnight.
CHAPTER VIII
RESULTS AND DISCUSSION

The GPC data of AJ5 copolymer is shown in the Table 8.1.

Table 8.1. GPC data of AJ5 copolymer

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Mn (kDa)</th>
<th>Mw (kDa)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJ5 copolymer</td>
<td>41</td>
<td>163</td>
<td>4.003</td>
</tr>
</tbody>
</table>

![Figure 8.1. GPC trace of AJ5 copolymer](image)

From the GPC trace which is shown in Figure 3.1 there is a shoulder on the trace. So it shows that two polymers may have formed during the polymerization. The erosion properties of the polymer were tested first. The thickness of films under irradiation (300 nm UV light) of different times will be tested by ellipsometer. 20 samples will be divided into 5 groups and every group will contain 4 samples for repeating experiments and error
analysis. Before irradiation, a drop of methanol will be added to the surface of the film. Then the methanol will be removed in the vacuum oven overnight.

The erosion properties will be analyzed and compared with polymers which are structurally similar to other polymers from the Joy Lab. Polymer films will be made by spin coating on silicon wafers with polymer solution (20 mg/mL).

If the results are not perfect, the polymerization condition will be modified. Dimethylformamide will be used as the solvent for the polymerization. Because of the low reaction rate for polyester formation, the shoulder in the GPC trace might be divided into two peaks. If the two polymers can be separated, the reaction rate of AJ5 and N,N-bis(2-hydroxyethyl)propionamide will be compared. The monomer with a lower reaction rate will be added into reaction system first, after a certain amount of time, the monomer with a higher reaction rate will be added.
CHAPTER IX

CONCLUSIONS

AJ3 will be degraded quickly in the liquid phase and it should be stored carefully. My suggestion is that the purification should be finished as soon as possible and the pure AJ3 should be reacted to AJ5 instead of storing it, if AJ3 is not needed for the specific usage.

From the GPC trace, two polymers might be formed during the polymerization, which will show that the AJ5 and N,N-bis(2-hydroxyethyl)propionamide have different reactivity ratios.
REFERENCES


$^1$H NMR spectroscopy of DP2
$^1$H NMR spectroscopy of DP4

2015.12.1_DP4_TL_DMSO_3SP

$^1$H NMR spectroscopy of DP8

2016.03.5_DP8_TL
$^1$H NMR spectroscopy of DP9

2015_07_20_DP0_TL_NEW1.ESP

$^1$H NMR spectroscopy of pre-polymer from refluxing

2015_10_19_PREPOLA_TL_ESP
$^1$H NMR spectroscopy of pre-polymer from DIC/DPTS catalyst system (6h)

$^1$H NMR spectroscopy of pre-polymer from DIC/DPTS catalyst system (12 h)
$^1$H NMR spectroscopy of pre-polymer from DIC/DPTS catalyst system (12 h) without cryogenic condition

$^1$H NMR spectroscopy of pre-polymer from DIC/DPTS catalyst system (24 h)
$^1$H NMR spectroscopy of pre-polymer from DIC/DPTS catalyst system (48 h)

$^1$H NMR spectroscopy of PLGA0505(24h)DP9
$^1$H NMR spectroscopy of PLGA0505(6.5h)DP9

$^1$H NMR spectroscopy of PLGA0505DP902
$^1$H NMR spectroscopy of PLGA0703DP902

2015_01_23_PLGA0703DP902_ONE POT_48H_1_Tl apo

Water

DMF

$^1$H NMR spectroscopy of PLGA0703DP902

2015_02_8_PLGA0703DP902_48H_2C_Tl2 apo

Water

DMF

64
$^1$H NMR spectroscopy of easy-to-dissolve polymer

$^1$H NMR spectroscopy of hard-to-dissolve polymer
Chloroform GPC curve of pre-PLGA0505 (6 h)

Chloroform GPC curve of pre-PLGA0505 (12 h) without cryogenic condition
Chloroform GPC curve of pre-PLGA0505 (12 h)

Chloroform GPC curve of pre-PLGA0505 (24 h)
Chloroform GPC curve of pre-PLGA0505 (48 h)

- Pre PLGA0505 (48h)
  - $M_n$: 53 kDa
  - $M_w$: 78 kDa
  - PDI: 1.458

Chloroform GPC curve of PLGA0505(24h)DP9

- PLGA0505(24h)DP9
  - Peak 1
    - $M_n$: 30 kDa
    - $M_w$: 46 kDa
    - PDI: 1.522
  - Peak 2
    - $M_n$: 3 kDa
    - $M_w$: 4 kDa
    - PDI: 1.498
Chloroform GPC curve of easy-to-dissolve polymer

Chloroform GPC curve of hard-to-dissolve polymer
Chloroform GPC curve of PLGA0505DP902

![Chloroform GPC curve of PLGA0505DP902](image1)

M_n: 26 kDa
M_w: 43 kDa
PDI: 1.640

Chloroform GPC curve of PLGA0703DP902

![Chloroform GPC curve of PLGA0703DP902](image2)

M_n: 17 kDa
M_w: 56 kDa
PDI: 3.373
Chloroform GPC curve of PLGA0703DP902 2g

![Graph showing GPC curve with elution time in minutes on the x-axis and RI signal in mV on the y-axis.]

- $M_n$: 16 kDa
- $M_W$: 41 kDa
- PDI: 2.631

$^1$H NMR spectroscopy of AJ2

![NMR spectrum with chemical shifts in ppm and peaks labeled a to g.]
$^1$H NMR spectroscopy of AJ3

2015_02_23_AJ3_TL_DL

$^1$H NMR spectroscopy of AJ4

2015_02_23_AJ4_TL_DL
$^1$H NMR spectroscopy of AJ5

$^1$H NMR spectroscopy of N,N-bis(2-hydroxyethyl)propionamide
$^1$H NMR spectroscopy of AJ5 copolymer