Published in final edited form as:

J Bioact Compat Polym. 2006 March ; 21(2): 123–133. doi:10.1177/0883911506062976.

Synthesis and Characterization of Salicylic Acid-Based Poly(Anhydride-Ester) Copolymers

Robert C. Schmeltzer and Kathryn E. Uhrich*

Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ 08854-8087, USA

Abstract

A series of poly(anhydride-esters) based on poly(1,10-bis(*o*-carboxyphenoxy)decanoate) (CPD) and poly(1,6-bis(*p*-carboxyphenoxy)hexane) (*p*-CPH) were synthesized by melt-condensation polymerization. Poly-(anhydride-esters) that contain CPD hydrolytically degraded into salicylic acid, however, these homopolymers have mechanical and thermal characteristics that limit their use in clinical applications. The synthesis and characterization of copolymers of CPD with *p*-CPH, a monomer known to generate mechanically stable homopolymers, was investigated. By changing the CPD to *p*-CPH monomer ratios, the salicylic acid loading and thermal/mechanical properties of the copolymers was a controlling factor; increasing the CPD concentration increased the salicylate loading but decreased the polymer stability; whereas increasing the *p*-CPH concentration increased the thermal and mechanical stability of the copolymers. Specifically, decreasing the CPD:*p*-CPH ratio resulted in lower salicylate loading and increased thermal decomposition temperatures. The glass transition temperatures (°C) varied from 27 to 38°C, a desirable range for elastomeric biomedical implants.

Keywords

poly(anhydride-ester); salicylic acid; drug loading; thermal properties; degradation; polyanhydride stability

INTRODUCTION

In the early 1980s, polyanhydrides were examined for sustained drug release for controlled drug delivery applications [1–4]. Over the next several decades, extensive research was conducted on polyanhydrides for various biomedical applications that yielded numerous new polymer systems [5–15]. Polyanhydrides have excellent controlled release characteristics and degrade *in vitro* and *in vivo* to their acid counterparts as non-cytotoxic products [4,6,16]. For example, polyanhydrides containing sebacic acid and 1,3-bis(*p*-carboxyphenoxy)-propane are hydrolytically degradable copolymers (**1**) used as implanted devices to control chemotherapeutic drug delivery (Figure 1) [15,17].

The degradation rate of biodegradable polyanhydrides, such as polymer **1**, was controlled by the manipulation of the polymer composition to release admixed drug molecules [18–21]. The polyanhydride copolymer (**1**) of sebacic acid and 1,4-bis(*p*-carboxyphenoxy)propane (CPP) (Figure 1) has excellent biocompatibility characteristics and degrades by a surface-erosion process [4,7,11,22,23]. The controlled, non-enzymatic degradation of

polyanhydrides make these polymers particularly desirable for a variety of drug delivery applications. In addition, these materials are potentially useful as anti-biofilm coatings [24–26], tissue adhesion [27–29], and non-inflammatory coatings for medical devices [30–32].

Previously, our laboratory reported the synthesis of polyanhydrides that hydrolytically degrade into drugs, that is, the drug molecules were chemically incorporated into the polymer backbone rather than being physically admixed [33]. These poly(anhydride-esters) (2) released salicylic acid (3) and sebacic acid (4) upon hydrolytic degradation of the Molar ratio $m:n = 80:20$; polyanhydride copolymer polymer backbone (Figure 2) [33–37]. Polymer 2 is unique in that the drug was chemically incorporated into the polymer backbone, not attached as a side group nor physically admixed by melting or co-dissolved with the polymer. The sebacic acid (4) is the “linker” in the polymer used to connect the salicylic acid units; it is also the major component of polymer 1 (Figure 1) [15].

A unique feature of this polymeric prodrug (2) design is that the polymer itself is a controlled drug-release system with high drug-loading capabilities (62wt% of polymer 2 is salicylic acid). Therefore, drug release is directly dependent on the hydrolytic cleavage of the anhydride and ester bonds, providing an advantage as a drug-delivery system; drug release was directly controlled by the composition of the polymer backbone [36–38]. An additional feature is that the polymeric prodrug can be easily manipulated to yield fibers by extrusion, films by solvent-casting, or microspheres by emulsion-precipitation methods [34,39].

A potential drawback to polymer 2 is that it has a low glass transition temperature (T_g) of 27°C, which means that the material softens at body temperature [39,40]. For medical applications that require load-bearing, such as orthopedic devices, it is necessary to enhance the thermal and mechanical stability of these polymers. In previous work, we investigated copolymers in which the polymer properties were modulated by modifying the ratio of comonomers such as sebacic acid (4) and *p*-CPH (5) [41–43]. In this study, we prepared a series of copolymers composed of CPD (2) and *p*-CPH (5). The monomer *p*-CPH (5) was chosen to improve the thermal and mechanical characteristics; it is also structurally related to the CPP compound in polymer 1 (Figure 1). Homopolymers of *p*-CPH have higher mechanical strength and improved stability over polymer 2 [34,35,40]. Homopolymer 2 is an amorphous polymer (no melting temperature) with a glass transition temperature near room temperature, which limits the fabrication of these polymers into biomedical devices. In contrast, homopolymer 5 is a crystalline polymer ($T_m = 147^\circ\text{C}$) with a higher T_g (48°C) [42]. Therefore, copolymers of CPD (2) and *p*-CPH (5) were anticipated to enhance the handling properties of CPD homopolymers (2). For example, a copolymer of CPD (2) and *p*-CPH (5) (50:50) generated stable membranes that withstand surgical implantation procedures [40]. In this paper, the synthesis and characterization of a series of poly(anhydride-esters) composed of CPD and *p*-CPH are described. The polymers were characterized by FT-NMR and FT-IR spectroscopy, as well as by molecular weight, polydispersity, thermal transition temperatures and drug loading capacity.

EXPERIMENTAL

Materials

Proton nuclear magnetic resonance (^1H -NMR) spectra were recorded on either a Varian 200MHz or 300MHz spectrometer. The deuterated solvent used to dissolve the samples (5–10mg) was DMSO- d_6 , or CDCl_3 , with the solvent as the internal reference. Infrared (IR) spectra were measured on a Thermo Nicolet/Avatar 360 FT-IR spectrometer, by depositing samples onto NaCl plates (if liquid) or solvent-casting samples from methylene chloride

onto NaCl plates (if solid). Elemental analyses were provided by QTI (Whitehouse, NJ). Melting points (T_m) were determined on a Thomas-Hoover apparatus.

Polymer Preparation

The CPD diacid (**6**) and *p*-CPH diacid (**7**) were synthesized according to methods previously reported [44]. In brief, the diacid (1.0g) was added to an excess of acetic anhydride (100mL), then stirred at room temperature (for CPH **6**) or reflux temperature (for *p*-CPH **7**) until a clear homogenous solution was observed (~120min). The monomer was isolated by removing excess acetic anhydride under vacuum, and then washed with diethyl ether (50mL); monomers (**8** and **9**) were isolated as white solids.

Different copolymers of CPD and *p*-CPH were synthesized by melt-condensation polymerization. The molar ratios of CPD to *p*-CPH ranged from 9:1, 7:3, 6:4, 5:5, 4:6, 3:7, and 1:9. A typical procedure was as follows: monomers (**8** and **9**) (1.5 to 2.0g total) were placed in a two-necked round-bottom flask equipped with an overhead stirrer (T-line Laboratory Stirrer, Talboys Engineering). The reaction mixture was heated to 180°C using a temperature controller (Cole Parmer) in a silicone oil bath under high vacuum (<2mmHg) for 3 to 6h. During this time, the melt was actively stirred at ~100rpm by the overhead stirrer. Polymerization was complete when the viscosity of the melt remained constant or solidified. The polymer (**10**) was cooled to room temperature, dissolved in a minimal volume of methylene chloride (5mL), and reprecipitated into a 20-fold excess of diethyl ether (100mL).

CPD:*p*-CPH Poly(anhydride-ester) (**10**)

The yield was quantitative (off-white to white solid). The $^1\text{H-NMR}$ and FT-IR data of all the copolymers were similar with only variations in peak intensities. $^1\text{H-NMR}$ (DMSO- d_6): δ 8.20 (b, 2H, ArH), 8.07 (b, 4H, ArH), 7.95 (b, 2H, ArH), 7.75 (b, 2H, ArH), 7.40 (b, 2H, ArH), 6.93 (b, 4H, ArH), 4.10 (b, 4H, CH_2), 2.20 (b, 4H, CH_2), 1.87 (b, 4H, CH_2), 1.55 (b, 8H, CH_2), 1.25 (b, 8H, CH_2). IR (NaCl, cm^{-1}): 1792 (C=O, anhydride), 1760 (C=O, ester), 1740 (C=O, anhydride), 1710 (C—O, ester), 1185 (C—O, ether).

Polymer Characterization

Weight-average molecular weights (M_w) were determined by gel permeation chromatography (GPC) on a Perkin-Elmer liquid chromatography system consisting of a Series 200 refractive index detector, a Series 200 LC pump, and an ISS 200 advanced sample processor. A Dell OptiPlex GX110 computer running Perkin-Elmer TurboChrom 4 software was used for data collection and processing, and to automate the analysis via Perkin-Elmer Nelson 900 Series Interface and 600 Series Link. Polymers were dissolved in methylene chloride (5mg/mL) and filtered through 0.45 μm poly(tetrafluoroethylene) (PTFE) syringe filters (Whatman, Clifton, NJ) before elution. Samples were resolved on a Jordi divinylbenzene mixed-bed GPC column (7.8 $\times$ 300mm) (Alltech Associates, Deerfield, IL) at 25°C, with methylene chloride as eluent at a flow rate of 0.5mL/min. Molecular weights were calibrated relative to narrow molecular weight polystyrene standards (Polysciences, Dorval, Canada).

Thermal analyses were performed on a Perkin-Elmer system consisting of Pyris 1 DSC and TGA 7 analyzers with TAC 7/DX instrument controllers. Perkin-Elmer Pyris software was used for data collection on a Dell OptiPlex GX110 computer. For DSC, samples (5mg) were heated under dry nitrogen gas. Data were collected at heating and cooling rates of 10°C/min with a two-cycle minimum. For TGA, samples (10mg) were heated under dry nitrogen gas. Data were collected at a heating rate of 10°C/min. Decomposition temperatures were defined as the onset of decomposition.

RESULTS AND DISCUSSION

A series of copolymers based on CPD and *p*-CPH were synthesized and the physicochemical properties compared as a function of polymer composition. The polymers described herein were prepared *via* melt-condensation polymerization methods as previously detailed [44]. An outline of the CPD:*p*-CPH poly(anhydride-ester) (**10**) synthesis, starting from the relevant diacids (**6** and **7**) is outlined in Figure 3.

Diacids **6** and **7** were synthesized as previously reported [33,44]. CPD (**6**) and *p*-CPH (**7**) were separately stirred in excess acetic anhydride at room temperature and reflux temperature, respectively. Monomers (**8** and **9**) were obtained as white solids. Various molar ratios of the two solids, **8** and **9**, (9:1, 7:3, 6:4, 5:5, 4:6, 3:7, 1:9) were melt-polymerized to yield the corresponding CPD:*p*-CPH copolymers (**10**). Melt-condensation polymerization was performed using a modular apparatus in conjunction with an overhead mechanical stirrer, the polymerization was deemed complete upon solidification.

The molecular weights obtained for these copolymers were typically above 25,000, corresponding to >50 repeat units. The molecular weights for these poly(anhydride-esters) characteristic for aromatic polyanhydrides synthesized by melt condensation [4,41,45]. The glass transition temperatures (T_g) ranged from 27 to 38°C, with no indication of a melting temperature (T_m) for five of the seven polymers, indicating that these are highly amorphous copolymers. CPD:*p*-CPH (9:1) copolymers gave the lowest T_g (27°C) and the CPD:*p*-CPH (1:9) copolymer yielded the highest T_g (38°C). Poly(*p*-CPH) is a biodegradable, highly crystalline polymer with a T_g = 48°C and T_m = 142°C [46]; whereas, poly(CPD) is a biodegradable, amorphous polymer with a T_g = 27°C [33,44]. By melt-polymerizing monomers of CPD and *p*-CPH to form a copolymer, a series of polymers with T_g values in a narrow range were obtained. Only copolymers with high *p*-CPH ratios (>70%) were crystalline.

This work expands upon our preliminary *in vivo* studies using a 50:50 copolymer, in which the copolymer displayed superior handling properties over the CPD homopolymer [39,40]. In addition to enhancing the mechanical and thermal properties, copolymerizing poly(CPD) and poly(*p*-CPH) at different ratios produced a series of salicylic acid-based poly(anhydride-esters) with drug loads of salicylic acid ranging from 6 to 50wt%.

CONCLUSIONS

A series of biodegradable polymers derived from CPD and *p*-CPH monomers were synthesized. By copolymerizing monomers of CPD and *p*-CPH at various ratios, a series of poly(anhydride-esters) that contain varying levels of salicylic acid (6 to 50wt%) were obtained. Overall, the addition of *p*-CPH as a monomer did not significantly influence the molecular weights or T_g values. Notably, most copolymer compositions were amorphous; T_m values were only observed for copolymers with 70 or 90% *p*-CPH composition and were very similar (27 to 38°C).

Acknowledgments

The authors thank the National Institutes of Health (DE 13207) for their financial support.

References

1. Langer R, Peppas N. Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review. *J Macromol Sci.* 1983; 23:61–126.

2. Langer R, Siegel R, Brown L, Leong K, Kost J, Edelman E. Controlled Release Systems: Some Recent Advances. *Polym Mater Sci Eng.* 1984; 51(51):115–118.
3. Langer R, Peppas N. Present and Future Applications of Biomaterials in Controlled Drug Delivery Systems. *Biomaterials.* 1981; 2:201–214. [PubMed: 7034798]
4. Domb A, Langer R. Polyanhydrides. I Preparation of High Molecular Weight Polyanhydrides. *J Polym Sci, Part A: Polym Chem.* 1987; 25:3373–2286.
5. Rosen H, Chang J, Wnek G, Linhardt R, Langer R. Bio-erodible Polyanhydrides for Controlled Drug Delivery. *Biomaterials.* 1983; 4:131–133. [PubMed: 6860755]
6. Leong K, Kost Y, Mathiowitz E, Langer R. Polyanhydrides for Controlled Release of Bioactive Agents. *Biomaterials.* 1986; 7:364–371. [PubMed: 3778996]
7. Mathiowitz E, Saltzman M, Domb A, Dor P, Langer R. Polyanhydride Microspheres as Drug Carriers. II Microencapsulation by Solvent Removal. *J Appl Polym Sci.* 1988; 35:755–774.
8. Park Y, Nam K, Ha S, Pai C, Chung C, Lee S. Porous Poly(L-lactide) Membranes for Guided Tissue Regeneration and Controlled Drug Delivery: Membrane Fabrication and Characterization. *J Control Rel.* 1997; 43:151–160.
9. Jain J, Modi S, Domb A, Kumar N. Role of Polyanhydrides as Localized Drug Carriers. *J Control Rel.* 2005; 103(3):541–563.
10. Qixiang C, Zhu K, Zhang J. Salicylic Acid and PEG-Contained Polyanhydrides: Synthesis, Characterization, and In Vitro Salicylic Acid Release. *Drug Delivery.* 2005; 12(2):97–102. [PubMed: 15824034]
11. Narasimhan B, Kipper M. Surface-Erodible Biomaterials for Drug Delivery. *Adv Chem Eng.* 2004; 29:169–218.
12. Vogel B, Mallapragada S. Synthesis of Novel Biodegradable Polyanhydrides Containing Aromatic and Glycol Functionality for Tailoring of Hydrophilicity in Controlled Drug Delivery Devices. *Biomaterials.* 2004; 26(7):721–728. [PubMed: 15350776]
13. Guo W, Huang I, Tang R, Chi Q. New Polyanhydrides Derived from C12, C13, C14, C15 Dibasic Acid: Synthesis and Characterization. *Polymer.* 2004; 45(16):5743–5748.
14. Quick D, Macdonald K, Anseth K. Delivering DNA from Photocrosslinked, Surface Eroding Polyanhydrides. *J Control Rel.* 2004; 97(2):333–343.
15. Brem H, Piantadosi S, Burger P, Walker M, Selker R, Vick N, Black K, Sisti M, Brem S, Mohr G, Muller P, Morawetz R, Schold S. Placebo-Controlled Trial of Safety and Efficacy of Intra-operative Controlled Delivery by Biodegradable Polymers of Chemotherapy for Recurrent Gliomas. *Lancet.* 1995; 345:1008–1012. [PubMed: 7723496]
16. Leong K, D'Amore P, Maletta M, Langer R. Bioerodible Polyanhydrides as Drug-Carrier Matrices. II Biocompatibility and Chemical Reactivity. *J Biomed Mater Res.* 1986; 20:51–64. [PubMed: 3949823]
17. Langer R. Biomaterials in Drug Delivery and Tissue Engineering: One Laboratory's Experience. *Acc Chem Res.* 2000; 33:94–101. [PubMed: 10673317]
18. Domb A, Langer R. Solid-State and Solution Stability of Poly(anhydrides) and Poly(esters). *Macromolecules.* 1989; 22:2117–2122.
19. Seidel J, Uhrich K, Laurencin C, Langer R. Erosion of Poly(anhydride-co-imides): A Preliminary Mechanistic Study. *J Appl Polym Sci.* 1996; 62:1277–1283.
20. Attawia M, Borden M, Herbert K, Katti D, Asrari F, Uhrich K, Laurencin C. Regional Drug Delivery with Radiation for the Treatment of Ewing's Sarcoma: In Vitro Development of a Taxol Release System. *J Control Rel.* 2001; 71:193–202.
21. Hanes J, Chiba M, Langer R. Degradation of Porous Poly(anhydride-co-imide) Microspheres and Implications for Controlled Macromolecule Delivery. *Biomaterials.* 1998; 19:163–172. [PubMed: 9678864]
22. Goepferich A. Mechanisms of Polymer Degradation and Erosion. *Biomaterials.* 1996; 17:103–114. [PubMed: 8624387]
23. Goepferich A, Langer R. Modeling Monomer Release from Bioerodible Polymers. *J Control Rel.* 1995; 33:55–69.

24. Cha D, Chinnan M. Biopolymer-Based Antimicrobial Packaging: A Review. *Crit Rev Food Sci Nutrition*. 2004; 44(4):223–237. [PubMed: 15462127]
25. Pascual A. Pathogenesis of Catheter-Related Infections: Lessons for New Designs. *Clin Microbiol Infect*. 2002; 8(5):256–264. [PubMed: 12047402]
26. Darouiche R. Device-Associated Infections: A Macroproblem that Starts with Microadherence. *Clin Infect Diseases*. 2001; 33(9):1567–1572. [PubMed: 11577378]
27. Spotnitz W, Prabhu R. Fibrin Sealant Tissue Adhesive –Review and Update. *J Long-Term Effects Med Implants*. 2005; 15(3):245–270.
28. Eaglstein W, Sullivan T. Cyanoacrylates for Skin Closure. *Dermat Clin*. 2005; 23(2):193–198.
29. Alam H, Burris D, DaCorta J, Rhee P. Hemorrhage Control in the Battlefield: Role of New Hemostatic Agents. *Military Med*. 2005; 170(1):63–69.
30. Harris L, Tosatti S, Wieland M, Textor M, Richards R. Staphylococcus Aureus Adhesion to Titanium Oxide Surfaces Coated with Non-Functionalized and Peptide-Functionalized Poly(L-Lysine)-Grafted-Poly(Ethylene Glycol) Copolymers. *Biomaterials*. 2004; 25(18):4135–4148. [PubMed: 15046904]
31. Su S. Novel Coating to Reduce Medical Device Encrustation. *Med Device Technol*. 2004; 15(1):12–14. [PubMed: 14994632]
32. Darouiche R. Treatment of Infections Associated with Surgical Implants. *New England J Med*. 2004; 350(14):1422–1429. [PubMed: 15070792]
33. Erdmann L, Uhrich K. Synthesis and Degradation Characteristics of Salicylic Acid-Derived Poly(Anhydride-Esters). *Biomaterials*. 2000; 20:1941–1946.
34. Whitaker-Brothers K, Uhrich K. Poly(anhydride-ester) Fibers: Role of Copolymer Composition on Hydrolytic Degradation and Mechanical Properties. *J Biomed Mater Res, Part A*. 2004; 70A(2):309–318.
35. Whitaker-Brothers K, Uhrich K. Investigation into the Erosion Mechanism of Salicylate-based Poly(anhydride-esters). *J Biomed Mater Res, Part A*. 2006; 76A(3):470–479.
36. Schmeltzer R, Schmalenberg K, Uhrich K. Synthesis and Cytotoxicity of Salicylate-Based Poly(anhydride-esters). *Biomacromolecules*. 2005; 72A(6):354–362.
37. Prudencio A, Schmeltzer R, Uhrich K. Effect of Linker Structure on Salicylic Acid-Derived Poly(anhydride-esters). *Macromolecules*. 2005; 38:6895–6901.
38. Anastasiou T, Uhrich K. Aminosalicylate-Based Biodegradable Polymers: Synthesis and In Vitro Characterization of Poly(anhydride-esters) and Poly(anhydride-amides). *J Polym Sci A: Polym Chem*. 2003; 41:3667–3679. (invited).
39. Harten R, Svach D, Schmeltzer R, Uhrich K. Salicylic Acid-Derived Poly(anhydride-esters) Inhibit Bone Formation and Resorption *In Vivo*. *J Biomed Mater Res, Part A*. 2005; 42A(4):354–362.
40. Erdmann L, Macedo B, Uhrich K. Degradable Poly(anhydride-ester) Implants: Effects of Localized Salicylic Acid Release on Bone. *Biomaterials*. 2000; 21:2507–2512. [invited]. [PubMed: 11071600]
41. Uhrich K, Gupta A, Thomas T, Laurencin C, Langer R. Synthesis and Characterization of Degradable Poly(anhydride-co-imides). *Macromolecules*. 1995; 28:2184–2193.
42. Uhrich K, Larrier D, Laurencin C, Langer R. *In Vitro* Degradation Characteristics of Poly(anhydride-imides) Containing Pyromellitylimidoalanine. *J Polym Sci, Part A: Polym Chem*. 1996; 34:1261–1269.
43. Uhrich K, Thomas T, Laurencin C, Langer R. *In Vitro* Degradation Characteristics of Poly(anhydride-imides) Containing Trimellitylimidoglycine. *J Appl Polym Sci*. 1997; 63:1401–1412.
44. Schmeltzer R, Anastasiou T, Uhrich K. Optimized Synthesis of Salicylate-Based Poly(anhydride-esters). *Polym Bull*. 2003; 49(6):441–448.
45. Kricheldorf H, Jurgens C. Soluble Polyanhydrides Derived from Isophthalic Acid, 4-Hydroxybenzoic Acid and Various Diphenols. *Macromol Chem Phys*. 1996; 197:2775–2783.
46. Uhrich K, Laurencin C, Langer R. Synthesis and Characterization of Poly(anhydride-co-imides): Solution Polymerization of Biodegradable Polymers Derived from Amino Acids. *Polym Mat Sci Eng*. 1994; 70:239.

Molar ratio m:n = 80:20; polyanhydride copolymer

Figure 1.
Polyanhydride copolymer matrix for drug delivery.

Figure 2.
Hydrolysis of salicylic acid-based poly(anhydride-ester).

Figure 3.
Synthesis of CPD:*p*-CPH copolymers.

Table 1

Comparison of CPD:p-CPH copolymer properties.

CPD:p-CPH ratio		M _w	PDI	T _g (°C)	T _m (°C)	T _d (°C)	Salicylic acid (wt%)	
Theor.	Observ. ^a						Theor.	Observ. ^a
9:1	8:1	29,500	1.2	27	<i>b</i>	390	56	50
7:3	6:3	76,300	1.3	32	<i>b</i>	392	44	38
6:4	5:4	37,400	1.6	28	<i>b</i>	393	37	32
5:5	5:5	47,500	1.4	33	<i>b</i>	407	31	31
4:6	4:6	27,800	2.0	28	<i>b</i>	416	25	25
3:7	3:7	43,000	3.1	34	51	428	19	19
1:9	1:9	28,500	1.2	38	128	431	6	6

^a Calculated from ¹H-NMR spectral data.^b Melting temperature (T_m) not observed.