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Stable polyanhydride synthesized from sebacic acid and ricinoleic acid

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ABSTRACT

Poly(anhydride) are unstable and prone to hydrolytic degradation and depolymerisation *via* anhydride interchange. They are stored at −20 °C, packed under inert atmosphere until use. We synthesized a new poly(anhydride) from ricinoleic (RA) and sebacic (SA) acid with alternating ester-anhydride structure that is stable at 25 °C for over 18 months. The copolymer is also stable in chloroform solution and under γ-irradiation. The polymer hydrolyses through anhydride cleavage lasting ~7 days to form oligoesters, which are stable for >30 days. The release of gentamycin from the synthesized alternate polymer matrix is sustained compared to the random copolymer.

1. Introduction

Polyanhydrides have been used as biodegradable drug carriers [1]. Hundreds of polymer structures made from various diacids have been reported. One of the most reported polyanhydride poly(CPP-SA) (synthesized from 1,3-bis(*p*-carboxyphenoxy)propane and sebacic acid) is the polymer carrier in Gliadel brain tumour implant. Gliadel releases bis-chloroethylnitrosourea (BCNU) for post-surgery complementary treatment for glioblastoma multiforme (GBM) [2]; it is stored at −20 °C until use. All these polymers are unstable at room temperature, and they decrease in molecular weight with time. Molecular weight is decreased due to hydrolysis (moisture accumulated during manufacturing or storage, penetrating through the package). Another cause for decrease in molecular weight is reversible depolymerisation *via* anhydride interchange [3,4]. Therefore, polyanhydrides require freezing storage conditions, thereby limiting their use in drug delivery systems.

Ricinoleic (RA)- sebacic (SA) acid poly(ester-anhydrides) have been used for drug delivery [1,5–8]. These RA-SA copolymers are composed of hydrophobic backbone, hydrolytically labile anhydride bonds, and ester linkages. Drug release may be manipulated by modulating the polymer composition [9–11]. These systems are unstable, when stored at room temperatures, they depolymerise with a sharp decline in molecular weights. At 4 °C the molecular weight dropped to about one third after 6 months. Hence, these polymers were only stable for one month at 4 °C, and for 48 h at 37 °C. Accordingly, these polymers need to be handled and stored in special conditions including airtight packages, under nitrogen atmosphere, away from moisture, and at sub-zero temperatures [5,9]. Hydrophobic nonlinear side chains of RA hinder anhydride interchange and hydrolysis [12].

Polyanhydrides lose their molecular weight through internal anhydride exchange reactions. This reaction between the polymer chains results in forming smaller fragments, resulting in decreased molecular weight [13]. We hypothesized that a hydrophobic fatty chain shielding each and every anhydride bond along the polyanhydride chain would reduce the ability of traces of water molecules to hydrolytically cleave

Abbreviations: RA, ricinoleic acid; SA, sebacic acid; PSA, polysebacic acid.

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the anhydride bonds resulting in a stable polyanhydride. Thus, alternating copolymer of ricinoleic acid (RA) and sebacic acid (SA), where each anhydride bond is shielded by the RA —$(CH_2)_6$—CH_3 fatty side chain, is expected to provide a stable polyanhydride. This report describes the synthesis and characterization of alternating poly(RA-SA) with the emphasis on storage stability at room temperature.

2. Experimental

2.1. Materials

Sebacic acid (SA, 99% pure; Aldrich, Milwaukee, WI), and acetic anhydride (Merck, Darmstadt, Germany) were used as received. Ricinoleic acid (RA) was prepared from the hydrolysis of castor oil as previously described. All solvents were analytical-grade from Sigma–Aldrich (Rosh HaAyin, Israel) or BioLab Jerusalem, and were used without further purification.

2.2. Spectral analysis

^1H and ^{13}C NMR spectra ($CDCl_3$) were obtained on a Varian 300 MHz or 500 MHz NMR spectrometer in tubes with 5 mm outside diameters. $CDCl_3$ containing tetramethylsilane served as a solvent and shift reference. All the reaction kinetics was evaluated by ^1H NMR, by calculating the relative integrals. Incorporation of RA, relative ester, and anhydride linkages in the reactions were quantified.

2.3. Molecular weight determination

The molecular weights were determined by gel permeation chromatography (GPC) system, Waters 1515. Isocratic HPLC pump with a Waters 2410 refractive index detector, a Waters 717 plus autosampler, and a Rheodyne (Cotati, CA) injection valve with a 20 μL-loop. The samples were eluted with $CHCl_3$ (HPLC grade) through linear Styragel HR5 column (Waters) at a flowrate of 1 mL/min. The molecular weights were determined relative to polystyrene standards (Polyscience, Warrington, PA) with a molecular-weight range of 500–100,000 Da.

2.4. DSC measurements

Samples (5–10 mg) were weighted by micro analytical balance ±1 μg. The thermal behaviors of random and alternating copolymers were investigated using DSC Q4000 (TA instruments). DSC thermograms were recorded by gradually heating from −40 °C to 100 °C at a rate 10 °C/min. A preheating and cooling cycle was also performed before measuring the actual thermograms from room temperature to 60 °C.

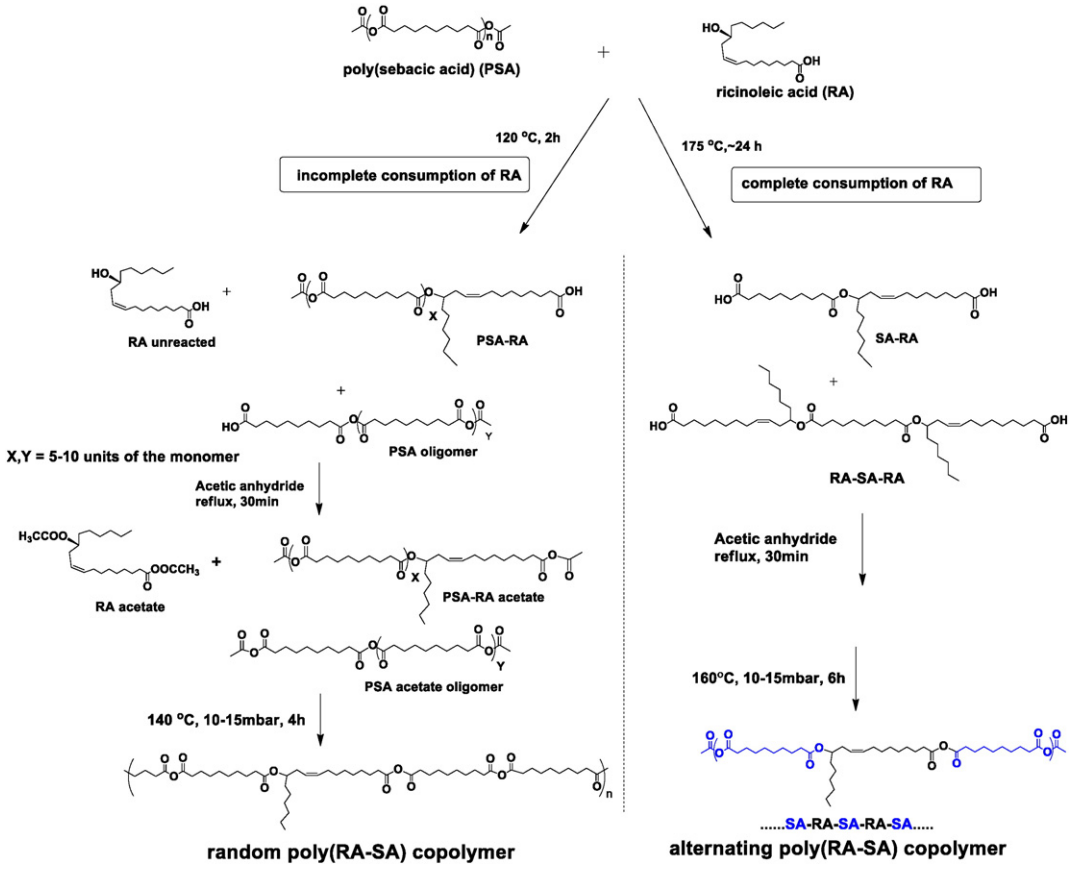
2.5. Synthesis

2.5.1. Poly(sebacic acid) (PSA)

Poly(sebacic acid) was synthesized by refluxing sebacic acid with acetic anhydride (1:5 w/v) for 30 min with constant stirring. The excess acetic anhydride was evaporated to dryness under vacuum. The clear, viscous residue was further polymerized by melt condensation at 160 °C for 4 h under vacuum (20 mbar) with constant stirring.

2.5.2. Ricinoleic acid oligomers

Ricinoleic acid oligomers were synthesized by heating ricinoleic acid at 160 °C to yield RA oligomers as characterized by ^1H NMR and GPC.



Scheme 1. One-pot synthesis of poly(RA-SA) under two different conditions, left side-synthesis under conditions where significant amount of RA (>20%) remain unreacted which result in a random block copolymer. The condition in the right side resulted in full consumption of RA in the first step to form a well-defined alternating polymer.