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Hydrolytic degradation of segmented polyurethane copolymers for biomedical applications

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ABSTRACT

The hydrolytic degradation of a series of segmented polyurethane (SPU) copolymers with potential for biomedical use has been investigated. A series of polyurethane copolymers were prepared from 1,6 - diisocyanatohexane (HDI), polycaprolactone diol (PCL), 2,2 - bis(hydroxymethyl) propionic acid (DMPA) and ethylene glycol (EG). The synthesized SPUs have a low soft segment glass transition temperature, a melting temperature around 50 °C, and a significant tailorable hardness for tissue engineering applications. Tensile testing of SPU films at 37 °C in phosphate buffered saline (PBS) indicated that the Young's modulus and elongation of the polyurethane copolymers could be tailored by altering the soft segment block length. All polyurethanes demonstrated hydrolytic degradability, which was measured in PBS solution at 37 °C, and the rate of degradation of the polyurethanes could be somewhat tailored by controlling the soft segment length.

1. Introduction

Tissue engineering has emerged as a promising way to offer new regeneration treatment of both soft and hard tissue [1]. An ideal implanted material must have the physico-mechanical properties similar to surrounding natural tissue, and it should be biocompatible and biodegradable in comparison to the native tissue regeneration process [2]. The primary objectives are to fill tissue defects and provide a biocompatible template allowing for the in growth of cells, blood vessels, and newly formed tissues, and the maintenance of extra cellular matrix [3]. Synthesis of new biocompatible and biodegradable segmented polyurethane polymers is of great interest for medical applications. The high degree of versatility of polyurethane chemistry allows the synthesis of novel biomaterials across a broad range of chemical, physical and biodegradation properties [4].

Segmented polyurethanes are extensively used polymers in biomedical applications because of their bio-stability, biodegradability and tailorable backbone structure from a wide range of available precursors. Segmented polyurethanes are composed of hard and soft segments. Long chain diols form the soft segments, whilst alternating diisocyanates and short chain diols (chain extenders) form the hard segments in the typically phase separated, micro-domain structure of segmented polyurethane copolymers [5]. A wide range of raw materials are available for synthesis of segmented polyurethane, which offers the opportunity to tailor the backbone structure to obtain polymers with different physical and physicochemical properties, and subsequently different biodegradability properties. Extra care has to be taken for the selection of raw materials prior to the biodegradable polyurethane copolymer synthesis so that the resulting biodegradation products of SPU are nontoxic and are capable of being metabolized or eliminated by the living organism [6]. For example, although widely used for non-degradable biomedical SPUs for chronic implantable device components, polyurethanes prepared from 4,4′-diphenylmethane diisocyanate (MDI) can produce toxic and carcinogenic degradation products such as aromatic diamines, thereby making them undesirable for use in degradable scaffold fabrication [7]. However, SPUs prepared from aliphatic diisocyanates have been reported to degrade into nontoxic decomposition products [8–11]; therefore, aliphatic diisocyanates are preferred over conventional aromatic diisocyanates for biodegradable segmented polyurethane copolymer synthesis.

Hydrolytic degradation of polymers have played a major role in the development of scaffold matrices suitable for facilitating tissue regeneration. Polyurethanes adequate for various biomedical applications require a wide range properties viz. hydrolytic

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degradability, biocompatibility, proper mechanical strength and ability to bind with other bio-molecules when implanted in a host animal [12]. In this paper, an approach to synthesis of segmented polyurethane copolymers based on polycaprolactone diol (PCL) as the soft segment, and ethylene glycol (EG), 2,2-bis(hydroxymethyl) propionic acid (DMPA) and 1,6-diisocyanatohexane (HDI) as the hard segment is presented. This particular SPU series was prepared with two different molecular weight polycaprolactone diols of $M_n \sim 2000$ and 530. Further, the copolymer structure was modified with 2,2-bis(hydroxymethyl) propionic acid. DMPA has two primary hydroxyl groups and one tertiary carboxylic group. The primary hydroxyl groups of DMPA will react with the isocyanate groups of HDI to form urethane linkages. Importantly, the hindered carboxylic group could bind with other bio-molecules in biomedical applications where multi-component scaffolds are desirable. The resulting polyurethanes displayed a wide range of physico-mechanical properties and their excellent hydrolytic degradability suggests that they could be very good candidates for several soft tissue engineering applications.

2. Experimental

2.1. Materials

All reagents used in this study were analytical grade, and were obtained from Aldrich Company. Polycaprolactone diol (PCL) ($M_n \sim 2000$ and 530) and 2,2-bis (hydroxymethyl) propionic acid (DMPA) were vacuum oven dried at 60 °C for 12 h prior to use. Ethylene glycol (EG) was vacuum oven dried at 60 °C for 3 h prior to use. N,N-dimethylformamide (DMF) was purified by auto solvent purifier (MBRAUN MB SPS-800, Germany) and used as the solvent for polymer synthesis. Stannous octoate used as catalyst which was dried over a molecular sieve (3 Å), and 1,6-diisocyanatohexane (HDI) was used as received.

2.2. Segmented polyurethane synthesis

Segmented polyurethane copolymers were synthesized by a two-steps polymerization process. In the first step, diisocyanate terminated pre-polymers were prepared by reacting of the polycaprolactone diol ($M_n \sim 2000$ and 530) and 2,2-bis (hydroxymethyl) propionic acid (DMPA) with excess of 1,6-diisocyanatohexane in N,N-dimethylformamide solvent under nitrogen flow at 80 °C for 3 h. Extra N,N-dimethylformamide solvent was added in the reactor when the viscosity of the reaction mixture was too high. In the chain extension step, diisocyanate terminated pre-polymer was reacted with ethylene glycol. EG was diluted with DMF and added slowly to the reaction mixture by dropping pipette. Chain extension was carried out at 80 °C for another 17 h. Stannous octoate, a US Food and Drug Administration approved food stabilizer was used as the catalyst for polyurethane synthesis [13]. Stoichiometric molar ratios of hydroxyl and isocyanate groups were kept at 1:1 to obtain linear polyurethane copolymers. The general structure of these segmented polyurethane copolymers is schematically shown in Fig. 1, and the molar compositions of feed raw materials for the various SPUs are tabulated in Table 1.

After completion of the reaction, the polyurethane in DMF solution was precipitated into deionised (DI) water for 24 h, washed thoroughly with DI water at room temperature to remove the solvent and then dried in a vacuum oven at 35 °C for 72 h. Dried polymers were kept in desiccators under vacuum before further use and characterizations.

2.3. Polymer membrane preparation

Hydrolytic degradation measurements of polyurethane copolymers were performed on dense membranes. Dense membranes were prepared by solvent casting in glass moulds. Vacuum oven dried segmented polyurethanes were dissolved in N,N-dimethylacetamide (concentration, 8.5% w/v). Polymer solutions were poured into glass moulds and the solvent was evaporated at 50 °C for 5 days under the flow of nitrogen in order to prevent any oxidation of polyurethane functional groups. Further, residual solvent was removed by vacuum oven drying at 35 °C for another three days. Membranes were kept in desiccators under vacuum for further use and testing. The membrane thickness was about 1 mm for testing.

Uniform thicknesses of polymer films for mechanical and thermo-mechanical testing were prepared by compression moulding at 110 °C and under 7.5 tons of loads. All segmented polyurethanes showed good thermal stability up to 220 °C as discussed in results and discussion section of thermo-gravimetric analysis. Therefore, compression moulding at this temperature would not degrade the polyurethane copolymer. Prior to the compression moulding, all polymers were cryo-milled to make a fine powder for the preparation of defect free membranes. A cryo-grinder (Freezer Mill 6870, SPEX SamplePrep, USA) was used to mill the samples in liquid nitrogen atmosphere at 10 cps for 5 min, followed by cooling for 2 min and grinded for another 5 min at 10 cps.

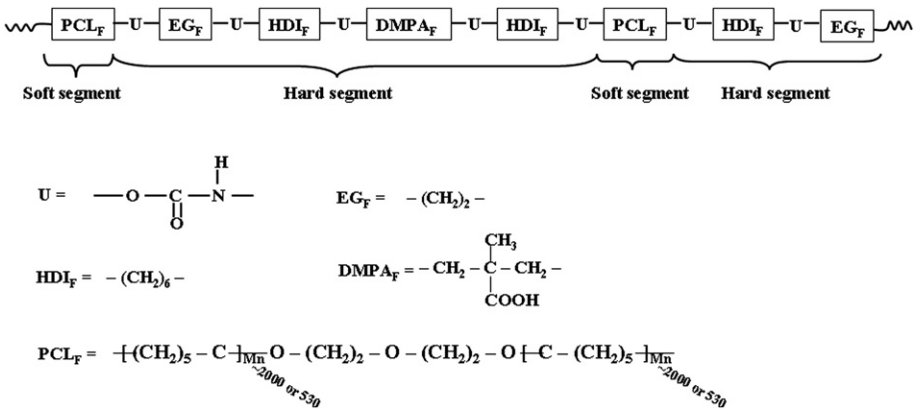

Fig. 1. Schematic representation for general structure of segmented polyurethane copolymer.