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Amino acid modified PHBHHx though N-carboxyanhydride ring-opening polymerization

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ABSTRACT

Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx) was grafted with N-carboxyanhydrides (NCA) to synthesize amino acid modified co-polymer. FT-IR and elemental analysis confirmed that amino acids were successfully grafted into PHBHHx with various NCA monomer. The hydrophilicity of modified PHBHHx was significantly enhanced by the amino acid segment incorperation, and the controlled trials revealed that the physical added amino acids in SBF solution almost display nearly no influence on PHBHHx degradation while the chemically grafted amino acids in co-polymers significantly promote PHBHHx degradation.

1. Introduction

PHBHHx is biocompatible to several cells, including chondrocytes [1], fibroblast [2] and bone marrow stromal cells [3,4], therefore, it is more practical for tissue engineering applications [5]. However, the relatively poor hydrophilicity of PHBHHx caused by HHx hinders the extensive usage in drug delivery, wound healing, anti-adhesive materials, gelatin, etc [6] Thus, it is necessary to introduce some hydrophilic segments into PHBHHx to broaden the scope of its performance and application. The effective methods to introduce a hydrophilic groups into PHBHHx backbone include surface hydrolysis [7], grafting technique [8], ultraviolet treatment [9], plasma treatment [10] and alkali treatment [11]. Surface modification by plasma treatment is not permanent performance changes since the surface tends to revert to the untreated state ("aging effect") in a short time. Alkali treatment can improve the wetting and adhesion property of polymer surface, but this method inevitably causes the break of molecular chain.

Amino acids have potential applications in tissue engineering, genetic engineering, clinical application and biorefinery application [12]. Herein, PHBHHx was modified with amino acids by polymerisation between PHBHHx and NCAs for first time. The amino acid modified PHBHHx was characterized, and the modified polymer degradation performance was also investigated.

2. Experimental section

2.1. Materials

PHBHHx ($Mn = 2.4 \times 10^4$, PDI = 2.2, HHx amount 12.0 mol%) was provided by Tsinghua University (China). N-(tert-butoxycarbonyl)-L-phenylalanine (BOC-Phe-OH) was supplied by Tokyo Chemical Industry Co. Ltd. (Japan). Other reagents were purchased from J&K Leon Technology Co. Ltd. NCA was synthesized from various amino acid and triphosgene at 50 °C in anhydrous THF [13]. Reaction mixture was poured into anhydrous petroleum ether, and the resulting suspension stored at −20 °C.

2.2. Phbhhx modification with NCA

Modified PHBHHx was synthesized through three-step process (Scheme 1). Firstly, PHBHHx-NH-BOC was obtained by the esterification between PHBHHx and N-(tert-butoxycarbonyl)-L-phenylalanine (BOC-Phe-OH) using N,N′-dicyclohexylcarbodie (DCC) as an dehydrating agent. The obtained organic solution and cold methanol were mixed together to precipitate a white solid material (PHBHHx-NH-BOC). PHBHHx-NH_2 was obtained from PHBHHx-NH-BOC cleavage to remove BOC group in presence of

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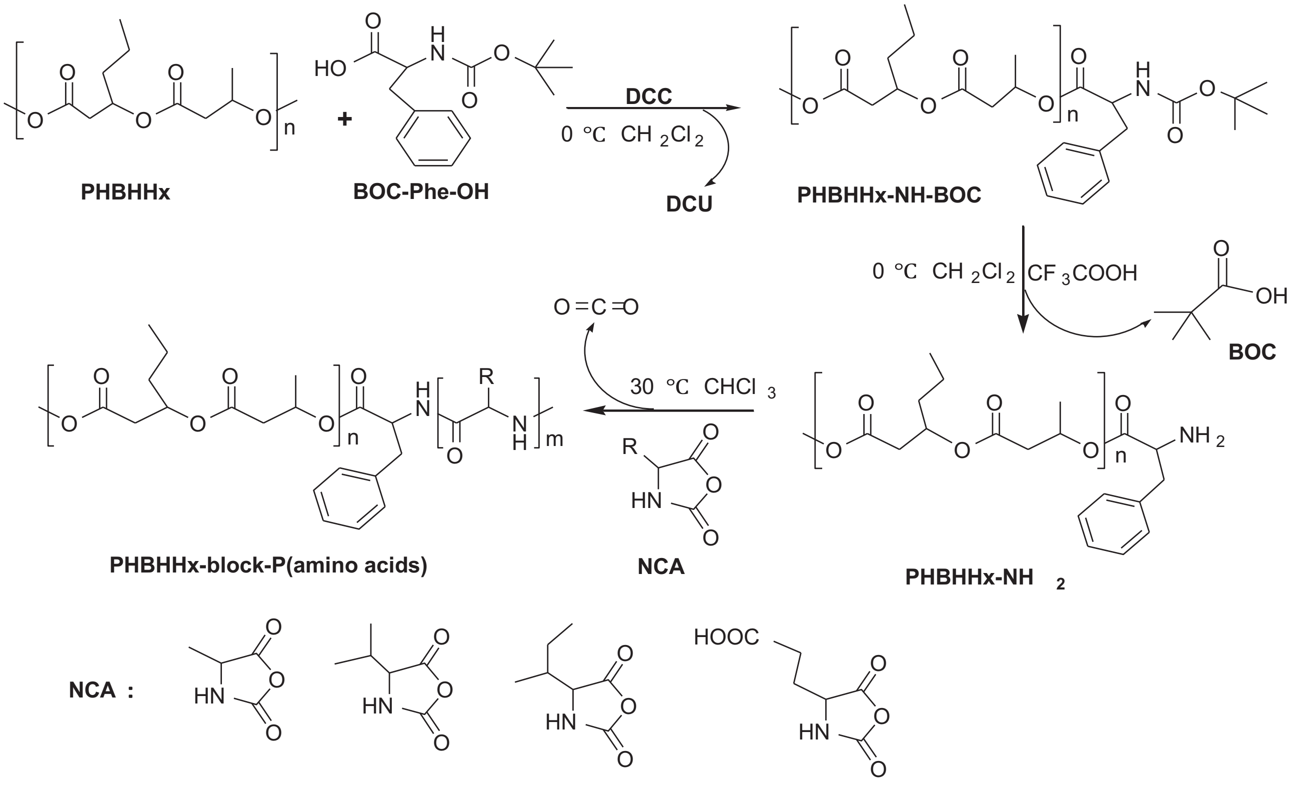

Scheme 1. Synthesis process of amino acid modified PHBHHx.

trifluoroacetic acid. After reaction, the solution was washed with saturated $NaHCO_3$ to neutralize the excess trifluoroacetic. Organic solution was dispersed into diethyl ether, and the obtained precipitate was filtered and dried at 40 °C under vacuum. Co-polymer came from the polymerisation between PHBHHx-NH_2 and NCA at 30 °C in chloroform.

2.3. Characterization

FT-IR was measured using a Nicolet IR 6700 (Thermo Electron, USA) spectroscope. Samples were carried out with 64 scans at a resolution of 2 cm^{-1} at room temperature. The bulk C, H and N contents of samples were determined by elemental analysis (Vario EL/micro cube elemental analyzer, Elementar Co. Ltd., Germany). Static contact angle was measured by the contact angle analyzer (Jinshenxin JYSP-180 Beijing, China) using pendant drop method at room temperature.

Simulated body fluid (SBF) was prepared from 7.996 g NaCl, 0.350 g $NaHCO_3$, 0.224 g KCl, 0.228 g $K_2HPO_4 \cdot 5H_2O$, 0.305 g $MgCl_2 \cdot 6H_2O$, 0.290 g $CaCl_2$, 0.071 g Na_2SO_4, and 4.093 g $NH_4C(CH_2OH)_3$ and distilled water, and solution buffered with 1 M HCl to pH 7.25 at 36.5 °C. Polymer films (approx. 1 cm × 1.5 cm) were degraded in 20 ml buffer solution (pH 7.25) at 36.5 °C. The residual weight was calculated as follows: Residual weight (%) = 100 × $(w_1\text{-}w_2)/w_1$, where w_1 and w_2 were the weights of films before and after degradation, respectively.

3. Results and discussion

3.1. The chemical structure characterization of co-polymer

FT-IR was an efficient method to characterize the chemical structure of co-polymer (Fig. 1). The typical carbonyl stretching band (vs, —C≡O) and methylene (s, —C—H) vibration originated from PHBHHx are presented at 1730 and 2980 cm^{-1}. Two new bands belonging to —NH derived from amino acids, were located at 3440 and 1630 cm^{-1}. [74] FT-IR results confirmed the successful synthesis of amino acid modified co-polymerization from PHBHHx and NCAs. From Table 1 we can see that the N contents of polymer rose from 0.04 to 1.46. The grafted amino acid amount in co-polymer was calculated in according to N content. The grafted amino acid amount has a great relationship with the amino acid steric hindrance, and the large steric hindrance of amino acids influenced the polymerization degree of amino acid.

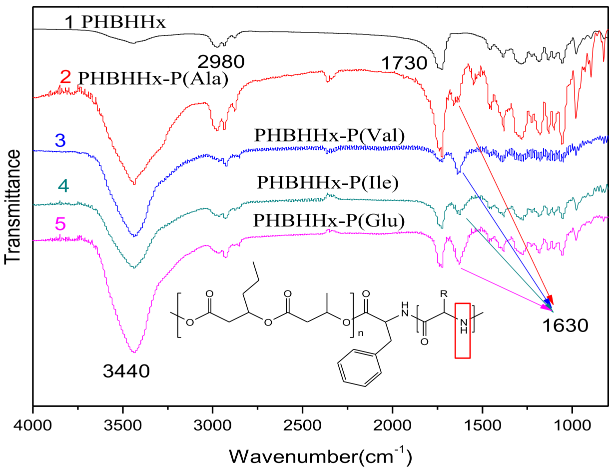

Fig. 1. FT-IR of PHBHHx and copolymers.

3.2. Static contact angle study

The contact angles were measured to determine their surface hydrophilicity (Table 1). It was found that the contact angles