

Improving hydrophilicity, mechanical properties and biocompatibility of poly[(*R*)-3-hydroxybutyrate-*co*-(*R*)-3-hydroxyvalerate] through blending with poly[(*R*)-3-hydroxybutyrate]-*alt*-poly(ethylene oxide)

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Abstract

Natural source poly[(*R*)-3-hydroxybutyrate-*co*-(*R*)-3-hydroxyvalerate] (PHBV) with a low hydroxyvalerate (HV) content (~8 wt.%) was modified by blending it with poly[(*R*)-3-hydroxybutyrate]-*alt*-poly(ethylene oxide) (HE) alternating block copolymer. We hypothesized that the adjoining PHB segments could improve the miscibility of the poly(ethylene oxide) segments of HE with the PHBV matrix and therefore improve the physical properties of the PHBV/HE blends. A differential scanning calorimetry study revealed the improved miscibility of PEO segments of HE characterized by the interference of the crystallization of PHBV. The decrease in water contact angle and the increase in equilibrium water uptake of the PHBV/HE blends indicated that both the surface and bulk hydrophilicity of PHBV could be improved through blending HE. The mechanical properties of the hydrated PHBV/HE blends were assessed by measuring their tensile strength. In contrast to the hydrated natural source PHBV, which failed in a brittle manner, the hydrated PHBV/HE blends were ductile. Their strain at break increased with increasing HE content, reaching a maximum of 394% at an HE content of 15 wt.%. The excellent integrity of the PHBV/HE blends in water is attributed to the strong affinity between the PHB segments of HE and the PHBV matrix. Platelet adhesion on the film surface of the PHBV/HE blends was investigated *in vitro* to evaluate their blood compatibility. The results demonstrated that the PHBV/HE blends effectively resisted the adhesion of platelets due to the anchored PEO segments from HE on the film surface.

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1. Introduction

Natural source poly(hydroxyalkanoates) (PHAs) are a class of biodegradable and biocompatible polyesters produced by numerous bacteria as an intracellular carbon and energy storage material [1]. Poly[(*R*)-3-hydroxybuty-

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rate-*co*-(*R*)-3-hydroxyvalerate] (PHBV) is one of the most extensively studied PHAs. Its ductility can be improved through increasing the hydroxyvalerate (HV) content. PHBV has been attractive because of its potential environmental, pharmaceutical and biomedical applications [2,3]. However, the practical applications of PHBV, particularly with an HV content higher than 15 mol.%, have often been limited by its high cost. Moreover, its intrinsic hydrophobicity restricts its applications as scaffold materials for cell colonizing. It is not blood-compatible and the exposure of PHBV surfaces to blood leads to platelet adhesion and subsequent thrombi formation [4].

Blending PHBV with other polymers is a practical and economical approach to improving its mechanical properties and other material properties [5–9]. Scandola et al. [5] studied the mechanical and degradation properties of the blends of natural source PHBV and synthetic atactic poly(3-hydroxybutyrate) (aPHB). The crystallinity of the PHBV/aPHB blends decreased with increasing aPHB content, and the strain at break of the blends with 50 wt.% of aPHB was 30 times that of the pure PHBV. Both hydrolytic and enzymatic degradation of blends was higher than that of pure PHBV. Recently, electrospun fiber mats of PHBV/poly[(*R*)-3-hydroxybutyrate] (PHB) blends as bone tissue engineering scaffolds were reported by Sombatmankhong et al. [6,7]. Much improvement in the tensile strength and the strain at break were observed for the blend fiber mats over the pure PHBV fiber mats. The PHBV/PHB (50/50, by wt.) blend fiber mats showed no cytotoxicity to human osteoblasts and the highest alkaline phosphatase activity.

Poly(ethylene oxide) (PEO) or poly(ethylene glycol) (PEG), as a hydrophilic and biocompatible polyether, has attracted considerable attention in biomedical research due to its low toxicity and non-immunogenicity, as well as its ability to minimize protein adsorption to surfaces [10]. Non-ionic PEO is a particularly effective surface-modifying additive to prevent platelet adhesion for blood-contacting devices. In general, surface modification is carried out through covalent coupling of PEO or physical adsorption of PEO-containing amphiphilic block copolymer [11–13]. PEO has also been employed to improve the physical properties of PHBV through blending [9]. It was reported that PHBV and PEO were miscible in the amorphous state and the crystallization rate of PHBV decreased with increasing PEO content under isothermal conditions. However, leaching of PEO from the blend matrix is a common problem, especially in the hydrated state, due to the weak interchain interaction between PEO and the matrix. This has an adverse effect on the materials properties. Normally, the mechanical property of material in the hydrated state is quite different from that in the dry state due to the water absorption and the distribution of the absorbed water [14,15]. This has a profound implication on biomaterials that are employed as tissue engineering scaffolds or implant devices. To the best of our knowledge, there have been no reports on the mechanical property of hydrated PHBV.

In recent years, our laboratory has developed a number of novel PHB-based amphiphilic block copolymers with various chain architectures and explored their biomedical applications [16–22]. Most recently, we reported the synthesis and characterization of poly[(*R*)-3-hydroxybutyrate]-*alt*-poly(ethylene oxide) (HE) alternating block copolymers [23]. Herein, we describe a new study on improving the properties of commercially available PHBV (HV, 8 wt.%) through blending with an HE alternating block copolymer. The adjoining PHB segments of HE are expected to improve the miscibility of the PEO segments with PHBV, which can further affect the water absorption and distribution in the PHBV matrix, leading to improved

mechanical property of the hydrated PHBV. Using HE instead of pure PEO is also expected to improve the integrity of the modified PHBV, especially in the hydrated state. The improved miscibility of the PEO segments with PHBV was tested by differential scanning calorimetry (DSC). The hydrophilicity of the PHBV/HE blends was investigated by measuring the water contact angle and water absorption content. The mechanical properties of the blends in the hydrated state were studied by performing tensile strength measurements, and their platelet adhesion property was also studied *in vitro*. The improved hydrophilicity and hydrated state mechanical properties as well as the reduced platelet adhesion all indicate that the PHBV/HE blends could be good candidate biomaterials for tissue engineering scaffolds or implant devices.

2. Materials and methods

2.1. Materials

Natural source PHB and PHBV with an HV content of 8 wt.% (M_w 600,000, $M_w/M_n = 3.7$) were purchased from Aldrich, and purified by dissolving in chloroform followed by filtration and subsequent precipitation in hexane. PEG was purchased from Aldrich, and purified by dissolving in methylene chloride, followed by precipitation in diethyl ether and further drying under a high vacuum at 35 °C for 48 h before use. Its M_n and M_w were found to be 3300 and 3400, respectively.

Bis(2-methoxyethyl) ether (diglyme, 99%), ethylene glycol (99%), dibutyltin dilaurate (95%), 1,3-*N,N'*-dicyclohexylcarbodiimide (DCC, 99%), 4-(dimethylamino)pyridine (DMAP, 99%), succinic anhydride (97%), triethylamine (99%), methanol, diethyl ether, 1,4-dioxane and methylene chloride were purchased from Aldrich. Glutaraldehyde solution (2.5%) and sodium citrate were provided by Sigma. Diglyme was dried with molecular sieves, and methylene chloride was dried by distilling over CaH_2 prior to use.

2.2. Synthesis of HE alternating block copolymer

The synthesis and characterization of HE were carried out following our previous report [23]. First, the telechelic hydroxylated PHB (PHB-diol) prepolymer with M_n of 2100 was prepared by transesterification between natural source PHB and ethylene glycol with dibutyltin dilaurate as the catalyst in diglyme, and the telechelic carboxylated poly(ethylene oxide) (A-PEO-A) prepolymer was prepared by reaction of PEG with succinic anhydride in the presence of DMAP and triethylamine in 1,4-dioxane, as reported previously [18]. Then HE was synthesized from equal molar amounts of PHB-diol and A-PEO-A in the presence of DCC and DMAP, as exemplified below. A-PEO-A (0.52 g, 0.153 mmol), PHB-diol (0.32 g, 0.153 mmol) and DMAP (4.4 mg, 0.036 mmol) were first dried under vacuum overnight at 60 °C and then further dried by azeotropic distillation in anhydrous methylene chloride. The solids

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