Materials Science and Engineering C 70 (2017) 1107–1119

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Reactive blends based on polyhydroxyalkanoates: Preparation and biomedical application

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ARTICLE INFO

Article history:
Received 16 January 2016
Received in revised form 6 March 2016
Accepted 31 March 2016
Available online 7 April 2016

Keywords:
Polyhydroxyalkanoate
Reactive polymer blending
Tissue engineering
Controlled drug delivery
H-bonding
Copolymer

ABSTRACT

Polyhydroxyalkanoates (PHAs) are a class of natural polyesters as carbon and energy reserves by >300 species of microorganisms. They are fully biodegradable, biocompatible and piezoelectric biopolymers that have attracted much attention recently as the biomaterial of choice for medical applications. However, the toughness, processability and hydrophilicity of PHAs need to tune to expand their applications as tissue engineering scaffolds or drug delivery systems. Reactive polymer blending is one of the most economic and versatile way to produce materials combining the desired properties *via* forming the compatibilizing agents *in situ* or inducing the chemico-physical interactions between polymer blends. This review focuses on the PHAs-based reactive blends aiming to present a brief introduction to the mechanism of reactive polymer blending technique, including the formation of H-bonding, branching/crosslinking copolymers, graft copolymers or complex copolymers during polymer blending process.

1. Introduction

Polyhydroxyalkanoates (PHAs) are a class of natural polyesters as a carbon/energy store for >300 species of Gram-positive and Gram-negative bacteria as well as a wide range of archaea [1–3]. Of the thousands of biopolymers, PHAs have attracted much attention since their physical properties are comparable to those of polyethylene and polypropylene [4]. The polyesters are perfectly isotactic/optically active, piezoelectric and thermoplastic [5–9]. These properties combined with biocompatibility, biodegradable and biocompatible make them promising materials for biomedical applications [10–14]. Short chain length hydroxyalkanoic acids contain 3–5 carbon atoms (Fig. 1) and are the most commercially available PHAs. Studies have been mainly focused on two of them, poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV).

Since being first isolated and characterized in 1926 by Lemoigne [15], PHB has been produced by the agricultural division of Imperial Chemical Industries *via* a controlled fermentation process using a variety of feedstocks [16]. PHB is a thermoplastic polymer with a glass transition temperature of 4–7 °C and a melting temperature of 175–180 °C. The processable window is very narrow because PHB degrades to crotonic acid through a β-scission reaction at temperature little higher than the melting temperature [17]. Moreover, the isotactic and linear chains of PHB result in formation of large spherulites during crystallization, which may lead to a highly crystalline (>60%) and consequently a brittle material [18].

The toughness and processability of PHB can be improved by incorporation of 3-hydroxyvalerate (3HV) in the bacterial fermentation process. PHBV is already commercially produced under the trade name Biopol. Increasing HV content compromises the yield strength and Young's modulus of PHB, meanwhile, increases the cost of materials. However, the crystallinity of PHBV is only slightly decreased due to the isodimorphism in PHBV [19]. The melting temperature of PHBV decreases with increasing component of 3HV, with a minimum value 75 °C at approximately 40 mol% 3 HV [20].

PHB and PHBV with a low HV content have not been fully utilized in biomedical areas due to the stiff and brittle nature, the thermal instability during processing, along with the prohibitive of its high production cost. They undergo secondary nucleation at ambient temperature because of the low glass transition temperatures, and possess low nucleation densities resulting in the formation of large spherulites. Under severe impact loading, the semi-crystalline PHAs can undergo a sharp ductile-to-brittle transition. The inherent crack can grow rapidly along the lamella boundaries and produce a significant structural weak point [21–23]. Consequently, it is of interest to find a more useful way to modify the properties of short chain length PHAs.

Polymer blending is the most economic and versatile way of producing materials combining the desired properties of different polymers that will allow a wider usage of these biopolymers. An easily processable

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http://dx.doi.org/10.1016/j.msec.2016.03.114
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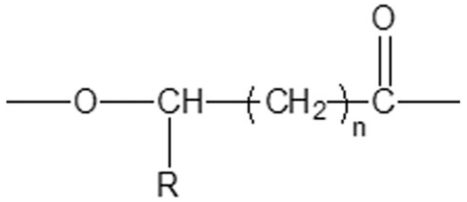

$$-O-\underset{\displaystyle R}{\underset{|}{CH}}-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{C}}-$$

Fig. 1. Structural formulas of short chain length PHAs, where R derived from radical represents different substituent: 3-hydroxybutyrate (3HB, R = CH_3, n = 1); 3-hydroxyvalerate (3HV, R = CH_2CH_3, n = 1); 4-hydroxybutyrate (4HB, R = H, n = 2); 5-hydroxyvalerate (5HV, R = H, n = 3); 3-hydroxypropionate (3HP, R = H, n = 1).

material preserving these tailored end properties can be produced by blending PHAs with small molecules such as β-carotene [24], soybean oil/eposidized soybean oil [25], or tri(ethylene glycol) bis(2-ethylhexanoate) [26] as nucleation agents or plasticizers to reduce the size of spherulites and prevent the occurrence of cracks. By blending homopolymers or copolymers with PHAs, high performance blends have also be produced to cover a large spectrum of specific needs, for example, poly(L-lactide) (PLA) [27–28], poly(ε-caprolactone) (PCL) [29], poly(propylene carbonate) [30–31], poly(dicyclohexyl itaconate) [32], poly(vinyl pyrrolidone) [33], poly(methyl acrylate) [34], poly(glycidyl methacrylate) [35], poly(vinylidene fluoride) [36–37], poly(butadiene-*co*-acrylonitrile) [38], poly(styrene-*co*-acrylonitrile) [39] poly(butylene succinate) [40], starch [41], chitosan [42–43], Ecoflex [44], cellulose acetobutyrates [45], and cellulose acetate butyrate/poly(ethylene glycol) copolymer [46]. These molecules could improve the crystallization rate and the processing properties, but the poor tension properties were not significantly improved probably due to phase separation and/or poor interfacial adhesion between PHAs and the other polymers. Compatibilization induces chemical or physical interactions within the blends, and may optimize the mechanical properties by transmitting stress from one phase to the other.

2. PHAs blends *via* reactive polymer blending

Binary polymer blends are usually immiscible due to the low combinatorial entropy of mixing, giving rise to a two-phase system generally characterized by an unstable morphology and a poor interfacial adhesion between the phases [47]. Compatible blends exhibit properties intermediate or even superior to that of the components, offering a way to enhance the properties of polymers without sacrifice any excellent characteristics. Compatibilization can occur either by adding compatibilizers (block/graft copolymers) and/or the induction of chemical or physico-chemical interaction during the blending process, for example, crosslinking the components, chemically modifying the homopolymers, *etc.* When these compatibilizing agents are generated *in situ* or the chemico-physical interactions are induced during the blending process, this case is quoted reactive polymer blending [48]. The major requirements for the reactive polymer blending is the presence of reactive groups on the backbone chains to create strong interactions (covalent bonds, ionic bonds) between two polymers in the melt or solvent, which produces a lower interfacial energy and a more stable morphology. Generally, the chemical interaction or ionic bond is limited to a few percent of the polymers chains, and this is sufficient to allow a good compatibilization between the two polymers.

2.1. Formation of H-bonding via reactive polymer blending

The introduction of intermolecular H-bonds to polymer blends is an effective method to improve the miscibility between two components (Table 1). The carbonyl groups in PHAs form an inter-H-bond with the hydroxyl groups of hydrogen bonding monomers, competing with the self-H bonding formed by the hydroxyl groups themselves. The crystallinity and melting temperature obviously decrease for PHB or PHBV in H-bonded miscible blends, which would be beneficial to modify the mechanical properties and enlarge their processing windows.

2.1.1. Reactive blends with polymers

Phenolic polymers such as poly(*p*-vinyl phenol) (PVPh) possess great potential for H-bonding interactions with proton-acceptor polymers due to the accessible hydroxyl groups in the *p*-position of the phenyl ring. PHB/PVPh blends were compatible in the entire range of composition, and the H-bonded carbonyl signals increased with PVPh contents. The amorphous PVPh component resulted in a reduction in the spherulite growth of PHB, and 40% PVPh could prevent PHB crystallization [49–51].

Lignin is an amorphous macromolecule composed of phenylpropane repeat units and possesses aliphatic and aromatic hydroxyl groups as well as carboxylic acid groups. The lignin/PHB blend (Table 1) was compatible when soda lignin was up to 40 wt%, associated with specific H-bonding interactions between the reactive functional groups in lignin with the carbonyl groups of PHB. The amorphous lignin suppressed the formation of large spherulites, retarded crystallization, and reduced secondary nucleation, all of which impacted on PHB brittleness [52].

Polyphenol poly(4,4′-dihydroxydiphenyl ether) (PDHDPE) is a mixture of phenylene and oxyphenylene units, obtained by the oxidative polymerization of DHDPE using horseradish peroxidase [53]. In PHB/PDHDPE blends, strong intermolecular H-bonds were formed between the carbonyl of PHB and the phenolic hydroxyl of PDHDPE (Table 1). However, when PHB was blended with DHDPE monomer, no obvious H-bonds were observed because of the phase separation and strong self-intermolecular H-bonds between DHDPE molecules [54].

Polypropylene (PP) has greater toughness and larger processing window than PHB, but PP and PHB usually formed an immiscible blend because of differences in their chemical structure and polarity. Compatibilizers to achieve strong H-bonding between PP and PHB is needed in order to achieve acceptable engineering properties, such as poly(propylene-g-maleic anhydride) (PP-MAH), poly(ethylene-*co*-methyl acrylate) [P(E-MA)]. H-bonds can form between oxygen atoms of MAH with hydrogen atoms of polyester OH and COOH end groups or between hydrogen atoms of hydrolyzed MAH with oxygen atoms of carbonyl groups presented in the repeating unit of polyesters. The MAH molecule may react with the polyester OH groups, but this reaction was reversible. P(E-MA) presented stronger physical effect because of the higher concentration of functional groups [55].

2.1.2. Reactive blends with small additives

Nowadays a variety of low-molecular-weight additives are included into polymers to modify their properties and greatly broaden their applications. Intermolecular hydrogen bonds thus arose between the PHAs and the additives in the blends. In general, the crystallinity decreased with increasing content of additives, but the crystal structures were hardly affected. Using H-bonding compound instead of polymer can reach higher efficiency of H-bond interaction.

A dynamic H-bonding network was found in blends of PHB, PHBV or poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) (PHBHHx) with 4,4′-dihydroxydiphenylpropane (BPA, Table 1) as a physical cross-link agent between the carbonyl groups in the amorphous phase of polyesters and the hydroxyl groups of BPA [56]. The intermolecular H-bond clearly suppressed the crystallization of PHAs, though there was still a certain part in PHAs that crystallized due to the dynamic character of H-bonds [57]. BPA distributed in the inter-lamellar region of PHBV so that the PHBV/BPA blends possessed larger crystals. The PHBV/BPA blends showed an enhanced glass transition temperature and a decreased melt temperature of PHBV. The tensile toughness of PHBV/BPA blends improved with an elongation at break of 370% and a yield stress of 16 MPa [58]. The formation of H-bonding was also influenced by the polymers themselves: The intermolecular interaction in PHBHHx/BPA was weaker than that in PHB/BPA owing to the steric hindrance of longer 3HHx side chains [59].