Preparation of biodegradable poly(3-hydroxybutyrate) and poly(ethylene glycol) multiblock copolymers

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Poly(3-hydroxybutyrate) (PHB) is a biodegradable polyester produced by a number of bacteria as a reserve of carbon and energy. It has many special properties such as biocompatibility [1], biodegradability [2], piezoelectric properties [3] and so on. In the biomedical area PHB can be used as surgical sutures, bone implant material, drug release systemand scaffold for tissue engineering [4] etc. Unfortunately PHB is fragile, hydrophobic and, for applications in which a biodegradable material is required, its degradation time is too long. Many efforts have been employed, including physical blending and chemical copolymerization, to overcome its shortcomings.

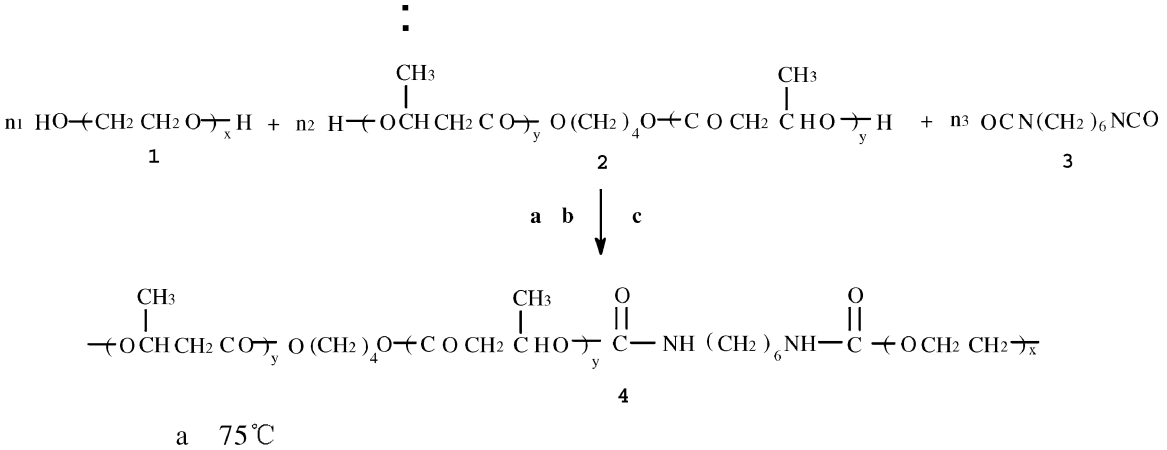
Since there are few reactive functionalities in the PHB main chain, acid catalyzed alcohololysis and methanolysis have been performed to obtain PHB oligomers with the desired molecular weight and specific chain end functionalities [5, 6]. PHB prepolymers prepared by methanolysis have been used to synthesize diblock copolymers by copolymerization with ε-caprolactone and lactide monomers. These copolymers may serve as emulsifiers for the binary blends [7]. PHB/PCL multiblock copolymers were also obtained through one-step condensation copolymerization of PHB-diol and Polycaprolactone (PCL)-diol prepolymers with diisocyanate as a coupling agent. Compared to pure PHB, this kind of material has adjustable mechanical properties and processability, but its hydrophilicity changes a little [8].

PEG is a synthetic polymer known to be highly hydrophilic, biocompatible and flexible. In order to satisfy different requirements, especially to address the need for biomedical materials, PHB and PEG blends have been investigated by our laboratory [9]. The incorporation of low molecular PEG into a PHB matrix can improve the hydrophilicity, flexibility and degradation time by increasing the availability of water with the matrix. On the other hand, its mechanical tensile strength and elongation at breaking are decreased.

In the studies reported in this paper, PEG as block segments were introduced into the main chain of PHB, and PHB/PEG multiblock copolymers were prepared. The approach taken in the effort described here is based on multiblock copolymers. First, natural-origin PHB of high molecular weight was degraded by alcohololysis to provide low molecular weight and dihydroxy-terminated prepolymers. Then PHB-diol and PEG were multiblock copolymerized with hexamethylene diisocyanate (HDI) as coupling agent.

The prepolymer of hydroxy-terminated PHB (PHB-diol) was prepared using a literature method [6]. The high molecular weight PHB (natural origin, obtained from Tianjin Tianlu Co. Ltd.) was purified by precipitation in *n*-hexane from chloroform solution, and subsequently precipitated in methanol from the same solution.

Purifed PHB (3 g) was dissolved in 10^{-4} m^3 1,2-dichloroethane (DCE) (distilled from anhydrous



Scheme 1 Synthesis pathway of the PHB/PEG multiblock copolymer.

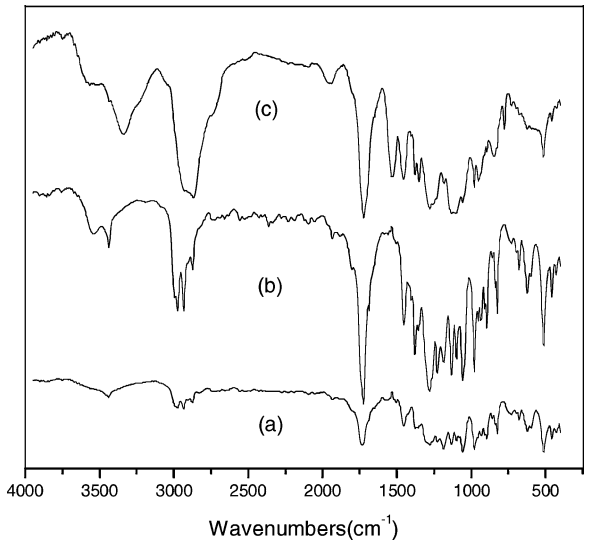


Figure 1 Infrared spectra of natural-origin PHB (a); PHB-diol (b); PHB/PEG multiblock polymer (c).

magnesium sulfate) to which anhydrous *p*-toluenesulfonic acid (1.18 g) and 1,4-butanediol (1,4-BD) (4.06 g) were added. The reaction was carried out at 60 °C under nitrogen atmosphere. When PHB was degraded to the desired molecular weight, the reaction solution was precipitated into rapidly stirred methanol (at ten times excess) which was cooled with an external ice water bath. The product was separated by vacuum filtration, dried at 60 °C under vacuum and washed successively with methanol, acetone and distilled water.

Preparation of various PHB/PEG multiblock copolymers was carried out by a modified method described elsewhere [8]. The synthetic pathway is shown in Scheme 1. The detailed synthesis process is as follows: First, a DCE solution of the desired composition of PHB-diol and PEG was prepared at as high a concentration as possible. An equivalent amount of HDI and a small amount of dibutyltin dilaurate (T-12) as catalyst were added. The system was mixed at 50 °C and then stirred at 75 °C under nitrogen atmosphere for 72 h. The resulting copolymer was precipitated in methanol and dried to constant weight under vacuum at 60 °C. By changing the PHB/PEG ratio, HDI/diols ratio and using different molecular weight PEG, a series of copolymers can be prepared (Table I).

TABLE I PHB/PEG multiblock copolymers prepared from PHB-diols and PEG with HDI

Mn (PEG)	Mn (PHB-diol)	PHB-diol/PEG (weight ratio)	HDI/diols (mole ratio)	$[\eta]$[a] (10^{-1} m^3/kg)
1000	2970	0.5	1.0	0.3926
4000	2970	0.5	1.0	0.2941
6000	2970	0.5	1.0	0.0821
1000	2970	0.5	0.9	0.1180
1000	2970	0.5	1.1	1.0071
1000	2970	0.5	1.3	–[b]
1000	2970	0.25	1.0	0.3945

[a] Chloroform as solvent.
[b] Crosslinked.

Characterization by means of nuclear magnetic resonance (NMR), infrared spectrum (IR) and gel permeation chromatograph (GPC) was carried out.

The IR (KBr, cm^{-1}) spectra ofnatural-origin PHB and PHB-diol were compared (Fig. 1). In contrast to the spectrum of original PHB (a), an absorbance at

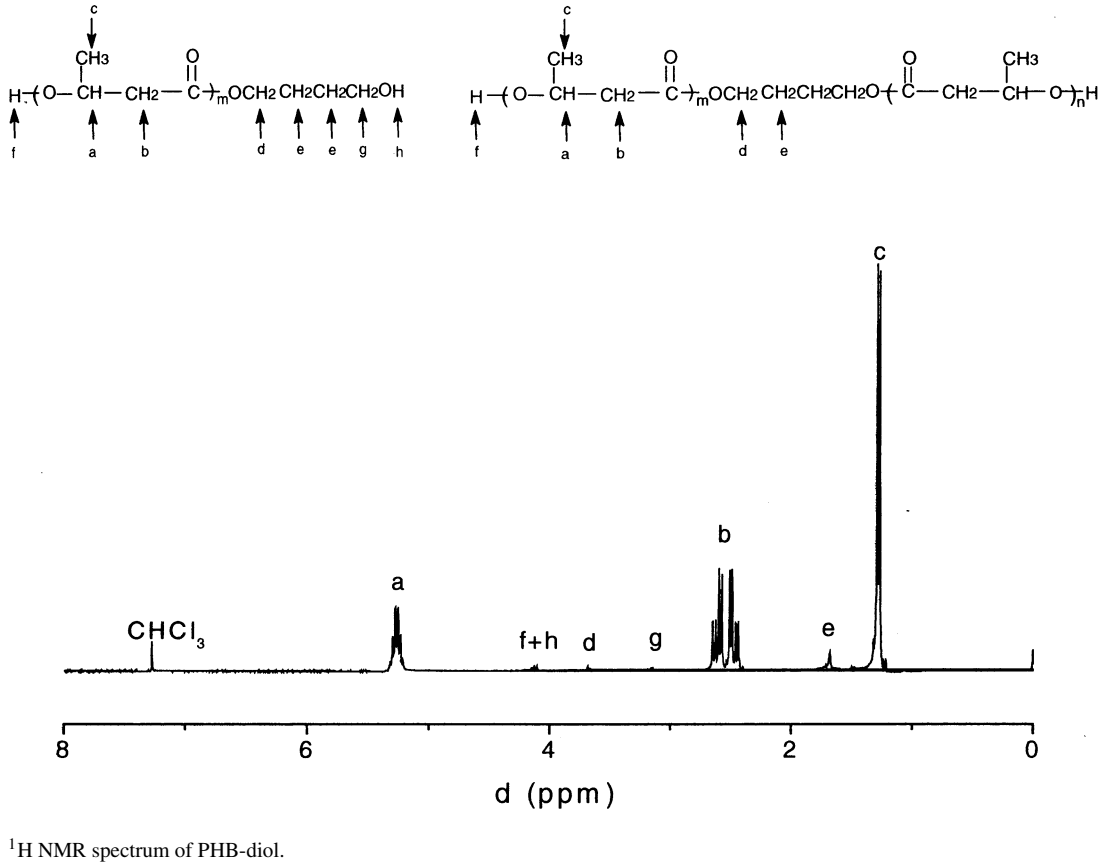


Figure 2 ^{1}H NMR spectrum of PHB-diol.

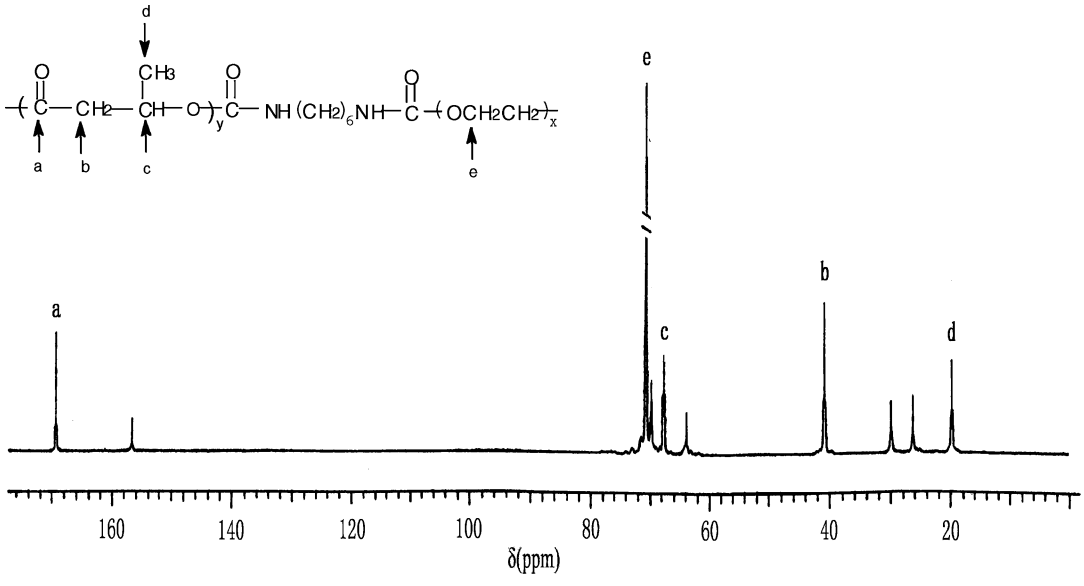


Figure 3 ^{13}C NMR spectrum of PHB/PEG multiblock copolymer.

3537 cm^{-1} in PHB-diol (b) was observed. It was assigned to the OH stretch of the terminated hydroxyl groups.

The PHB-diol was further identified by ^{1}H NMR ($CDCl_3$, ppm). The peaks at 5.25 ppm (CH), 2.54 ppm (CH_2), 1.29 ppm (CH_3) were assigned to the repeated unit of 3-hydroxybutyric acids, and the peak at 1.68 ppm was assigned to the methylene groups of 1,4-BD. The characteristic peak at 4.13 ppm (OH) from the end-groups of the PHB-diol was well defined (Fig. 2).

The formation of multiblock copolymers was confirmed by IR, ^{13}C NMR, and also by GPC.

Fig. 1c shows the typical IR spectrum of PEG/PHB multiblock copolymer. A CH stretching band, belonging to the PEG block appeared at 2869 cm^{-1}. The absorbances at 3340 and 1530 cm^{-1} were assigned to the stretch and deformation of NH. It is clearly seen that the copolymer exhibits peaks characteristic of both PEG and PHB blocks. The ^{13}C NMR ($CDCl_3$, ppm) shown in Fig. 3 ascertained the chemical composition of the copolymer. The peaks at 67.7 ppm (CH), 40.9 ppm (CH_2), 19.9 ppm (CH_3), 169.3 ppm (CO) belonged to PHB blocks and the peak at 70.67 ppm was characteristic of main chain methylene units in the PEG blocks. The GPC chromatographs of synthesized multiblock copolymers showed, in all cases, peaks which were unimodal and higher in molecular weight than the PHB prepolymers. This indicates that PHB and PEG in the presence of HDI did copolymerize in a random condensation.

These multiblock copolymers, which consist of hydrophobic segments of PHB crystalline domain and hydrophilic segments of PEG, are amphiphilic copolymers. When changing temperature, the crystalline melting of PHB domains and hydrophobic interactions along the polymer chains may introduce phase transitions. The detailed study on temperature-dependent phase transitions is under investigation in our laboratory.

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