Available online at www.sciencedirect.com

SCIENCE DIRECT®

Polymer 46 (2005) 10561–10567

polymer

www.elsevier.com/locate/polymer

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

Qiang Zhao, Guoxiang Cheng*, Haiming Li, Xiaolu Ma, Liguang Zhang

School of Materials Science and Engineering, Tianjin University, Tianjin 300072, China

Received 7 January 2005; received in revised form 29 June 2005; accepted 5 August 2005
Available online 19 August 2005

Abstract

Novel poly(3-hydroxybutyrate) and poly(ethylene glycol) (PHB/PEG) multiblock copolymers were synthesized through one-step copolymerization with hexamethylene diisocyanate (HDI) as a coupling agent by varying the block composition. Molecular structures and chemical compositions were confirmed by NMR and FTIR spectral analysis. Thermal properties and mechanical properties were investigated using differential scanning calorimetry (DSC) and stress–strain experiments, respectively. The hydrophilicity and degradability were also assessed in different media at 37 °C. The results show that this kind of copolymers exhibit good toughness and moderate strength in comparison with homopolymer PHB, the degradation rate and equilibrium water content (EWC) are much higher than those of the PHB homopolymer.

Keywords: Poly(3-hydroxybutyrate) (PHB); Poly(ethylene glycol) (PEG); Multiblock copolymers

1. Introduction

Poly(hydroxyalkanoates) (PHAs) are a class of biodegradable aliphatic polyesters, which are produced by many types of micro-organisms [1]. Poly(3-hydroxybutyrate) (PHB) was the first identified member of PHA family. It was first discovered in *Bacillus megaterium* by Lemoigne in 1920's. In recent years, PHB has been intensively studied due to its special properties, such as biocompatibility [2], biodegradability [3], and so on. In biomedical area, PHB can be used as surgical sutures [4], drug release carriers, and scaffolds for tissue engineering [5], etc. PHB also offers potential advantages over the currently used materials in that it is known to exhibit piezoelectric properties [6], and its mechanical properties closely resemble those of cortical bone. So it has been considered in a number of orthopedic uses [7].

Because of the high isotactic stereoregularity of PHB, it readily crystallizes to yield materials with high degrees of crystallinity. When crystallizing from melting state, PHB may form large spherulites, which give rise to its brittle properties [8–10]. Meanwhile, high crystallinity also influences other properties of PHB including degradability and hydrophilicity. The degradation of PHB proceeds at a relatively slower rate than those of other degradable polymers, such as PLA (polylactide) or PCL (polycaprolactone). Besides, the hydrophilicity of PHB is relatively poor. All these restrict the applications of PHB, especially the applications in medical field.

Many efforts have been employed, including biological modification, physical blending and chemical copolymerization, to overcome its shortcomings [11–21]. PEG, as a highly hydrophilic, biocompatible and flexible polyether, has been widely used for the modification of biomedical materials [22–24]. Recent attention of our lab has been focused on blending of PHB with PEG. The studies showed that the incorporation of low molecular weight PEG into a PHB matrix could improve its hydrophilicity, biocompatibility and degradability. On the other hand, the tensile strength decreased and the fragility became more serious [15].

Low molecular weight PEG (PEG200) has been selected by Fernandes et al. as plasticizer in the PHB/beech wood flour blend system. Incorporation of PEG was found to compromise thermal stability of PHB as demonstrated by

---

* Corresponding author. Tel.: +86 22 27404432; fax: +86 22 27404724.
E-mail address: gxcheng@tju.edu.cn (G. Cheng).

0032-3861/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2005.08.014

the higher decrease on the onset decomposition temperature (T_d). This behavior can be attributed to the hydroxyl groups in PEG, which may accelerate the degradation of PHB [16].

Shi et al. added PEG to cultivation media of *Alcaligines eutrophus* during fermentation process and studied its effects on control of the molecular weight and the structure. Their results showed that addition of low molecular weight PEG can regulate the molecular weight of the yield, P3HB [17]. When 4-hydroxybutyrate was used as carbon source, PEG can modulate the repeat unit composition and repeat unit sequence distribution in the yield. The final products are a mixture of random copolyesters with different compositions of 3HB, 3HV and 4HB repeat units. In some cases, PEG was covalently linked to terminal position of the PHA chain, but the content was relatively low. So they cannot really act as block copolymers [18].

Diblock copolymers of PHB and PEG (PHB-*block*-mPEG) have been synthesized by catalyzed transesterification of bacterial PHB and monomethoxy PEG in the melt [19]. Li et al. [20] have synthesized a PEG-PHB-PEG triblock copolymers from telechelic hydroxylated PHB (PHB-diol) and methoxy-PEG-monocarboxylic acid (M-PEG-A) by esterification reaction. Because of the relative low molecular weight, tri- and diblock copolymers do not hold the sufficient mechanical strength for direct applications. The potential applications of these copolymers are to act as amphiphilic drug carriers based on self-association and micro- or nanoscaled ordering behavior. They may also serve as the emulsifier for corresponding binary blends [21].

Among many known block copolymers, polyurethanes display good mechanical properties since they are though, moderately extensible elastomers. In this paper, the approach based on polyurethane multiblock copolymers was adopted to conjugate PHB and PEG. Telechelic hydroxylated PHB (PHB-diol) with low molecular weight was first prepared by alcohololysis of bacterial PHB. PHB/PEG multiblock copolymers were synthesized from PHB-diols, as hard segments and PEGs as soft segments, with hexamethylene diisocyanate (HDI) as a coupling agent. Furthermore, the control of the polymer properties, such as mechanical properties and degradability can be achieved by varying the block composition. The structures and properties of the copolymers including thermal properties, mechanical properties, degradability and hydrophilicty were also systematically investigated.

2. Experimental section

2.1. Materials

PHBs were kindly supplied by Tianlu Co. Ltd (Tianjin, China). Natural original PHBs were purified by precipitation in *n*-hexane from chloroform solution, subsequently precipitation in methanol from same solution. PEGs were imported and sub-packaged by Tiantai Fine Chemicals Co. Ltd (Tianjin, China). PEGs were dried under vacuum at 60 °C for over 12 h before use. Hexamethylene diisocyanate (HDI, >99%, Acros Organics, Belgium) was used as received, without further purification. 1,2-dichloroethane was purified by distillation from anhydrous magnesium sulfate. 1,4-butanediol (1,4-BD), *p*-toluene sulfonic acid, dibutyltin dilaurate (T-12) and phosphate buffered saline (PBS, Sigma) were all of AR grade and were used as received. All the above chemicals, except those indicated, were all obtained from Kewei Chemicals Co. Ltd (Tianjin, China).

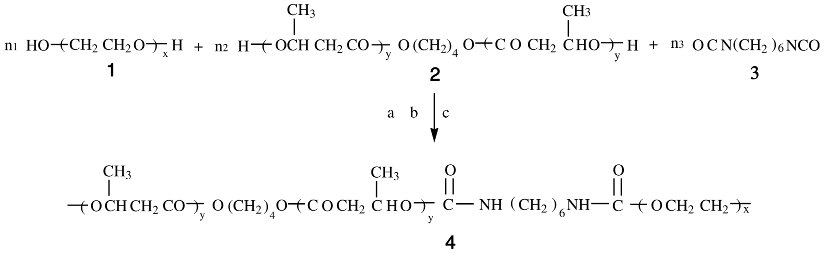
2.2. Synthesis of PHB/PEG multiblock copolymer

Dihydroxy-terminated PHB prepolymers with low molecular weight ($M_w = 4862$, $M_n = 2673$, $M_w/M_n = 1.82$, determined by GPC) were prepared by our previous work. Its chemical structure has been ascertained by IR and ^1H NMR [25].

Preparation of various PHB/PEG multiblock copolymers was carried out by a modified method described elsewhere [13]. The synthetic pathway is shown in Scheme 1. The detailed synthesis process is as follows. First, a DCE solution of 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 ether and dried to constant weight under vacuum at 60 °C.

2.3. Preparation of copolymer films

Thin films of copolymers (0.2–0.4 mm thickness) were prepared by solution-casting method. The films were dried



$$n_1\ \mathrm{HO{+}CH_2CH_2O{+}_x H} \;+\; n_2\ \mathrm{H{+}O\overset{CH_3}{CH}CH_2CO{+}_y O(CH_2)_4O{+}COCH_2\overset{CH_3}{C}HO{+}_y H} \;+\; n_3\ \mathrm{OCN(CH_2)_6NCO}$$

1 2 3

$$\xrightarrow{a\ b\ c}$$

$$\mathrm{{+}O\overset{CH_3}{CH}CH_2CO{+}_y O(CH_2)_4O{+}COCH_2\overset{CH_3}{C}HO{+}_y \overset{O}{\overset{\|}{C}}{-}NH(CH_2)_6NH{-}\overset{O}{\overset{\|}{C}}{+}OCH_2CH_2{+}_x}$$

4

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

under vacuum to constant weight and then were left to attain equilibrium crystallinity for more than 2 weeks at room temperature.

2.4. Characterization

^{13}C nuclear magnetic resonance (^{13}C NMR) spectra of PHB/PEG multiblock copolymers were performed on a Varian UNITY-plus 400 system operating at 400 MHz. The polymers were dissolved in $CDCl_3$ with tetramethylsilane as an internal reference.

Fourier transform infrared (FTIR) spectra were recorded on a Bio-Rad FTS 135 spectrometer.

Studies by gel permeation chromatography (GPC) were carried out using a Waters Model 510 pump and Model 410 refractive index detector with Shodex KF-802.5, KF-804 columns. Chloroform was used as eluent at a flow rate of 1.0 ml/min. Polystyrene standards with a low polydispersity were used to establish the calibration curve.

Thermal properties were investigated using differential scanning calorimetry (DSC) on a NETZSCH DSC-204 under nitrogen atmosphere. In the DSC experiments, at first, at the heating rate 10 °C/min, the sample was heated from −80 to 180 °C (first heating scan), and kept for 2 min at 180 °C. After eliminating thermal history, the sample was rapidly cooled from 180 to −80 °C (−80 °C/min). Then the sample was heated from −80 to 180 °C at the heating rate 10 °C/min (second heating scan) and kept at 180 °C for 2 min before the melt was slowly cooled to −80 °C (−5 °C/min). In the final heating run (third heating scan), the sample was reheated to 180 °C with the same heating rate. The transition temperature and the enthalpy were determined from endothermic and exothermic peaks in the second and third run.

Mechanical properties were assessed by stress–strain experiments. The copolymer films were tested on a M350 Testometric tensile tester according to ASTM standard D882-83 at ambient temperature. The crosshead speed was 5 mm/min. The sample dimensions were 10 mm × 30 mm × 0.2–0.4 mm. Each experiment was repeated 3 times and reported data were determined on the average of three specimens.

For the determining of degradability, samples were cut from dry films and were incubated in PBS buffer solution at 37 °C. The degradation process was monitored by weekly recording of the changes in the molecular weight of the copolymers.

To measure the hydrophilicity of copolymers, the dry films were cut into squares and were immersed in deionized water at 37 °C. At given intervals, the weight of swollen polymers was measured after removing the excess water on the surface by tapping with filter paper until they reached swelling equilibrium.

3. Results and discussion

3.1. Synthesis of PHB/PEG multiblock copolymers

By changing the copolymer composition, HDI/diols ratio and using PEGs with different molecular weight, a range of copolymers were prepared. The progress of this reaction was monitored by GPC. The GPC chromatographs showed, in all cases, peaks which were unimodal and higher in molecular weight than those of starting materials (PHB-diol and PEG1000). Meanwhile, no peaks related to PHB-diol and PEG1000 were observed, which indicates that no starting materials remain in final products. All these can prove that PHB and PEG in the presence of HDI did copolymerize in a random condensation. Table 1 lists the relationship between the composition of reactant mixtures and the molecular weight of the synthesized copolymers. It can be seen that the molecular weight of the products decreases with increasing PHB component. This might be attributed to some end groups of low reactivity in the PHB-diol, which might be crotonic acid esters [26], and the relative concentration of these end groups increases with increasing the PHB content. In addition, the HDI/Diols ratio is a key factor in determining the molecular weight of the copolymers. Considering the requirements of practical applications, three kinds of final products were selected for further studies (Table 2).

Table 1
PHB/PEG multiblock copolymers prepared from PHB-diols and PEGs with HDI

M_n (PEG)	M_n (PHB-diol)	PHB-diol/PEG (weight ratio)	HDI/diols (mole ratio)	M_w[a]	M_w/M_n[a]
1000	2673	0.5	1.0	34659	1.98
4000	2673	0.5	1.0	22166	2.19
6000	2673	0.5	1.0	15268	2.65
1000	2673	0.5	1.1	132568	2.52
1000	2673	1	1.1	95590	2.92
1000	2673	0.5	1.3	–[b]	–
1000	2673	0.25	1.1	146780	2.43

[a] Measured by gel permeation chromatography (GPC).

[b] Crosslinked.

Table 2
Representative yields prepared from PHB-diols and PEGs with HDI

Sample code	M_n (PHB-diol)	M_n (PEG)	PHB-diol wt% (mol%)	PEG wt% (mol%)	Junction unit wt % (mol %)	M_w[a]	M_w/M_n[a]
BHG-1	2673	1000	44.3 (33.8)	44.3 (66.2)	11.4 (110)	95590	2.92
BHG-2	2673	1000	29.1 (20.4)	58.1 (79.6)	12.8 (110)	132568	2.52
BHG-3	2673	1000	17.2 (11.3)	68.9 (88.7)	13.9 (110)	146780	2.43

[a] Measured by gel permeation chromatography (GPC).

3.2. Structure characterization

The molecular structures and chemical compositions of copolymers were determined by FTIR and ^{13}C NMR. Fig. 1 shows the typical IR spectrum of PEG/PHB multiblock copolymer. A CH stretching band, belonging to the PEG block appeares at 2869 cm^{-1}. The absorbances at 3340 and 1530 cm^{-1} are assigned to the stretch and deformation of NH. This indicates that isocyanates did react with diols through chain-extension polymerization. The ^{13}C NMR ($CDCl_3$, ppm) shown in Fig. 2 ascertained the chemical composition of the copolymer. The peaks at 67.7 ppm (CH), 40.9 ppm (CH2), 19.9 ppm (CH3), 169.3 ppm(CO) belong to PHB blocks and the peak at 70.67 ppm is characteristic of main chain methylene units in the PEG blocks. It is clearly seen that the copolymer exhibits peaks characteristic of both PEG and PHB blocks.

3.3. Thermal properties

Thermal properties of copolymers were investigated by DSC. Figs. 3 and 4 are the typical DSC thermograms of the second and third scan, respectively. It can be seen that the copolymers passed through five typical transitions in the second heating scan. The low temperature inflection point is related to the glass transition; the next peak corresponds to the crystallization of soft PEG segments. The endothermic peak in the middle is the melting of PEG phase. The last two peaks are related to the exothermic crystallization and endothermic melting of PHB hard segments, respectively.

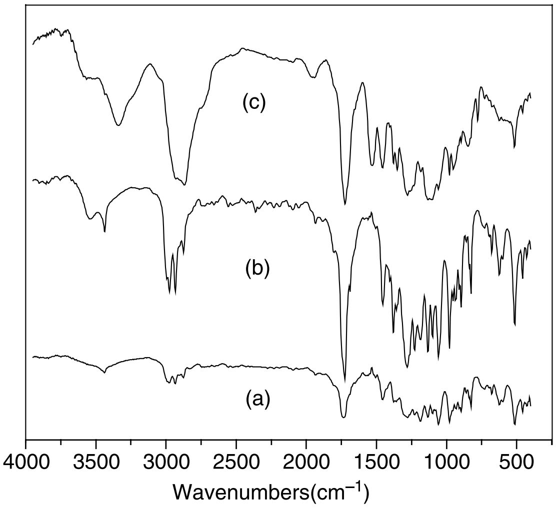


Fig. 1. Infrared spectra of natural-origin PHB (a); PHB-diol (b); PHB/PEG multiblock polymer (c).

The correlative data are shown in Table 3. It appears that the T_gs of copolymers lie between those of two prepolymers employed, and it is much lower than that of homopolymer PHB.

In the DSC thermogram of the third run, no cold crystallization peaks of PHB and PEG segments were observed. The reason for this phenomenon is that the process of crystallization is time-dependent. Slow cooling promotes the nucleation and crystallization to take place. When quenched from the melt, there is no adequate time for the PHB and PEG segments to crystallize, so they are still in amorphous phases [27].

According to the heat of fusion obtained from the areas under peaks, the crystallinity, X_c, of PHB or PEG phase can be calculated from the following formula:

$$X_c\ (\%) = \left(\frac{\Delta H_m}{\Delta H_m^0 W}\right) \times 100\%$$

Where ΔH_m^0 is the heat of fusion of 100% crystalline PHB or PEG; ΔH_m is the heat of fusion of the PHB or PEG phase in the copolymers, and W represents the weight fraction of PHB or PEG component in the copolymer. The data are also shown in Table 3. The results show that the crystallinities of PHB and PEG phase are apparently lower in the copolymer than in their respective homopolymers, and they all moderately decrease with the increase of the second component content.

It is of interest to note that the melting of PHB hard segments in the third scan showed bimodal peak. It has been found that a melt-recrystallization process was responsible for this behavior. The lower peak corresponds to the crystals formed from the slow cooling, while the other one is attributed to the more perfect crystals produced by recrystallization in the heating scan [19,28].

3.4. Mechanical properties

To improve the mechanical properties, especially to overcome the brittleness is one of the important aspects in the modification of PHB. The tensile properties of copolymers were determined at ambient temperature by stress–strain curves (Fig. 5). In comparison with homopolymer PHB, this

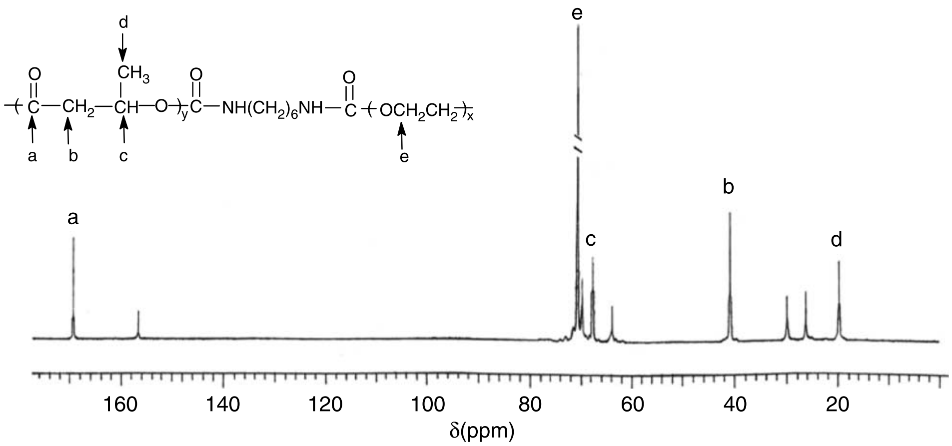


Fig. 2. ^{13}C NMR spectrum of PHB/PEG multiblock copolymer.

Table 3
Fusional transitions of PHB/PEG multiblock copolymers, determined from DSC

Sample	Scan[a]	T_g/°C	PHB-segment			PEG-segment		
			T_m/°C	ΔH_m/J/g	Xc/%	T_m/°C	ΔH_m/J/g	X_c/%
BHG-1	1	−47.1	138.7	–	–	12.1	–	–
	2	−33.3	135.9	43.46	29.8	20.0	17.80	8.2
	3	−41.5	135.9	39.64	27.1	19.6	29.87	13.8
BHG-2	1	−47.8	133.9	–	–	17.9	–	–
	2	−39.7	134.1	27.05	18.5	25.0	25.89	12.0
	3	−39.3	134.6	22.14	15.2	26.3	26.07	12.1
BHG-3	1	−44.7	133.3	–	–	21.7	–	–
	2	−45.6	134.1	25.54	17.5	23.8	27.34	12.7
	3	−38.2	134.1	14.85	10.2	25.2	29.12	13.5

[a] Number indicates the heating scan recorded.

kind of copolymers exhibit good toughness and moderate strength. No obvious yield point was observed in stress–strain curve. In Table 4, the results are listed for a series of copolymers with different PHB/PEG ratios. It appears that the mechanical properties of the copolymer can be adjusted in a wide range by changing the block composition. The hard segments (PHB) act as physical cross-links and polymer reinforcement in the copolymer, and when increasing the PHB content, tensile strength and Young's modulus increase, but the elongation at break decreases.

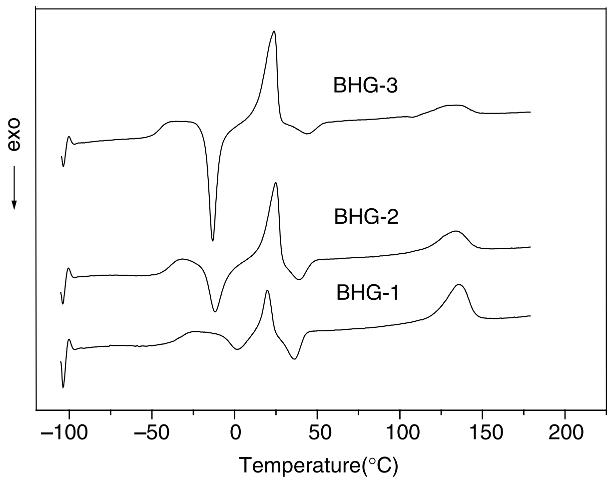


Fig. 3. DSC thermograms of PHB/PEG multiblock copolymers, during the second run (10 °C/min).

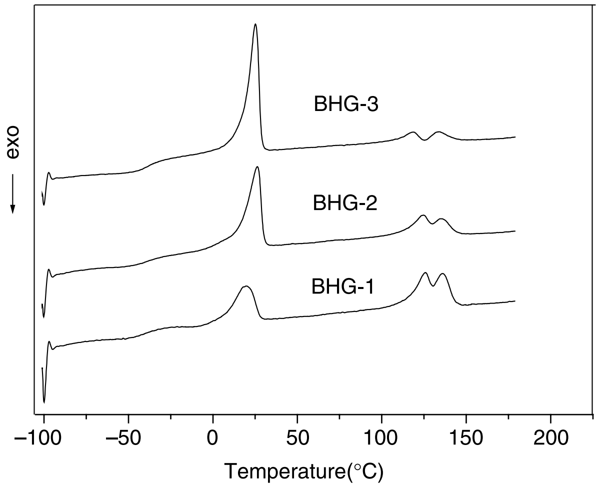


Fig. 4. DSC thermograms of PHB/PEG multiblock copolymers, during the third run (10 °C/min).

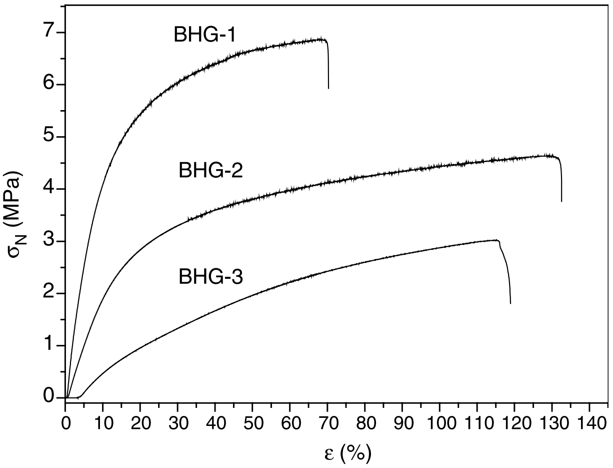


Fig. 5. Stress–strain diagrams of PHB/PEG multiblock copolymers.

3.5. Hydrophilic behavior

The hydrophilicity of copolymers was investigated by measuring the water content within the matrix. The equilibrium water content (EWC) was calculated from the following formula:

$$\mathrm{EWC}\ (\%) = \left(\frac{W_\mathrm{s} - W_\mathrm{d}}{W_\mathrm{s}}\right) \times 100\%$$

Where W_s and W_d donate the weight of swollen and dry copolymers, respectively. The hydrophilicity of materials is apparently improved due to the introduction of water-soluble PEG segments (Fig. 6). As a general rule, as the PEG content is increased, the EWC increases, and the desired hydrophilic properties can be further optimized depending on specific applications.

3.6. Degradation in vitro

The degradability of these PHB/PEG multiblock copolymers were investigated in our study. The samples were incubated in PBS buffer solution at 37 °C. The changes in molecular weight were monitored weekly to reflect the profile of the degradation, and the correlative data were plotted in Fig. 7. It can be seen that the degradation rates of copolymers are much higher than that of homopolymer PHB. After 10 weeks, they were approximately 35% of the original product. This phenomenon is attributed to two factors. First, PEG is a water-soluble polymer; the introduction of it can increase the availability of water within the matrix [29]. Meanwhile, the crystallinity of the copolymer has a significant effect on the hydrolysis, and the rate of the degradation decreases as the crystallinity increases. Because the degradation begins at chains in the amorphous region and crystalline domains remain almost untouched at first. The incorporation of PEG segments into the main-chain disturbs the regularity of molecular chains to some degree, so the crystallinity of PHB phase in copolymers apparently decreases. All these factors accelerate the hydrolysis process of copolymers.

Table 4
Mechanical properties of the copolymers, determined from stress–strain diagrams

Sample	PHB	BHG-1	BHG-2	BHG-3
E (MPa)	1472.4	55.0	21.0	4.6
σ_max (MPa)	27.0	7.5	4.6	2.7
ε_max (%)	3.0	74.3	129.4	114.8
σ_B (MPa)	24.5	1.0	0.9	1.6
ε_B (%)	3.4	75.8	132.6	119.0

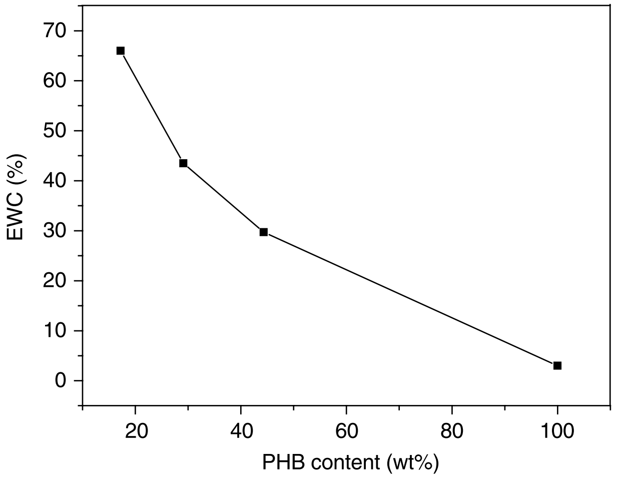


Fig. 6. Equilibrium water content (EWC) of copolymers as a function of compositions.

4. Conclusions

A series of multiblock copolymers composed of PHB and PEG segments were synthesized through one-step condensation copolymerization with HDI as a coupling agent. The

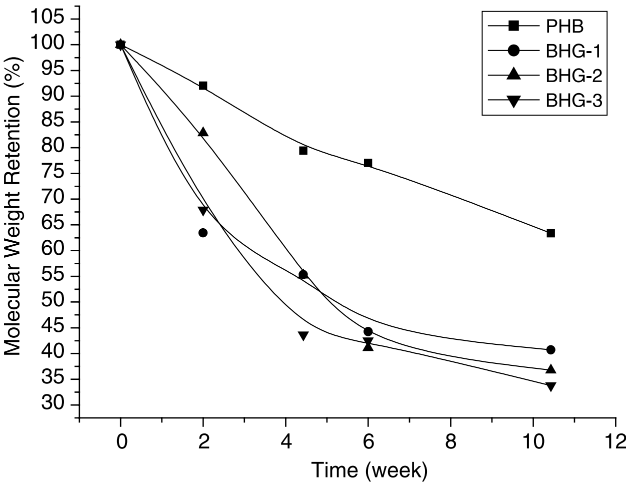


Fig. 7. Molecular weight retention of PHB/PEG multiblock copolymers as a function of incubation time at 37 °C in phosphate buffered saline.

GPC analysis was used in combination with IR and NMR to confirm that we did form these new PHB/PEG multiblock copolymers. DSC results showed that both two phases (PHB and PEG) are able to crystallize. The T_gs of copolymers are much lower than that of homopolymer PHB and lied between those of the two prepolymers employed. The tensile properties of copolymers were determined at ambient temperature by stress–strain experiments. In comparison with homopolymer PHB, this kind of copolymers exhibit good toughness and moderate strength. Because the introduction of PEG segments can increase the availability of water within the matrix, the hydrophilicity and degradability of the materials are apparently improved. The EWC and degradation rate both increase with the increase of PEG content. Furthermore, depending on specific applications, a wide range of controllable properties can also be obtained by changing the composition of the copolymers.

Theoretically, the disparity in hydrophobicity between the blocks and the crystallinity of the hydrophobic segments are two important parameters that dictate the phase behavior of amphiphilic block copolymers. When the temperature is raised, the melting of PHB crystalline domains and the hydrophobic interaction along polymer chains may introduce phase transitions. The potential applications of these block copolymers based on phase behavior may lie in controlled drug delivery system and degradable shape-memory polymers [30–33]. The detailed content will be discussed in a different paper.

Acknowledgements

The authors thank the National Natural Science Foundation of China (grant number: 50373032) and the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, P.R.C. (2002-123) for supporting this research work.

References

[1] Anderson AJ, Dawes EA. Microbiol Rev 1990;54:450–72.
[2] Nebe NB, Forster C, Pommerenke H, Fulda G, Behrend D, Bernewski U, et al. Biomaterials 2001;22:2425–34.
[3] Freier T, Kunze C, Nischan C, Kramer S, Sternberg K, Saβ M, et al. Biomaterials 2002;23:2649–57.
[4] Volova T, Shishatsksya E, Sevastianov V, Efremov S, Mogilnaya O. Biochem Eng J 2003;16:125–33.
[5] Cai ZJ, Cheng GX. J Mater Sci Lett 2003;22:153–5.
[6] Ando Y, Fukada E. J Polym Sci, Polym Phys Ed 1984;22(10):1821–34.
[7] Doyle C, Tanner ET, Bonfield W. Biomaterials 1991;12:841–7.
[8] Alper R, Lundgren DG, Marchessault RH, Cote WA. Biopolymers 1963;1:545–56.
[9] Barham PJ, Keller A, Otun EL. J Mater Sci 1984;19:2781–94.
[10] El-Taweel SH, Hohne GWH, Mansour AA, Stoll B, Seliger H. Polymer 2004;45(3):983–92.
[11] Verhoogt H, Ramsay BA, Favis BD. Polymer 1994;35(24):5155–69.
[12] Wang TZ, Cheng GX, Ma SH, Cai ZJ, Zhang LG. J Appl Polym Sci 2003;89(8):2116–22.
[13] Hirt TD, Neuenschwander P, Suter UW. Macromol Chem Phys 1996;197:4253–68.
[14] Andrade AP, Neuenschwander P, Hany R, Egli T, Witholt B, Li Z. Macromolecules 2002;35:4946–50.
[15] Cheng GX, Cai ZJ, Wang L. J Mater Sci, Mater Med 2003;14:1073–8.
[16] Fernandes EG, Pietrini M, Chiellini E. Biomacromolecules 2004;5:1200–5.
[17] Shi F, Ashby R, Gross RA. Macromolecules 1996;29:7753–8.
[18] Shi F, Gross RA. Macromolecules 1996;29:10–27.
[19] Ravenelle F, Marchessault RH. Biomacromolecules 2002;3:1057–64.
[20] Li J, Li X, Ni XP, Leong KW. Macromolecules 2003;36:2661–7.
[21] Reeve MS, Mccarthy SP, Gross RA. Macromolecules 1993;26(5):888–94.
[22] He F, Li S, Vert M, Zhuo R. Polymer 2003;44(18):5145–51.
[23] Boschet F, Branger C, Margaillan A, Condamine E. Polymer 2002;43(19):5329–34.
[24] Najafi F, Sarbolouki MN. Polymer 2002;43(23):6363–8.
[25] Zhao Q, Cheng GX. J Mater Sci Lett 2004;39:3829–31.
[26] Hirt TD, Neuenschwander P, Suter UW. Macromol Chem Phys 1996;197:1609–14.
[27] Saad GR, Lee YL, Seliger H. J Appl Polym Sci 2002;83:703–18.
[28] Hao JY, Deng XM. Polymer 2001;42:4091–7.
[29] Yu C, Kohn J. Biomaterials 1999;20:253–64.
[30] Huh KM, Bae YH. Polymer 1999;40:6147–55.
[31] Lee JW, Hua F, Lee DS. J Controlled Release 2001;73:315–27.
[32] Lendlein A, Langer R. Science 2002;296:1673–6.
[33] Sosnik A, Cohn D. Polymer 2003;44(23):7033–42.