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Polymer 47 (2006) 32–36
polymer
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Polymer Communication

A novel biodegradable poly(*p*-dioxanone)-grafted poly(vinyl alcohol) copolymer with a controllable in vitro degradation

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Received 25 April 2005; received in revised form 17 August 2005; accepted 3 October 2005
Available online 28 November 2005

Abstract

A novel biodegradable copolymer was synthesized from poly(vinyl alcohol) and poly(*p*-dioxanone) by ring-opening polymerization. The molecular structure of the copolymer was characterized by one- and two-dimensional NMR spectroscopy. The results of differential scanning calorimetry (DSC) show that the amphiphilic and comb grafted structure of the copolymer make its crystalline behavior different from that of the poly(*p*-dioxanone) homopolymer (PPDO). The in vitro degradation rate of the copolymers can be controlled via adjusting the number and length of PPDO segments of PVA-*g*-PPDO copolymers. The copolymer has a potential application in biomedical materials or in the controlled release of drug.

Keywords: Poly(vinyl alcohol); Poly(*p*-dioxanone); Copolymer

1. Introduction

Biodegradable aliphatic polyester, such as polylactide (PLA), poly(ε-caprolactone) (PCL), copolymer of lactide and glycolide (PLGA), poly(β-hydroxybutyrate) (PHB), and poly(*p*-dioxanone) (PPDO) have attracted many attentions in recent years due to their excellent biocompatibility and biodegradability, and have been widely used in biomedical and pharmaceutical applications such as surgery repair materials and drug delivery systems [1–3]. As one of the biodegradable and biocompatible aliphatic polyesters, PPDO has highly flexibility and good tensile strength [4]. which can be used not only in medical materials but also in films, molded products, laminates, foams, non-woven material, adhesives and coatings [5–7]. However, high cost and discontinuous degradation rate are the key factors limiting the wide application of PPDO, for example, controlled release of drug. Graft copolymerization is a versatile method for providing functionality to the resulting polymers, and for regulating polymer properties. However, there are few reports about graft copolymerization of PPDO with other polymers [8].

In the present paper, we synthesized the copolymer of PPDO grafted onto poly(vinyl alcohol) (PVA) by ring-opening polymerization with stannous octoate ($SnOct_2$) as catalyst. The introduction of aliphatic polyester onto PVA by graft polymerization would lead to the controllability of degradability and physical properties via controlling the chemical structure of the graft copolymer by changing polymerization conditions. The molecular structures of the obtained copolymers were characterized carefully via NMR. The in vitro degradability of the copolymer was studied with a phosphate buffered saline solution. To our best knowledge, this is the first paper on the copolymer of PPDO grafted PVA.

2. Materials and methods

2.1. Materials

PVA (PVA-500, degree of polymerization 500, degree of hydrolysis 88%, $M_n = 24{,}500$) as purchased from Kuraray company (Tokyo, Japan) and was used after drying under vacuum at 40 °C for more than 1 week. *p*-dioxanone (PDO) with a melt point of 25 °C was provided by the pilot plant of the center for degradable and flame-retardant polymeric materials (Chengdu, China). Stannous octoate ($SnOct_2$) was purchased from Sigma (USA) and used as received. Dimethyl sulfoxide (DMSO) and other solvents with AP grade were purchased from

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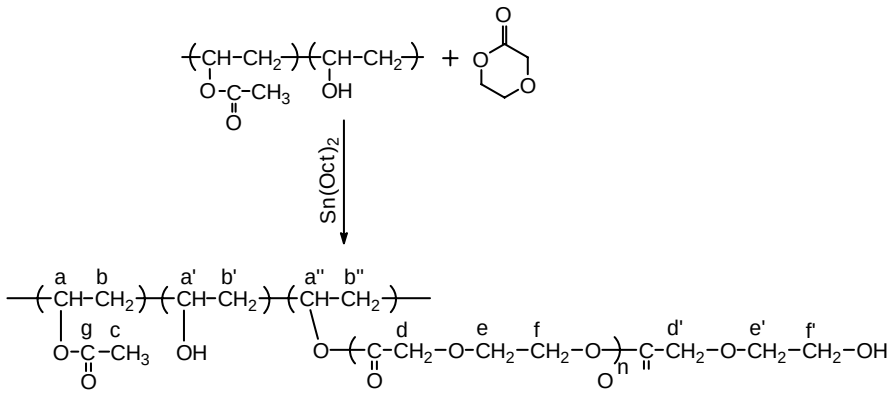
doi:10.1016/j.polymer.2005.10.008



Scheme 1. The synthesis process of PVA-*g*-PPDO.

Hehong Chemical Factory (Chengdu, China) and used without further purification.

2.2. Synthesis of PVA-g-PPDO

The synthesis process of PVA-*g*-PPDO is shown in Scheme 1. Under nitrogen, 0.5 g(0.01 mol repeated unit) PVA was charged into a rigorously dried 50 mL flask and then was degassed at 50–55 °C in a vacuum line for 2 h, purging three times with dry nitrogen. Then 10.2 g (0.1 mol) PDO was charged into flask. The flask was then immersed into a preheated oil bath (T = 120 °C) for about 30 min to obtain a clear homogeneous melt system of PDO and PVA. Then the catalyst was injected under nitrogen at 60 °C and the reaction was allowed to proceed for 2 h at 100 °C. After cooling to zero centigrade, the crude products were dissolved in DMSO and then precipitated in excess anhydrous methanol. The products were dried at 40 °C in vacuum until constant weight was obtained.

2.3. Characterization and test

One- and two-dimensional NMR spectroscopy was used to characterize the structure of PVA-*g*-PPDO. One-dimensional NMR measurements were obtained on both ^{1}H and ^{13}C nuclei. ^{1}H NMR spectroscopy was obtained on a Varian Inova 400 operating at 400 MHz, and ^{13}C NMR spectra were obtained at

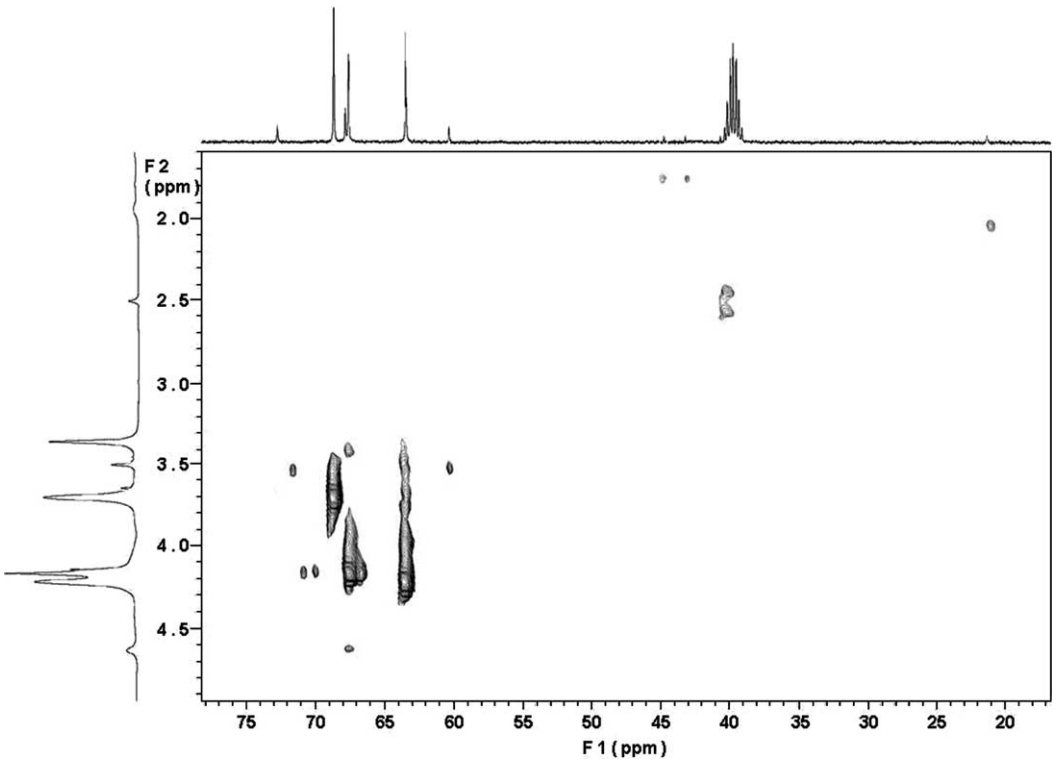


Fig. 1. Typical HMQC of PVA-*g*-PPDO.

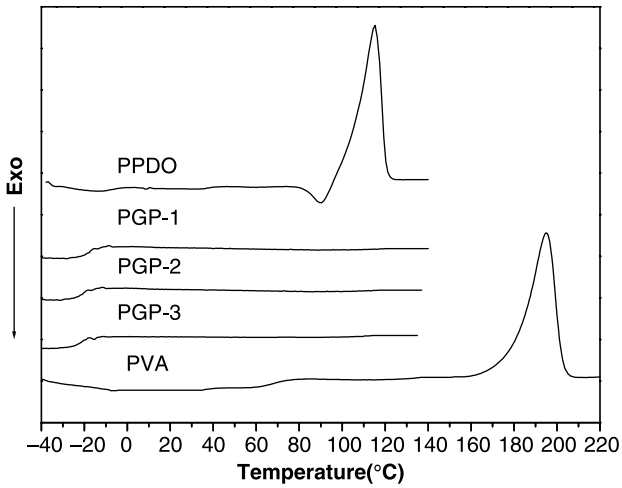


Fig. 2. The second heating runs of DSC thermogram of neat PPDO, PVA and PVA-*g*-PPDO copolymers.

125 MHz for a carbon-13 isotope. The PVA-*g*-PPDO samples were dissolved in dimethyl sulfoxide-d_6, and the solution concentration was 15% (w/v). The spectra were obtained with a pulse angle of 25°, a delay time of 10 s, and an acquisition time of 2 s. All chemical shifts were reported in parts per million with tetramethylsilane as a reference. Two-dimensional heteronuclear multiple quantum coherence (HMQC) spectroscopy was also used to obtain detailed information on the direct C–H connectivity in the structure of PVA-*g*-PPDO.

DSC measurement was performed with SEIKO EXSTAR60000 in sealed aluminum pan under nitrogen atmosphere. The samples were preheated up to 140 °C and kept for 5 min to eliminate the thermal history, then cooled to −50 °C at a cooling rate of 2.5 °C/min. The samples (PPDO and PVA-*g*-PPDO) were again heated up to 140 °C at the same rate, and the PVA sample was heated to 220 °C. The glass transition temperature (T_g), the crystallization temperature (T_c) and the melting temperature (T_m) were obtained from the thermogram.

The in vitro degradation tests were carried out in a phosphate buffer solution with pH = 7.4 at 37 °C. Films were cut into $20 \times 10\ mm^2$ slabs with a thickness of 0.3 mm. The samples were prepared by compression molding at 140 °C, followed by rapid cooling at room temperature.

3. Results and discussion

The structure of PVA-*g*-PPDO expected is shown in Scheme 1. To obtain detailed information on the microstructure of PVA-*g*-PPDO, including the degree of substitution (DS) and degree of polymerization (DP) and PPDO/PVA mole ratio, one and two-dimensonal NMR experiments were performed.

Proton NMR spectroscopy is one of the most powerful tools for the quantitative analysis on the polymer microstructure. However, it has limitations in peak resolution in many cases due to the peak overlap caused by its narrow spectral range. Therefore, we assigned at first the peaks for all carbon species in PVA-*g*-PPDO structure from its ^{13}C NMR spectrum, which has a spectral range wide enough to resolve easily each peak in the spectrum. Then, spectroscopy was used to find out the direct C–H connectivity between each carbon and the proton attached directly to it, and to correlate the ^{13}C NMR with the ^{1}H NMR spectrum. Fig. 1 shows the typical HMQC spectrum of PVA-*g*-PPDO sample. The longitudinal axis of the spectrum corresponds to the chemical shift of the one-dimensional ^{1}H NMR spectrum, and the transverse axis corresponds to that of the one-dimensional ^{13}C NMR spectrum.

The results of the peak assignment are summarized in Table 1. Indeed, in the ^{1}H NMR spectrum for the neat PVA, methylene protons of the backbone appear at 1.30–1.50 ppm and the methine protons attached to –OH and $–OCOCH_3$ appear at 3.82 and 3.90 ppm, respectively. The $–CH_3$ protons of the acetate group have a characteristic peak at 1.95 ppm. And the hydroxyl protons (–OH) of PVA are separated into triads at 4.22/4.47/4.67 ppm due to the hydrogen bonding between –OH groups of the polymer and DMSO [9]. However, when PPDO is grafted to PVA, the proton spectrum shows methylene resonance of the backbone at 1.5–2.0 ppm and methine resonance at 5.10 ppm ($H_{b''}$, attached to PPDO, and H_b, attached to $–OCOCH_3$), 4.03 ppm ($H_{b'}$, attached to –OH), respectively. These shifts in NMR are in excellent agreement with data reported previously for modified PVA [10]. Besides

Table 1
Chemical shifts for ^{13}C and ^{1}H species in PVA-*g*-PPDO

^{13}C	Chemical shift (ppm)	^{1}H	Chemical shift (ppm)
C_a, $C_{a''}$	70.07	H_a, $H_{a''}$	5.10
$C_{a'}$	66.74	$H_{a'}$	4.03
C_b, $C_{b''}$	46.10	H_b, $H_{b'}$, $H_{b''}$	1.5–2.0
$C_{b'}$	42.62		
C_c	21.06	H_c	1.95
C_d, $C_{d'}$	67.89	H_d, $H_{d'}$	4.16
C_e	68.75	H_e, $H_{e'}$	3.69/3.70/3.71
$C_{e'}$	65.81		
C_f	63.59	H_f	4.22
$C_{f'}$	62.12	$H_{f'}$	3.62
C=O	170.3	H_OH	4.67

Table 2
Results of the graft polymerization of PDO on PVA

Trial	Sample	PVA:PDO (mol:mol)	Temp. (°C)	Time (h)	Cat:OH (mol:mol)	Yield (%)	Determined by ^{1}H NMR			
							PPDO:PVA[a] (mol:mol)	DP[b]	DS[c]	M_n[d]
1	PVA-*g*-PPDO-1	1:10	120	2	1:500	46.2	66:34	11.2	0.17	121.43
2	PVA-*g*-PPDO-2	1:10	120	2	1:100	55.3	73:27	12.3	0.22	162.84
3	PVA-*g*-PPDO-3	1:10	120	2	1:50	67.5	82:18	15.1	0.31	262.60
4	PVA-*g*-PPDO-4	1:10	120	1	1:100	45.4	69:31	12.3	0.18	137.41
5	PVA-*g*-PPDO-5	1:10	120	4	1:100	60.3	79:21	16.2	0.23	214.29

[a] The ratio of the repeated units of the PPDO and PVA, calculated by NMR as follows: DS×DP(PPDO)/1(PVA).
[b] The degree of polymerization of PPDO, calculated by ^{1}H NMR: $DP = I_{f'}/(I_f + I_{f'})$.
[c] The degree of substitution of copolymer, calculated by ^{1}H NMR: $DS = I_{f'}/(I_a + I_{a'} + I_{a''})$.
[d] The M_n was calculated by NMR as follows: $M_n = 24500 + DS \times DP \times 500 \times 102$.

these peaks, the PPDO-*g*-PVA gives extra peak at 4.16 ppm (H_d and $H_{d'}$) and 3.69–3.71 ppm (H_e and $H_{e'}$), and the peaks at 4.22 ppm corresponding to methylene group (H_f) and 3.62 ppm corresponding to the end group ($H_{f'}$) of the PPDO, respectively. These data confirmed unequivocally the grafting of PPDO onto PVA. It is worth noticing that signals of the methylene groups (H_e, H_f) of PPDO chains in grafting copolymer are lower than those in PPDO homopolymers (3.79 ppm for H_e, 4.34 ppm for H_f, respectively) [11]. These shifts may be caused by the interaction of the adjacent molecules groups. And the steadfastness of the H_d signal may be attributed to the π-bond of C–O–C.

In order to investigate the influence of reaction conditions on copolymerization processes and the molecular structure of copolymers, we carried out the copolymerization of PVA: PDO = 1:10 (mol/mol) under different reaction conditions. The results are summarized in Table 2. Trials 1–3 were conducted with different amounts of catalyst at fixed reaction time and temperature. It is clear that the yield, the molecular weight (M_n), the degree of polymerization (DP) and substitution (DS) almost linearly increase with the increase of the $Sn(Oct_2)$ content, indicating that the amount of the catalyst has a great effect on copolymerization. And a similar trend was observed for trial 2, 4, 5, which were carried out with different reaction times at fixed cat./OH ratio. The experiment made by Schwach et al. [12] suggested that the $Sn(Oct_2)$ may act as an assistant catalyst which co-initiated the ring opening polymerization (ROP) of lactones with the hydroxyl groups in the polymerization process. This means that, in the present experiment, the increasing amount of $Sn(Oct_2)$ could increase the polymerization propagation centers with the hydroxyl groups of PVA, and the prolongation of reaction time may promote the polymerization when polymerization is dominant over the depolymerization during the reaction process.

As we know, graft polyesters have different thermal properties compared with their linear counterparts owing to their molecular architecture. In our DSC measurement (Fig. 2 and Table 3), T_g and T_m (the figures are not shown here) of the graft copolymers were all increased slightly with the increase of molecular weight. But they were lower than the corresponding transition temperatures of neat PPDO (−9, 110 °C, respectively) and PVA (68.87, 194.99 °C). Moreover, the crystallization rate of the copolymer was so slow that the crystallization peak could hardly be observed during the cooling scanning even if the scanning rate is decreased to 2.5 °C/min, but the T_m could be observed during the first heating scanning. This phenomenon may be due to its particular molecular architecture, in which the short PPDO chains were grafted onto linear PVA, which destroyed to a certain extent the regularity of the molecular structure. However, these polymers offer the possibility of specifically adjusting the degree and the speed of crystallization by variation of the chain length and number. On the other hand, the molecular architecture of grafting short hydrophobic PPDO chains to a hydrophilic backbone can generate a new biodegradable copolymer with a faster degradation rate, which will be demonstrated below, and a lower melting point was observed. These changes will benefit the drug delivery and drug release [13–16].

The in vitro degradation behavior of PPDO and copolymers are shown in Fig. 3. As we know, the crystallinity is one of the key factors contributing to degradability of PPDO by random hydrolytic ester bond cleavage. As described above, branched PVA-*g*-PPDO has much lower crystallinity than neat PPDO itself. Moreover, the incorporation of the hydrophilic backbone

Table 3
DSC data of PPDO, PVA and PVA-*g*-PPDO copolymers from the heating and cooling scans

Sample		PPDO	PVA-*g*-PPDO-1	PVA-*g*-PPDO-2	PVA-*g*-PPDO-3	PVA
Determined by DSC	T_g/°C	−9	−18.06	−17.58	−16.8	68.87
	T_m/°C	110	83.86	85.52	87.01	194.99

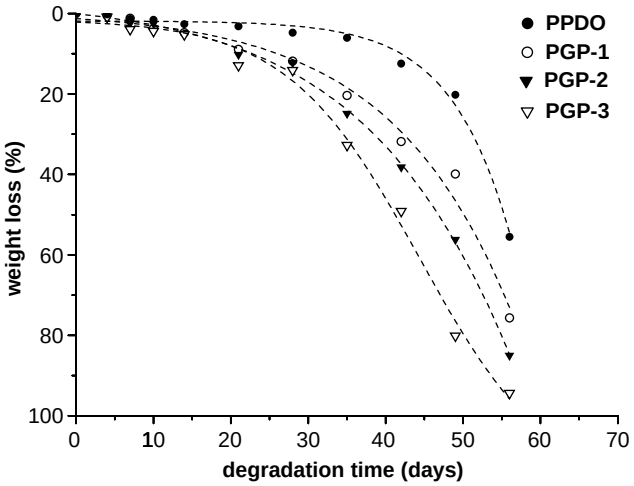


Fig. 3. The in vitro degradation behavior of PPDO and PVA-*g*-PPDO copolymers.

PVA offered additional possibilities to manipulate the hydrophilicity and hence the water penetration. Thus, it is reasonable that the copolymers have faster and more continuous weight-loss rate than the neat PPDO (Fig. 2). Furthermore, the degradation rate of the copolymers increases with increasing DS of graft copolymers. This may be due to the fact that the increase of the PPDO segment number in copolymers increased the content of the end –OH group of copolymers and the surface area of copolymers, which promoted the penetration of water into amorphous regions, resulting in an acceleration of chain cleavage of PPDO segments. Therefore, the degradation rate of PVA-*g*-PPDO can be adjusted by controlling the content of PPDO segments of the copolymer.

4. Conclusion

A novel biodegradable copolymer, PVA-*g*-PPDO, can be synthesized via poly(*p*-dioxanone) grafted onto poly(vinyl alcohol) by ring opening polymerization. The amount of catalyst has great influence on the molecular weight, DS and DP value of the copolymer. The thermal properties of the copolymer differ from the homopolymer PPDO, and its crystallization rate is very slow so that the crystallization peak can hardly be observed during the cooling scanning even at a very low rate in DSC measurement. The in vitro degradation rate increases with the increase numbers of PPDO grafts, indicating that the degradation rate can be controlled via adjusting the number and length of PPDO segments of PVA-*g*-PPDO copolymers.

Acknowledgements

This work was supported financially by the National Natural Science Foundation of China (Grant No. 50303012), the National Science Fund for Distinguished Young Scholass (50525309) and the Key Project of International Cooperation of China (2004DFA04700).

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