Synthesis and Characterization of Novel Biodegradable Poly(*p*-dioxanone-*co*-ethyl ethylene phosphate)s

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ABSTRACT: Poly(*p*-dioxanone-*co*-ethyl ethylene phosphate)s were successfully synthesized by the ring-opening copolymerization of *p*-dioxanone and ethyl ethylene phosphate with triisobutyl aluminum as an initiator; this was confirmed by ^{1}H-NMR and infrared spectra. The effects of the reaction conditions, such as the feeding ratio of the monomers and the reaction temperature and time, on the molecular weight of the copolymers were also studied. The *in vitro* degradation results showed that the introduction of phosphate segments into the backbone chains of the copolymers led to an enhancement of the degradation rate of the copolymers. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 5507–5511, 2006

Key words: biodegradable; copolymerization; degradation

INTRODUCTION

Poly(*p*-dioxanone) (PPDO), an aliphatic polyester, has attracted great interest from researchers in recent decades. Because of the existence of both ester groups and ether groups in its polymer chains, PPDO possesses many favorable properties, such as biodegradability, bioabsorbability, biocompatibility, and good flexibility. Thus, it has received the approval of the Food and Drug Administration to be used as a suture material in gynecology.[1] Unfortunately, PPDO needs about 6 months to degrade completely in the body.[2] Its slower degradation rate undoubtedly limits its applications, especially for short-term purposes. To adjust the properties of PPDO, other components have been incorporated into polymer chains, usually by ring-opening copolymerization with some monomers, such as lactide, caprolactone, and trimethylene carbonate.[3–6]

Polyphosphates are another important class of biodegradable polymers and have been investigated as biomaterials for almost 2 decades, initially in drug delivery and more recently in gene delivery and tissue engineering, because of their good biocompatibility, biodegradability, and pendant chain functionality. Furthermore, as copolymerization components, they can improve processability by increasing the solubility of the polymer in common solvents or by lowering the glass-transition temperature (T_g).[7–10] In our previous publications,[11,12] we have reported that the incorporation of phosphates into polylactide or polycarbonates resulted in an enhancement of their degradation rate. To combine the appealing features of PPDO and polyphosphate, novel copolymers were synthesized by the one-step ring-opening polymerization of *p*-dioxanone (PDO) and ethyl ethylene phosphate (EEP) with triisobutyl aluminum [Al(^{i}Bu)$_3$] as an initiator, and the *in vitro* degradation of the copolymer was investigated.

EXPERIMENTAL

Materials

PDO was synthesized according to a published procedure[13] and distilled over CaH_2 at 91–93°C/10 mmHg just before polymerization. EEP was synthesized according to ref. 12 and also distilled at 82–84°C/1 mmHg just before use. Al(^{i}Bu)$_3$ (1*M* solution in hexane) was purchased from Aldrich. Stannous octoate [Sn(Oct)$_2$] was distilled under reduced pressure and dissolved in dry toluene before use. All other reagents were analytical reagents and were dried and purified by general methods before use.

Measurements

Infrared (IR) spectra were recorded on a Nicolet DX spectrometer. ^{1}H-NMR spectra were recorded on a Varian Mercury VX 300 apparatus in $CDCl_3$ with tetramethylsilane as the internal standard. The number-average molecular weight (M_n) of the polymers

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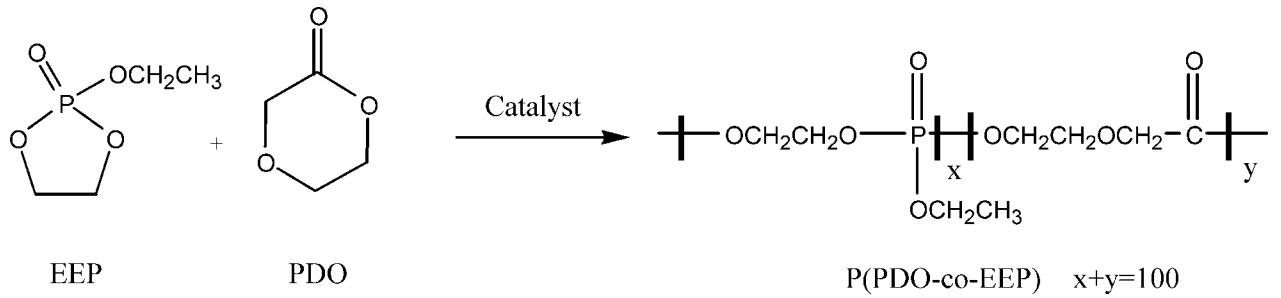

Scheme 1 Copolymerization of PDO and EEP.

was determined by gel permeation chromatography (GPC), which was accomplished with a Waters high-performance-liquid-chromatography system equipped with a model 2410 refractive-index detector, a model 2690D separations unit, and a Shodex K803 column. Chloroform at a flow rate of 1.0 mL/min was used as the eluent. Waters Millennium module software was used to calculate the molecular weights on the basis of a universal calibration curve generated by narrow molecular weight distribution polystyrene standards. Differential scanning calorimetry (DSC) measurements were carried out on a PerkinElmer DSC 7 thermal analyzer at a heating rate of 10°C/min. The morphologies were observed with polarizing light microscopy (PLM; BX51, Olympus) with a heating stage (THMS-600, Linkam). The sample was viewed with crossed polarizers, between which a retardation plate of 530 nm was inserted. The optical images were recorded with Linksys version 2.43 software.

General procedure for the copolymerization of PDO and EEP

PDO and EEP were copolymerized with $Al(^{i}Bu)_3$ as the initiator in a thoroughly cleaned and dried glass flask (10 mL) with a stirring bar. A monomer/initiator molar ratio of 1000 was used for all the copolymerizations. The vessel was vacuumed and then purged with argon gas. This process was repeated several times to remove the solvent introduced from the catalyst solution. The flask was then sealed under argon and placed in an oil bath for a period of time. After the reaction, the product was dissolved in dichloromethane. Then, the CH_2Cl_2 solution was poured into a

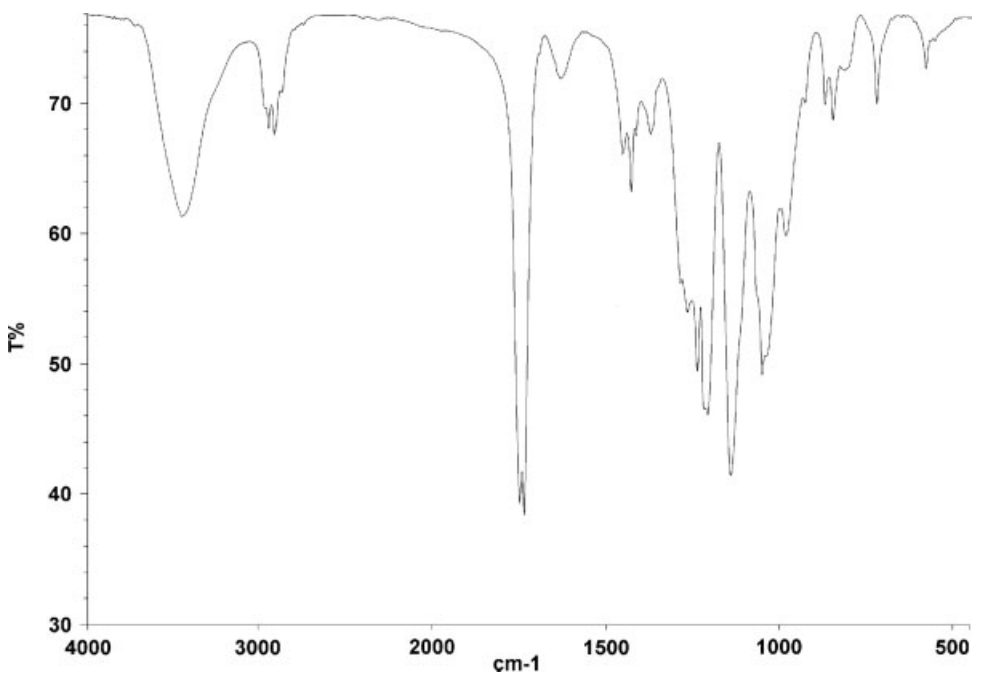

Figure 1 IR spectrum of P(PDO-*co*-EEP) (T = transmittance).

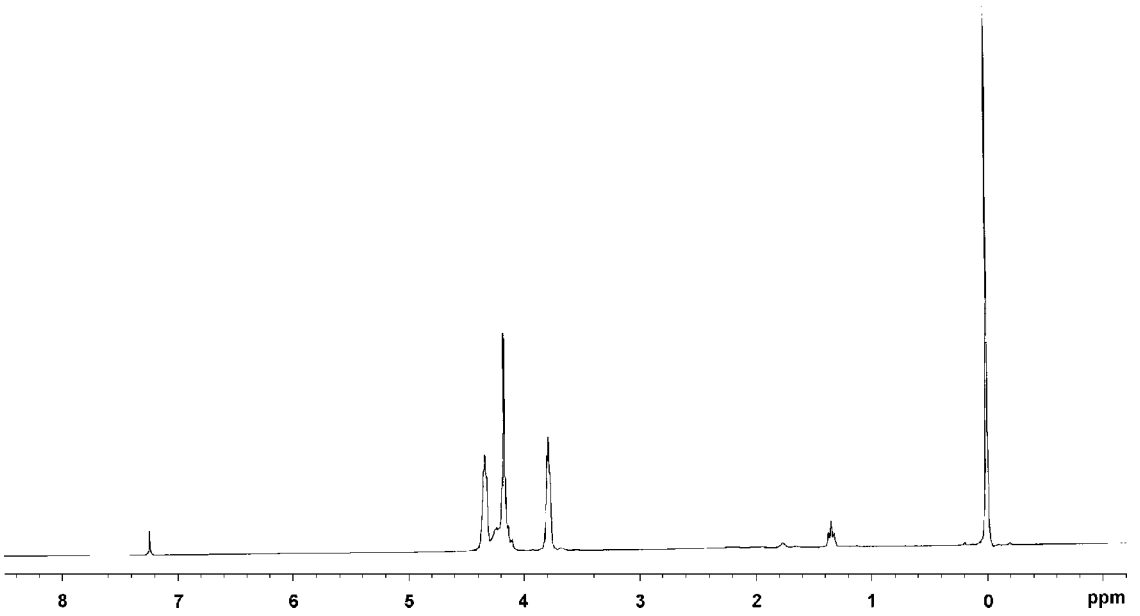

Figure 2 ^{1}H-NMR spectrum of P(PDO-*co*-EEP).

large amount of ethyl ether. A white precipitate was obtained and dried *in vacuo* to a constant weight.

In vitro degradation

Pellet samples were prepared by compression molding with about 100 mg of polymer. Degradation was performed in a pH 7.4 phosphate buffer solution at 37°C, and the buffer was changed daily. After degradation for a predetermined time, the samples were withdrawn and washed three times with distilled water and then dried to a constant weight *in vacuo*. The degradation rate was determined by the weight loss and the variation of the molecular weight of the polymer.

RESULTS AND DISCUSSION

Poly(*p*-dioxanone-*co*-ethyl ethylene phosphate) [P(PDO-*co*-EEP)] copolymers were synthesized by the one-step ring-opening polymerization of PDO and EEP in bulk with $Al(^iBu)_3$ as a catalyst. The copolymerization reaction is illustrated in Scheme 1.

The structure of the copolymer was confirmed with ^{1}H-NMR and IR spectra. The characteristic signals of PPDO and poly(ethyl ethylene phosphate) (PEEP) segments were observed in the IR spectrum of the copolymer (Fig. 1). The peaks at 1268 (P=O) and 1051 cm^{-1} (P—O—C) were assigned to the PEEP segment, and those at 1750 (C=O), 1140, and 1210 cm^{-1} (C—O—C) and at 1432 cm^{-1} were attributed to the PPDO segment. Figure 2 shows the

TABLE I
Copolymerization of PDO and EEP Under Different Reaction Conditions

Entry	$f_{PDO/EEP}$	Temperature (°C)	Time (h)	Yield (%)	M_n[b]	M_w/M_n[b]	$F_{PDO/EEP}$
1	5:1	70	24	—[a]	—	—	—
2	5:1	100	24	60	5300	1.47	5.16:1
3	5:1	130	24	65	5200	1.59	5.14:1
4	5:1	160	24	65	4800	1.72	5.20:1
5	5:1	100	8	43	4700	1.74	5.27:1
6	5:1	100	16	54	5100	1.77	5.22:1
7	5:1	100	24	69	5600	1.87	5.14:1
8	5:1	100	48	73	6100	1.74	5.19:1
9	5:1	100	72	68	7400	1.48	5.34:1
10	5:1	100	96	70	6700	1.60	5.28:1
11	1:1	100	24	41	1600	2.12	1.09:1
12	2:1	100	24	52	4700	1.61	2.15:1
13	10:1	100	24	71	5400	1.73	10.1:1
14	10:1	100	72	66	7100	1.52	9.81:1

[a] No precipitate was obtained in ether.
[b] Determined by GPC.

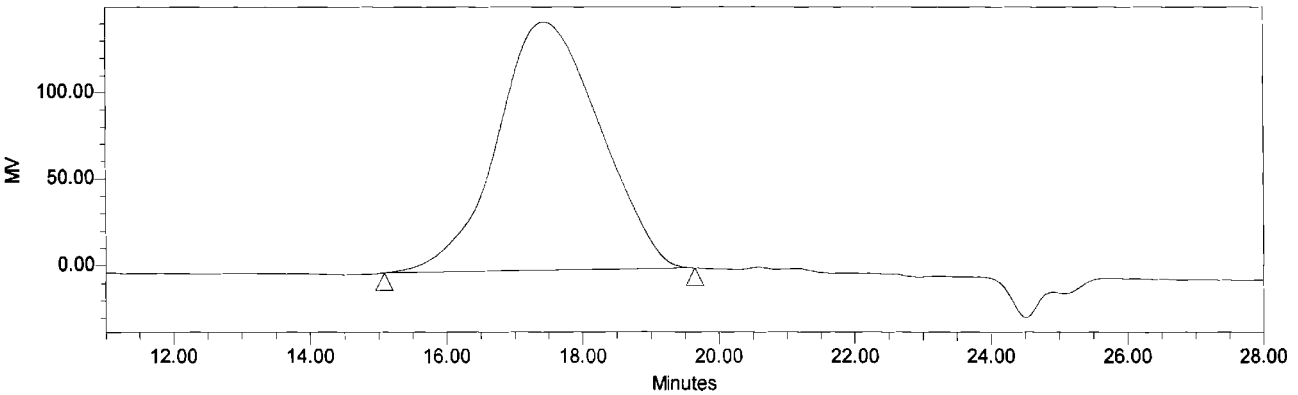

Figure 3 Typical GPC elution profile of P(PDO-*co*-EEP).

^{1}H-NMR spectrum of copolymer 9 in Table I. The triple peaks at 4.3 ppm belonged to the two protons of —O—CH_2—CH_2—OCO— in the PDO unit, and the triple peaks at 3.8 ppm were attributed to another two protons of —O—CH_2—CH_2—OCO— in the PDO unit. The triple peaks at 1.3 ppm belonged to the three protons of —CH_3 in the EEP unit, and the multiple peaks at 4.1 ppm were assigned to the protons of —O—CH_2—CO— in the PDO unit and —CH_2— in the EEP unit. The PDO/EEP molar ratio in the copolymer ($F_{PDO/EEP}$) was determined from the ^{1}H-NMR spectrum by a comparison of the signal integration of the PPDO segments at 3.8 ppm and that of PEEP at 1.3 ppm. The results indicated that the final molar ratio of PPDO to PEEP in the copolymer was in rather good agreement with the feeding ratio of the monomers ($f_{PDO/EEP}$). For example, $F_{PDO/EEP}$ of copolymer 9 was 5.34 : 1, whereas $f_{PDO/EEP}$ was 5 : 1. Figure 3 shows a typical GPC elution profile of the copolymer. A unimodal molecular weight distribution confirmed the successful copolymerization of PDO and EEP.

The influence of the reaction conditions on the copolymerization was studied by the variation of the feed ratio, reaction temperature, and reaction time (Table I). The results showed that the reaction temperature and reaction time might affect the molecular weight of the copolymers (entries 1–10 in Table I). With increasing reaction time, the molecular weight of the copolymers could increase gradually during 72 h of polymerization at 100°C. However, when the temperature was less than 70°C, nothing was obtained after the precipitation of the reactant in ether, probably because the temperature was too low for ring-opening copolymerization. Moreover, when the temperature was elevated to 160°C for 24 h or the reaction time exceeded 72 h at 100°C, the product turned brown, and at the same time the molecular weight decreased; this may have been due to transesterification.[14] The effect of $f_{PDO/EEP}$ on the copolymers was also studied (entries 7 and 11–13 in Table I). On the whole, the molecular weight increased with an increase of $f_{PDO/EEP}$. However, when $f_{PDO/EEP}$ was higher than 5, the molecular

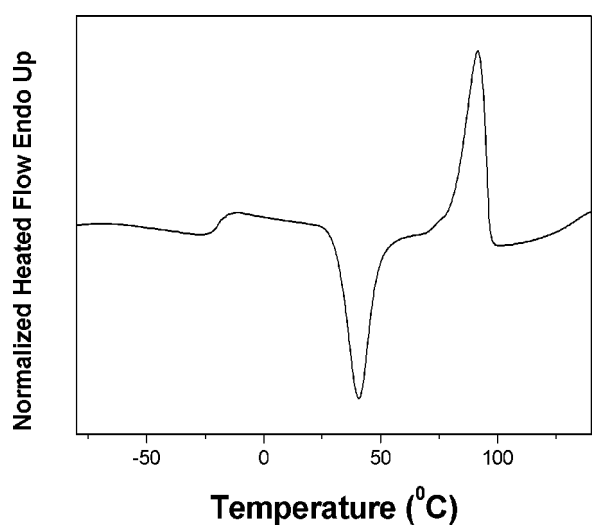

Figure 4 DSC heating scan at 10°C/min for P(PDO-*co*-EEP) (entry 9 in Table I).

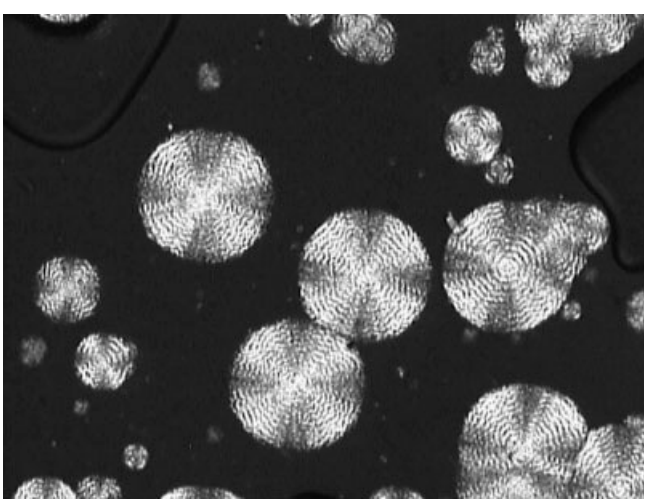

Figure 5 Morphology of P(PDO-*co*-EEP) (entry 9 in Table I) observed by PLM.

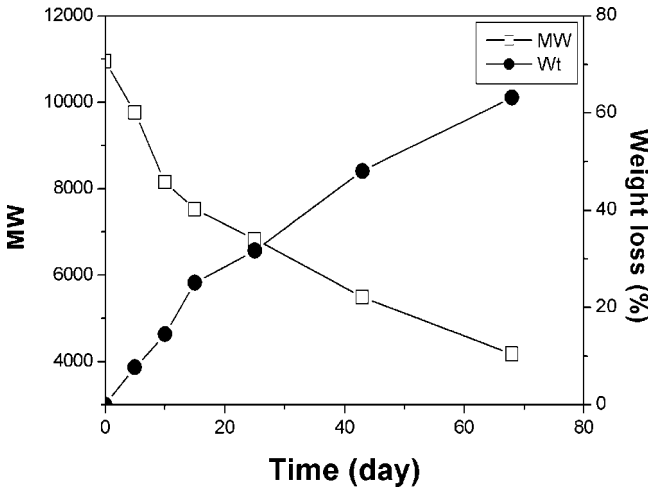

Figure 6 Molecular weight (MW) variation and weight loss of P(PDO-*co*-EEP) (entry 9 in Table I) during the degradation process (PBS, pH 7.4, 37°C).

weight decreased a little (entries 7 and 13 and entries 9 and 14). In addition, the variety of the initiators also influenced the results of the copolymerization. When $Sn(Oct)_2$ was used as the initiator instead of $Al(^iBu)_3$, no precipitate in ether could be obtained after polymerization.

As is well known, PPDO is a semicrystallized polymer that possesses a T_g at −8°C as well as a crystallization temperature at 46°C and a melting temperature at 109°C. However, the P(PDO-*co*-EEP) copolymers exhibited a decrease of T_g from −17.2 to −40.2°C when the EEP molar content increased from 9 to 50%. On the other hand, the copolymer with a high PPDO component (entry 9 in Table I) still remained crystalline like pure PPDO[15] (Fig. 4). This was also proved by PLM (Fig. 5). When the copolymer was cooled from the melt slowly, it formed banded spherulites that could exhibit a well-defined Maltese cross.

As is known, because of the existence of ether bonds in the backbone, PPDO shows low degradation via hydrolysis.[1] For example, in phosphate-buffered saline (PBS; pH 7.4) at 37°C, a weight loss of about 20% occurred in pure PPDO with a viscosity-average molecular weight (M_v) of 15,190 after 2 months.[16] This hydrolysis rate is much faster than that reported in the literature,[17] in which a PPDO suture lost only 3 wt % after 10 weeks of hydrolysis. This may be due to the differences in the molecular weights of the PPDO samples. As expected, the introduction of the phosphate units into the backbone accelerated the degradation rate. The degradation course of the copolymer (entry 9 in Table I) is shown in Figure 6. The weight-average molecular weight (M_w) of degrading P(PDO-*co*-EEP) dropped rapidly, reaching a 30% decline in 15 days. Beyond this initial phase, the rate of degradation slowed, with the molecular weight decreasing with an addition of 30% (vs the original M_w) in the following 53 days. A similar result was found for the weight loss of the same copolymer. An initially rapid weight loss was followed by a stage of slower weight loss. This might have been due to the presence of EEP segments. These more labile and hydrophilic phosphate groups were responsible for the initially rapid degradation of the copolymer. As the number of phosphate bonds in the copolymer decreased, the molecular weight drop became gradually dependent on the degradation of PDO bonds, which led to the slower degradation stage.[18]

CONCLUSIONS

PDO and EEP were ring-opening-copolymerized in the presence of $Al(^iBu)_3$, providing P(PDO-*co*-EEP) copolymers. Many reaction conditions, such as the feeding ratio and the reaction temperature and time, could greatly affect the copolymerization. We found that the degradation rate of the copolymer was faster than that of pure PPDO, and an initially rapid degradation rate was followed by a slower one. This was perhaps due to the introduction of phosphate segments into the backbone chains of the copolymers.

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