Synthesis, Characterization, and Properties of ε-Caprolactone and Carbonate Copolymers

Hui Chen, Guo-Ping Yan, Liang Li, Chao-Wu Ai, Xiang-Hua Yu

School of Material Science and Engineering, Wuhan Institute of Technology, Wuhan 430074, People's Republic of China

Received 8 February 2009; accepted 19 May 2009
DOI 10.1002/app.30889
Published online 28 July 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: A series of copolymers were synthesized by the ring-opening bulk polymerization of ε-caprolactone (CL) and 2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate (PTC) with tin(II) 2-ethylhexanoate as a catalyst. These copolymers were further reduced with a palladium/carbonate catalyst to obtain partly deprotected copolymers. The two types of copolymers that were obtained were characterized with ^{1}H-NMR, Fourier transform infrared spectroscopy, UV, gel permeation chromatography, differential scanning calorimetry, and automatic contact-angle measurements. The influences of the monomer feed molar ratio, catalyst concentration, and reaction time as well as the reaction temperature on the copolymerization process were also studied. The copolymerization of CL and PTC monomers was a nonideal copolymerization, and the copolymerization reactivity ratio of CL was higher than that of PTC in the polymerization process. *In vitro* degradation tests indicated that the partly deprotected copolymers possessed faster degradation rates and greater hydrophilicity than the unreduced copolymers. *In vitro* release profiles of fluorouracil from the copolymers showed that these two types of copolymers had steady drug-release rates and good controlled-release properties. Moreover, the partly deprotected copolymers had faster drug-release rates than the unreduced copolymers. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 114: 3087–3096, 2009

Key words: biodegradable; diblock copolymers; drug delivery systems; polycarbonates; ring-opening polymerization

INTRODUCTION

In recent years, poly(ε-caprolactone) (PCL) has attracted great interest for use as a biodegradable material in drug delivery and tissue engineering because of its good medicine permeability, low immunogenicity, and good biocompatibility and degradability.[1–7] Meanwhile, some polymers, such as poly(ethylene glycol) (PEG), poly(D,L-lactic acid), and aliphatic polycarbonates [e.g., poly(trimethylene carbonate) (PTMC)], have been used as amorphous polymers with flexible molecular chains and elasticity under room temperature, usually to modify PCL to change its semicrystalline nature.[8–12]

Biodegradable polycarbonates, such as homopolymers and copolymers of 1,3-dioxan-2-one [trimethylene carbonate (TMC)], 5,5-dimethyl-1,3-dioxan-2-one[5,5-dimethyl trimethylene carbonate (DTC), and 2-phenyl-5,5-bis(hydroxymethyl)] trimethylene carbonate (PTC), have also been widely used in drug delivery, soft tissue implants, and tissue regeneration because of their good biodegradation of surface erosion, biocompatibility, elasticity, and low toxicity.[13–17]

The biodegradation rates of aliphatic polycarbonates mostly depend on the structures of the polycarbonates.[18–20] For instance, the average weight losses of hydrophobic PTMC with a relatively low glass-transition temperature (T_g; 0°C) were less than 3.4% when PTMC films were incubated in a phosphate buffer solution (PBS; 0.1 mol/L, pH 7.4, at 37°C) for 100 days. However, the average weight losses of copolymers of DTC, TMC, and PEG such as poly[poly (ethylene glycol)-block-5,5-dimethy trimethylene carbonate] P(PEG-*b*-DTC) and poly[poly(ethylene glycol)-block-trimethylene carbonate] P(PEG-*b*-TMC)

Correspondence to: G.-P. Yan (guopyan@hotmail.com).

Contract grant sponsor: National Natural Science Foundation of China; contract grant number: 50773060.
Contract grant sponsor: Hi-Tech Research and Development Program of China; contract grant number: 2007AA0218-09.
Contract grant sponsor: New Century Excellent Talents in University, State Education Ministry; contract grant number: [2007]70:NCET-07-0649.
Contract grant sponsor: Scientific Research Foundation for Returned Overseas Chinese Scholars, State Education Ministry; contract grant number: [2007]1108.
Contract grant sponsor: Hubei Provincial International Project for Science and Technology Cooperation; contract grant number: 2007CA015.
Contract grant sponsor: Hubei Provincial Key Technologies Research and Development Program; contract grant number: 2007AA301B24.
Contract grant sponsor: Youth Chenguang Project of Science and Technology of Wuhan City, China; contract grant number: 200750731257.

after 6 weeks of incubation under the same conditions were 28.9 and 31.4%, respectively, indicating that the copolymers possessed higher degradation rates than the polycarbonate homopolymers of DTC and TMC, presumably because the hydrophilic PEG segments promoted water permeation into the copolymer matrix.[21,22] Therefore, various modification strategies must be employed to enhance the hydrophilicity and reduce the T_g values and crystallinity of aliphatic polycarbonates to improve their biodegradation rates.[23,24] Therefore, copolymerization and graft polymerization with other polymers, such as PEG and PCL, have the obvious advantage of easy accessibility to the targets.[25,26]

PTC is a novel six-membered cyclic carbonate monomer and contains potential functional groups. The aim of molecular design is to produce poly[ε-caprolactone-co-2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate] [P(CL-*co*-PTC)] copolymers by the anionic copolymerization of ε-caprolactone (CL) and PTC and to subsequently obtain copolymers containing some of the side-chain hydroxyl groups after deprotection. This not only increases the hydrophilicity and accelerates the degradation rates but also makes them conducive to chemical modification with the introduction of hydroxyl groups. These P(CL-*co*-PTC) copolymers and partly deprotected copolymers are expected to possess advantages between those of PCL and polycarbonates and to have potential as polymeric carriers for drug delivery.

In this work, we report the copolymerization of the six-membered cyclic carbonate monomers PTC and CL. These copolymers were further reduced with a palladium/carbonate (Pd/C) catalyst to obtain partly deprotected copolymers. The two types of copolymers that were obtained were characterized with ^{1}H-NMR, Fourier transform infrared (FTIR) spectroscopy, UV, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and automatic contact-angle measurements. The influences of the feed molar ratio of the monomers, catalyst concentration, and reaction time as well as the reaction temperature on the copolymerization process were also studied. The degradation and drug-release properties *in vitro* of the copolymers were evaluated as well.

EXPERIMENTAL

Instruments and reagents

All chemicals and solvents were analytical-grade. Tin(II) 2-ethylhexanoate [$Sn(Oct)_2$] and ethyl chloroformate were purchased from Sigma–Aldrich (St. Louis, MO) and purified by redistillation *in vacuo* before use. Toluene and tetrahydrofuran (THF) were

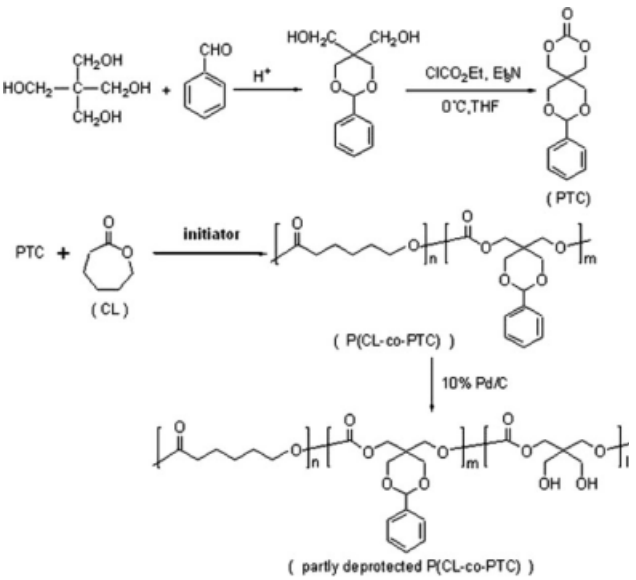

Figure 1 Synthetic route of the copolymers.

purified by redistillation over sodium. Triethylamine was refluxed under phthalic anhydride and dried over calcium hydride (CaH_2) before use. CL was dried over CaH_2 for 2 days and distilled under reduced pressure before use. PTC and poly[2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate] were prepared according to the literature.[23,24]

The prepared compounds were characterized with a Nicolet 510 FTIR spectrometer (ThermoFisher Scientific Inc., Madison, WI), a UV spectrophotometer (UV-2800 series, Unico, Shanghai, China), a Varian Mercury-VX300 NMR spectrometer, Varian, Columbia, MD, and an automatic contact-angle meter (SL200A/B/D series, Solon Tech. Inc. Ltd, Shanghai, China). The molecular weight was measured by GPC with a Waters 2965D separations module, a Waters 2414 refractive-index detector, Shodex K802.5 and K805 columns with a Shodex K-G guard column, a polystyrene standard, and dimethylformamide (DMF) as the solvent (flow rate = 1.0 mL/min; column temperature = 323 K; detector temperature = 318 K, Waters, Milford, MA). T_g of the copolymer was measured by DSC (DSC 200 F3, Netzsch Co., Selb/Bavaria, Germany).

Synthesis of the copolymers (Fig. 1)

CL (0.29 g, 2.5 mmol) and PTC (0.62 g, 2.5 mmol, 1 equiv) were added to a polymerization tube and then dried by several cycles of argon purging followed by exposure to a high vacuum. A solution of $Sn(Oct)_2$ in dry toluene (0.1 mol/L, 80 μL, 1/1000 equiv) was added to the dried mixture via a syringe. After further drying under a high vacuum, the tube was sealed and immersed into a thermostatically controlled oil bath at 180°C for 24 h. The resultant

solid residue was dissolved in dichloromethane (2 mL) and then reprecipitated with ethanol (40 mL). The precipitated solid was filtered, washed with ethanol and diethyl ether (1 : 1 v/v), and dried *in vacuo* for 48 h to yield a white powder of P(CL-*co*-PTC) (0.728 g, 80%).

^{1}H-NMR ($CDCl_3$, δ, ppm): 7.25–7.45 (m, C_6H_5—), 5.43 [s, C_6H_5—*CH*—$(O)_2$—], 4.46–4.54 [s, —COO—$CH_2C(CH_2O—)_2$—CH_2O—], 4.12 [s, —COO—$CH_2C(CH_2O—)_2$—CH_2O—], 3.97–4.02 [s, —COO—$CH_2C(CH_2O—)_2$—CH_2O—], 3.87–3.94 (t, —$OOCCH_2CH_2CH_2CH_2CH_2O$—), 2.29–2.34 (t, —$OOCCH_2CH_2CH_2CH_2CH_2O$—), 1.58 (m, —$OOCCH_2CH_2CH_2CH_2CH_2O$—), 1.39 (m, —$OOCCH_2CH_2CH_2CH_2CH_2O$—). IR (KBr, cm^{-1}): 2932, 2854 (—CH_2), 1737 (C=O), 1390 (C—C), 1099 (C—O). UV ($CHCl_3$, λ, nm): 212, 256.

The number-average molecular weight (M_n) was measured with GPC, and the average copolymer compositions of CL and PTC repeat units (mol %) were determined with ^{1}H-NMR.

P(CL-*co*-PTC) copolymers with different average copolymer compositions of CL and PTC repeat units (mol %) were synthesized by the same method under different reaction conditions. Their M_n's were also measured with GPC, and the average copolymer compositions of CL and PTC repeat units (mol %) were also determined with ^{1}H-NMR.

Deprotection of P(CL-*co*-PTC)

A 10% Pd/C catalyst (0.351 g) and 30 mL of anhydrous methanol were both added to a solution of P(CL-*co*-PTC) (2.343 g, 0.014 mol) dissolved in DMF (30 mL). Hydrogen was continually inflated into the reaction mixture for 48 h at 60°C under atmospheric pressure. The mixture was filtered, and the catalyst was then removed. After evaporation under reduced pressure, the residue was precipitated with *n*-hexane. The precipitated solid was filtered, washed with *n*-hexane, and dried *in vacuo* for 48 h to yield a light yellow powder of partly deprotected P(CL-*co*-PTC) (1.921 g, 81.9%).

^{1}H-NMR ($CDCl_3$, δ, ppm): 7.26–7.46 (m, C_6H_5—), 5.44 [s, C_6H_5—*CH*—$(O)_2$—], 4.59 [(s, $HOCH_2C(CH_2O)_2$—CH_2OH], 4.49 [s, —COO—$CH_2C(CH_2O—)_2$—CH_2O—], 4.12–4.18 [s, —COO—$CH_2C(CH_2O—)_2$—CH_2O—], 4.06–4.07 [s, —COO—$CH_2C(CH_2O—)_2$—CH_2O—], 3.75–3.78 (t, —$OOCCH_2CH_2CH_2CH_2CH_2O$—), 3.56–3.64 [t, $HOCH_2C(CH_2O)_2$—CH_2OH], 2.29–2.37 (t, —$OOCCH_2CH_2CH_2CH_2CH_2O$—), 1.56–1.68 (m, —$OOCCH_2CH_2CH_2CH_2CH_2O$—), 1.39–1.41 (m, —$OOCCH_2CH_2CH_2CH_2CH_2O$—). IR (KBr, cm^{-1}): 3450 (—OH), 2958, 2858 (—CH_2), 1752 (C=O), 1390 (C—C), 1104 (C—O). UV ($CHCl_3$, λ, nm): 212, 256. ^{1}H-NMR ($CDCl_3$ + D_2O, δ, ppm): 7.25–7.45 (m, C_6H_5—), 5.44 [s, C_6H_5—*CH*—$(O)_2$—], 4.47 [s, —COO—$CH_2C(CH_2O—)_2$ —CH_2O—], 4.11–4.13 [s, —COO—$CH_2C(CH_2O—)_2$— CH_2O—], 3.95–4.07 [s, —COO—$CH_2C(CH_2O—)_2$ —CH_2O—], 3.84–3.91 (t, —$OOCCH_2CH_2CH_2CH_2$ CH_2O—), 2.27–2.34 (t, —$OOCCH_2CH_2CH_2CH_2$ CH_2O—), 1.61–1.64 (m, —$OOCCH_2CH_2CH_2CH_2CH_2$ O—), 1.37–1.39 (m, —$OOCCH_2CH_2CH_2CH_2CH_2$ O—).

M_n was measured with GPC, and the average copolymer compositions of CL, PTC, and deprotected PTC repeat units (mol %) were determined with ^{1}H-NMR.

In vitro degradation test

The copolymers (0.1 g) were pressed into tablets and then dried *in vacuo* for 24 h. The tablets were suspended in 10 mL of PBS in a dialysis bag. The dialysis bag was sealed and then slowly shaken in 90 mL of PBS at 37°C in a 250-mL Erlenmeyer flask. At predetermined time intervals, the samples were taken out of the degradation medium, rinsed with distilled water, and dried *in vacuo* for 48 h; the weight loss and molecular weight loss were calculated.

In vitro drug-release study

Fluorouracil (5-Fu; 10 mg) and P(CL-*co*-PTC) or partly deprotected copolymers (100 mg) were dissolved in 20 mL of THF. The solution was homogenized by sonication for 30 s and then allowed to evaporate. The resulting film was collected and pressed in a tablet press to obtain 5-Fu-incorporated P(CL-*co*-PTC) tablets.

The tablets were suspended in 10 mL of PBS in a dialysis bag. The dialysis bag was sealed and then slowly shaken in 90 mL of PBS at 37°C in a 250-mL Erlenmeyer flask. Aliquots of the solution outside the dialysis membrane (25 mL) were replaced with 25 mL of PBS at various time intervals and tested at 256 nm with a high-performance liquid chromatography spectrophotometer. The changes in the concentration of 5-Fu were obtained from curves of absorption A versus concentration C of 5-Fu in PBS on the basis of the Lambert–Beer law.

Statistical analysis

All results were expressed as mean differences and were tested for significance by a t test, $P < 0.05$ being considered a significant difference.

RESULTS AND DISCUSSION

Synthesis of the copolymers

A cyclic carbonate monomer, PTC, was prepared by two-step reactions from pentaerythritol, and its structure was confirmed by melting-point measurements, FTIR, ^{1}H-NMR, and UV according to the literature.[13–15] The P(CL-*co*-PTC) copolymers were synthesized by the anionic ring-opening

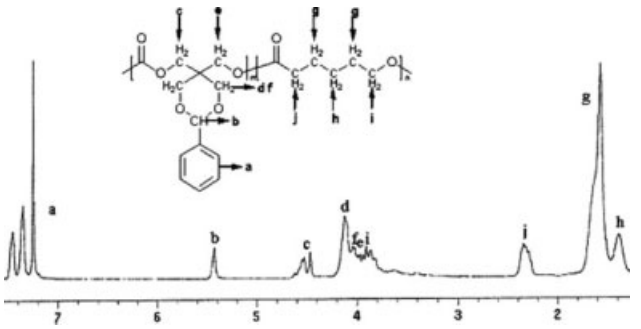

Figure 2 ^{1}H-NMR spectrum of the copolymers [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 1 mol/mol].

copolymerization of PTC and CL with $Sn(Oct)_2$ as a catalyst. These copolymers could readily dissolve in $CHCl_3$, CH_2Cl_2, THF, and DMF at room temperature. The FTIR spectra of the copolymers showed a characteristic peak at 1737 cm^{-1}, which represented the absorption peak of C=O groups. In the ^{1}H-NMR spectra (Fig. 2) of the copolymers, the typical signals for CL and PTC repeat units in the backbone of the copolymer structures can be observed at 7.25–7.45 (PTC repeat units: —C_6H_5) and 1.58 ppm (CL repeat units: —$OOCCH_2CH_2CH_2CH_2CH_2O$—), respectively. Thus, the average copolymer compositions of PTC and CL repeat units (mol %) could be calculated according to the integration values of the 7.25–7.45 ppm (—C_6H_5) peaks and the 1.58 ppm (—$OOCCH_2CH_2CH_2CH_2CH_2O$—) peak. The effects of the polymerization conditions, including the molar ratio of the monomers, monomer/catalyst molar ratio, reaction time, and temperature, on the molecular weights of the copolymers are listed in Tables I and II.

The effects of the CL/PTC monomer feed molar ratio on the polymerization with $Sn(Oct)_2$ as the catalyst are shown in Table I. The polymerization conditions were as follows: the monomer/catalyst feed molar ratio was 1000/1, the reaction temperature was 180°C, and the reaction time was 24 h. The CL/PTC repeat unit molar ratio in the backbone of the copolymers increased when the CL/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1. The molecular weight of P(CL-*co*-PTC) decreased appreciably when the CL/PTC monomer feed molar ratio increased from 1 : 8 to 1 : 1 and then increased rapidly when the CL/PTC monomer feed molar ratio increased from 1 : 1 to 8 : 1. Moreover, the CL/PTC repeat unit molar ratio in the backbone was always correspondingly larger than the CL/PTC monomer feed molar ratio in the polymerization process. Thus, the results indicated that the CL monomers had higher reactivity than the PTC monomers, and the content of CL repeat units in the backbone of P(CL-*co*-PTC) was greater than that of PTC repeat units. The contact angles of the P(CL-*co*-PTC) copolymers decreased when the CL/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1. It could be concluded that the hydrophilicity of P(CL-*co*-PTC) was improved when the CL/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1.

According to the copolymerization mechanism and the equation of the copolymerization reactivity ratio [eqs. (1)–(5)],[27] the monomer copolymerization reactivity ratios and the characteristic of the copolymerization of CL and PTC could be calculated. In the copolymerization process, the copolymer composition of the CL/PTC repeat unit molar ratio in the backbone at time t can be described by eq. (1):

$$\frac{-d[M_1]/dt}{-d[M_2]/dt} = \frac{d[M_1]}{d[M_2]} \tag{1}$$

$$F_1 = \frac{d[M_1]}{d[M_1] + d[M_2]} = 1 - F_2 \tag{2}$$

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]} \cdot \frac{r_1[M_1] + [M_2]}{r_2[M_2] + [M_1]} \tag{3}$$

TABLE I
Effect of the CL/PTC Feed Ratio on Copolymerization with $Sn(Oct)_2$ as a Catalyst

CL/PTC monomer feed molar ratio (mol/mol)	CL/PTC repeat unit in the copolymer (mol/mol)	M_n ($\times 10^4$)	M_w/M_n	Contact angle (°)	T_g (°C)
0 : 1	0 : 1	1.73	1.16	77.06	68.2
0.125 : 1	0.980 : 1	1.53	1.19	71.53	66.3
0.25 : 1	1.049 : 1	1.30	1.12	71.51	44.2
0.5 : 1	1.451 : 1	1.19	1.20	63.55	41.1
1 : 1	1.433 : 1	1.09	1.17	62.88	43.3
2 : 1	2.378 : 1	1.53	1.21	54.33	12.6
4 : 1	4.208 : 1	2.59	1.06	50.38	−13.3
8 : 1	8.434 : 1	2.88	1.19	54.04	−49.1
1 : 0	1 : 0	3.13	1.24	68.89	−50.1

Polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h. M_w = weight-average molecular weight.

TABLE II
Effects of the Catalyst Concentration, Reaction Time, and Reaction Temperature on Copolymerization with $Sn(Oct)_2$ as a Catalyst

Monomer/catalyst concentration ratio	Time (h)	Temperature (°C)	M_n ($\times 10^4$)	M_w/M_n
250	24	180	1.09	1.11
500	24	180	1.83	1.13
1000	24	180	2.59	1.06
2000	24	180	2.01	1.12
1000	8	180	1.45	1.15
1000	16	180	2.08	1.33
1000	36	180	1.78	1.14
1000	48	180	1.43	1.11
1000	24	170	1.34	1.09
1000	24	190	1.64	1.13

M_w = weight-average molecular weight.

$$f_1 = \frac{[M_1]}{[M_2] + [M_1]} = 1 - f_2 \quad (4)$$

$$F_1 = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2 f_1 f_2 + r_2 f_2^2} \quad (5)$$

where $[M_1]$ and $[M_2]$ are the monomer concentrations of CL and PTC at time t in the polymerization process, respectively; $d[M_1]$ and $d[M_2]$ are the copolymer molar compositions of repeat units CL and PTC in the backbone at time t, respectively; F_1 and F_2 are the repeat unit CL and PTC molar composition ratios of the copolymer at time t, respectively; f_1 and f_2 are the monomer concentration ratios of CL and PTC in the total monomer concentration at time t in the polymerization process, respectively; and r_1 and r_2 are the copolymerization reactivity ratios of monomers CL and PTC in the polymerization process, respectively.

The average copolymer compositions of CL and PTC repeat units (mol %) could be determined from ^{1}H-NMR spectra of the copolymers obtained from the copolymerization of monomers CL and PTC with $Sn(Oct)_2$ as the catalyst. The polymerization conditions were as follows: the feed monomer/catalyst molar ratio was 1000/1, the reaction temperature was 180°C, and the reaction time was 24 h. Therefore, the relationship curve of F_1 versus f_1 can be worked out as shown in Figure 3. r_1 and r_2 can calculated with eqs. (1)–(5) as follows:

$$r_1 = 1.34, r_2 = 0.626, r_1 r_2 = 0.839 < 1$$

This result demonstrated that the copolymerization of monomers CL and PTC was a nonideal copolymerization and that the copolymerization reactivity ratio of monomer CL was higher than that of PTC in the polymerization process.

The effects of the feed monomer/catalyst molar ratio, reaction temperature, and reaction time are shown in Table II. The polymerization conditions were as follows: the CL/PTC monomer feed molar ratio was 4 : 1 in the polymerization with $Sn(Oct)_2$ as the catalyst. The molecular weights of the copolymers increased and subsequently decreased with the increase in the catalyst dosage. The highest M_n value of the copolymer was 2.59×10^4 when the feed monomer/catalyst molar ratio was 1000, the reaction temperature was 180°C, and the reaction time was 24 h. This result indicated that an overly high dosage of the catalyst would result in a reduction of the molecular weight of the copolymer.

The molecular weights of the copolymers changed when the reaction time was varied from 8 to 36 h under the following polymerization conditions: a feed monomer/catalyst molar ratio of 1000 and a reaction temperature of 180°C. The molecular weights of the copolymers reached the maximum value ($M_n = 2.59 \times 10^4$) when the reaction time was 24 h and then came down rapidly when the time was increased. The reaction temperature of the bulk copolymerization was chosen to be above 170°C because the melting point of PTC is 169.5–170°C. However, a higher reaction temperature would induce the molecular weights of the copolymers to decrease. The long reaction time and high reaction temperature probably would induce degradation and interchange esterification reactions in the copolymers.

Deprotection of poly(PTC-*co*-CL)

Subsequently, these copolymers were further reduced with the Pd/C catalyst to obtain partly deprotected copolymers. The ^{1}H-NMR and IR

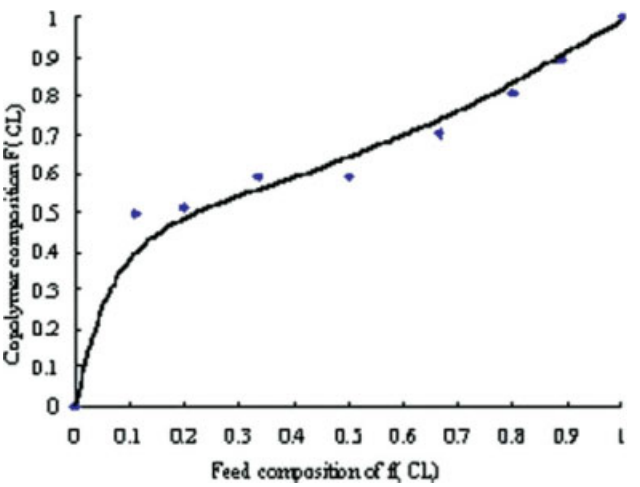

Figure 3 Relationship curve of F_1 as a function of f_1 [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

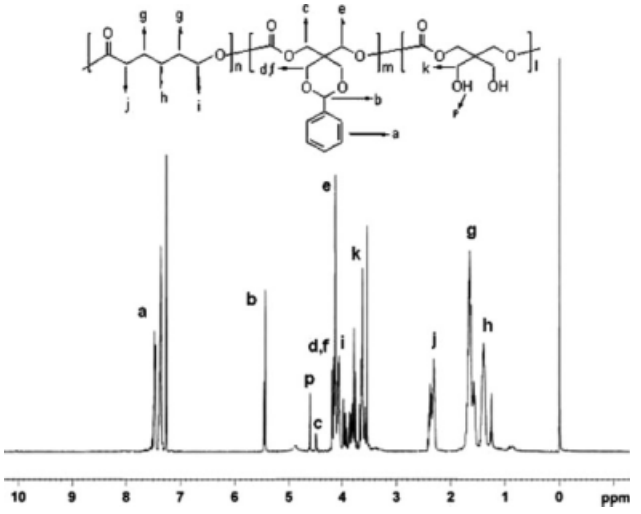

Figure 4 ^{1}H-NMR spectrum ($CDCl_3$) of partly deprotected copolymers [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 1 mol/mol].

spectra showed that the benzene ring and hydroxyl group both existed in the structures of the partly deprotected copolymers, and this indicated that parts of the benzene rings in the PTC repeat units of the copolymers were reduced. The FTIR spectra of the partly deprotected copolymers showed a characteristic peak at 3450 cm^{-1}, which represented the absorption peak of —OH groups; moreover, the intensity of the characteristic peak at 1737 cm^{-1}, which represented the absorption peak of C=O groups, decreased. In the ^{1}H-NMR spectra (Figs. 4 and 5) of the copolymers, the typical signals for benzene rings ($—C_6H_5$) can be observed at 7.25–7.45 ppm, and the integration values of the peaks decrease. Thus, the average copolymer compositions of CL, PTC, and partly deprotected PTC repeat units (mol %) could

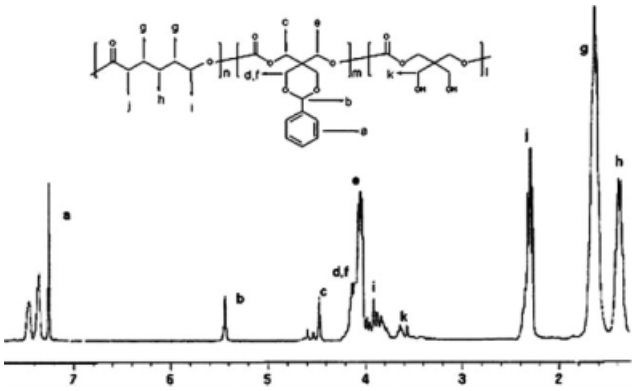

Figure 5 ^{1}H-NMR spectrum ($CDCl_3$ + D_2O) of partly deprotected copolymers [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 1 mol/mol].

TABLE III
Average Copolymer Compositions

	PTC (mol %) in P(CL-*co*-PTC)		
	8 : 1 CL/PTC[a]	1 : 1 CL/PTC[a]	1 : 8 CL/PTC[a]
Reduced copolymer	38.27	10.79	6.10
Unreduced copolymer	60.49	28.29	10.29
Reduction rate	36.73%	61.86%	40.72%

Polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h.
[a] Monomer feed molar ratio (mol/mol).

be calculated according to the integration values of the 7.25–7.45 ppm ($—C_6H_5$) peaks and the 1.58 ppm ($—OOCCH_2CH_2CH_2CH_2CH_2O—$) peak (Table III).

The introduction of hydroxyl-functional groups into the side chains of partly deprotected copolymers is expected to improve amphiphilic properties, enhance the biodegradation rate, increase the drug-release rate, and potentially provide a platform for chemical modification to readily attach drugs, environmentally sensitive groups, and tissue or organ-targeting groups to drug delivery systems. In comparison with unreduced P(CL-*co*-PTC), the water contact angles of the partly deprotected copolymers decreased because the hydrophilicity of the copolymers was enhanced, whereas some of the benzene rings in the repeat unit PTC segments in the copolymers were replaced by hydroxyl groups. Meanwhile, the T_g values (Figs. 6 and 7) of the partly deprotected copolymers fell, probably because of the steric effect elimination and molecular flexibility improvement when the partly rigid benzene rings were reduced to hydroxyl groups after the deprotection reaction (Table IV).

In vitro degradation test

According to the degradation mechanism and the equations of the weight loss and molecular weight loss [eqs. (6) and (7)], the weight loss and molecular weight loss could be calculated.

The weight loss was defined as follows:

$$\text{Weight loss } (\%) = (1 - M_t/M_0) \times 100 \qquad (6)$$

where M_t is the weight of the polymer at time t and M_0 is the initial weight of the polymer.

The molecular weight loss was defined as follows:

$$\text{Molecular weight loss } (\%) = (1 - M_{nt}/M_{n0}) \times 100 \qquad (7)$$

where M_{nt} is the molecular weight of the polymer at time t and M_{n0} is the initial molecular weight of the polymer.

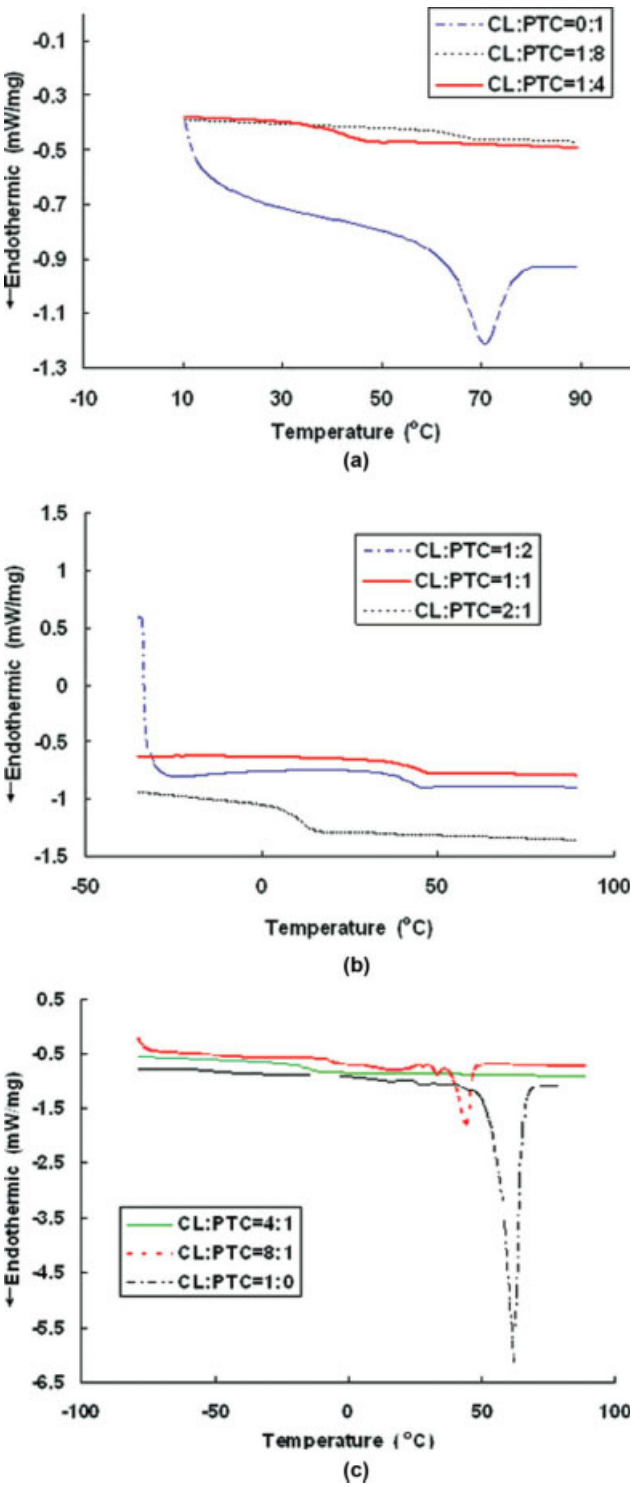

Figure 6 DSC curves of copolymers with different CL/PTC monomer feed molar ratios: (a) 0 : 1, 1 : 8, and 1 : 4; (b) 1 : 2, 1 : 1, and 2 : 1; and (c) 4 : 1, 8 : 1, and 1 : 0 mol/mol [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The *in vitro* degradation of the copolymers and partly deprotected copolymers was measured in PBS. Their degradation rates were denoted by the weight loss (Figs. 8 and 9) and molecular weight loss (Figs. 10 and 11) during 100 days in PBS at 37°C. The weight loss and molecular weight loss of the reduced copolymers were all higher than those of the corresponding unreduced copolymers after 100 days of degradation. For example, the weight loss of the partly deprotected P(CL-*co*-PTC) copolymers (1 : 8) was 17.91% and the molecular weight loss was 23.57% after 100 days of degradation. However, the weight loss of the corresponding unreduced P(CL-*co*-PTC) copolymers (1 : 8) was 4.56% and the molecular weight loss was 11.29% under the same conditions. Therefore, the degradation rates of the reduced copolymers became faster than those of the corresponding unreduced copolymers, presumably because the hydrophilic hydroxyl groups enhanced the hydrophilicity and promoted water absorption and permeation into the copolymer matrix to improve their biodegradation rates.

During the degradation process in PBS, the unreduced copolymers with different CL/PTC monomer feed molar ratios in copolymerization experienced almost the same weight loss but different molecular weight loss. The unreduced copolymers with a CL/PTC feed molar ratio of 1 : 1 in the copolymerization had higher molecular weight loss and degradation rates than the unreduced copolymers with CL/PTC feed molar ratios of 8 : 1 and 1 : 8.

On the other hand, the partly deprotected copolymers with different CL/PTC monomer feed molar ratios in the copolymerization showed different weight loss and molecular weight loss (Figs. 10 and 11). The partly deprotected copolymers with a lower CL/PTC feed molar ratio in the copolymerization experienced higher weight loss. However, the partly deprotected copolymers with a CL/PTC feed molar

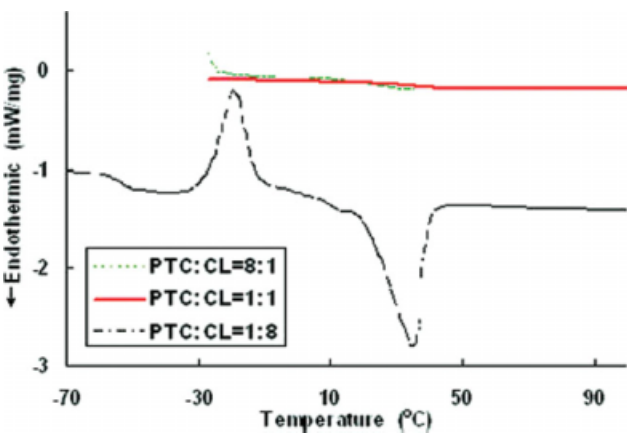

Figure 7 DSC curves of partly deprotected copolymers [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 8 : 1, 1 : 1, or 1 : 8 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience. wiley.com.]

TABLE IV
Experimental Data for Partly Deprotected P(CL-*co*-PTC) Copolymers with Different CL/PTC Feed Molar Ratios

CL/PTC monomer feed molar ratio (mol/mol)	CL/PTC repeat unit in the copolymer (mol/mol)	M_n ($\times 10^4$)	M_w/M_n	Contact angle (°)	T_g (°C)
0.125 : 1	1.613 : 1	1.50	1.17	63.80	31.3
1 : 1	8.264 : 1	0.96	1.21	60.73	37.8
8 : 1	15.385 : 1	2.22	1.19	46.58	−52.4

Polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h. M_w = weight-average molecular weight.

ratio of 8 : 1 in the copolymerization experienced higher molecular weight loss than the partly deprotected copolymers with a CL/PTC feed molar ratio of 1 : 1 and lower molecular weight loss than the partly deprotected copolymers with a CL/PTC feed molar ratio of 1 : 8 during the earlier degradation process in PBS. The molecular weight loss of the partly deprotected copolymers with a CL/PTC feed molar ratio of 1 : 8 as well as the corresponding unreduced copolymers improved rapidly and became faster than the others after 100 days of degradation.

In vitro drug-release properties of the copolymers

The overall process of drug release from polymeric tablets is mostly controlled by drug diffusion, drug dissolution, and polymeric degradation.[18–22] The 5-Fu release profiles of partly deprotected copolymers and unreduced copolymers are shown in Figures 12 and 13. The substantial release rates of the 5-Fu-incorporated P(CL-*co*-PTC) tablets could be maintained for more than 25 days of measurement. The 5-Fu-incorporated P(CL-*co*-PTC) tablets had no obvious phenomenon of abrupt release; the initial drug release was fast, but the trend was gentle as the time lengthened. The release rate became faster when the CL/PTC monomer feed molar ratio decreased, presumably because of the higher degradation rates of P(CL-*co*-PTC).

The release rates of the partly deprotected copolymers were higher than those of the corresponding

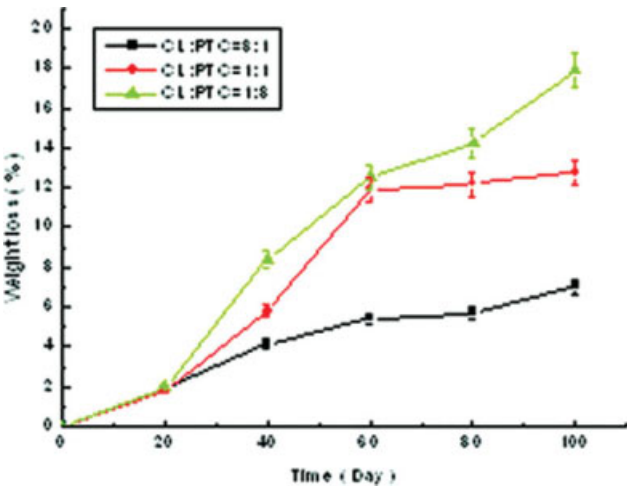

Figure 9 Weight loss (%) of partly deprotected P(CL-*co*-PTC) copolymers during degradation in PBS [polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 8, 1 : 1, or 8 : 1 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

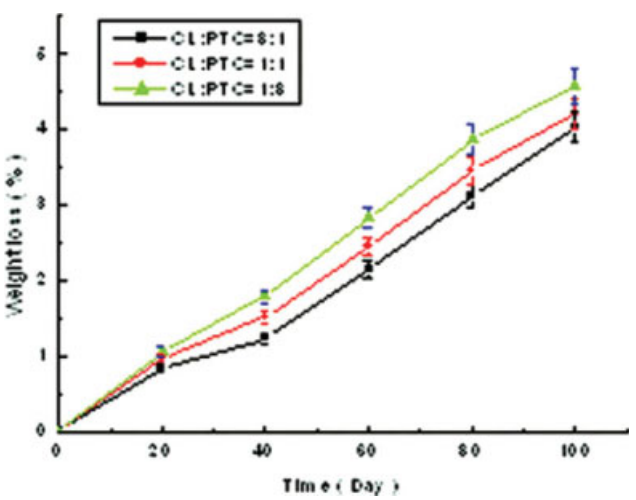

Figure 8 Weight loss (%) of P(CL-*co*-PTC) during degradation in PBS [polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 8, 1 : 1, or 8 : 1 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

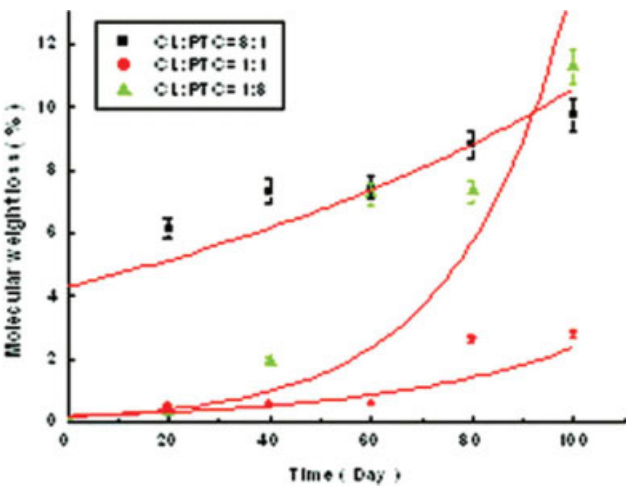

Figure 10 Molecular weight loss (%) of P(CL-*co*-PTC) during degradation in PBS [polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 8, 1 : 1, or 8 : 1 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

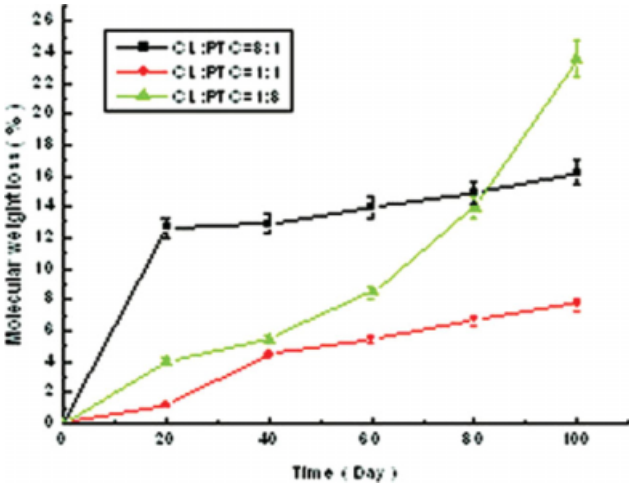

Figure 11 Molecular weight loss (%) of partly deprotected P(CL-*co*-PTC) copolymers during degradation in PBS [polymerization conditions: monomer/catalyst (molar ratio) = 1000; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 8, 1 : 1, or 8 : 1 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

unreduced copolymers with the same CL/PTC monomer feed molar ratio. The cumulative percentage release of reduced P(CL-*co*-PTC) (1 : 8) reached 70.24%, whereas the cumulative percentage release of reduced P(CL-*co*-PTC) (1 : 1) and P(CL-*co*-PTC) (8 : 1) reached 56.87 and 44.26%, after controlled drug release for 25 days. This indicated that the hydrophilic hydroxyl groups enhanced the hydrophilicity and biodegradation rates and promoted water absorption and drug diffusion coefficients.

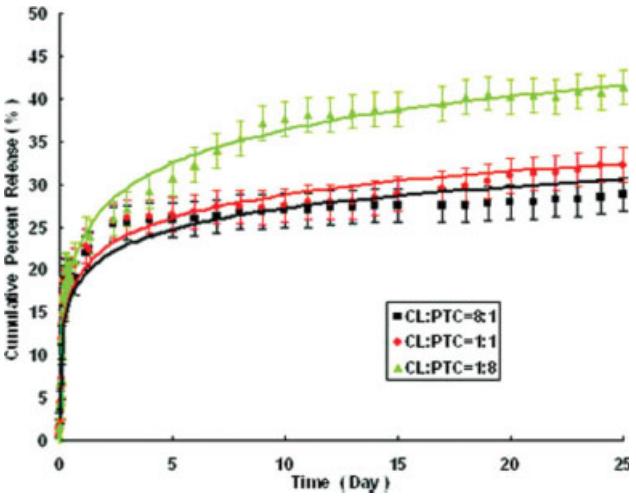

Figure 12 5-Fu release profiles from P(CL-*co*-PTC) copolymers in PBS [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 8, 1 : 1, or 8 : 1 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

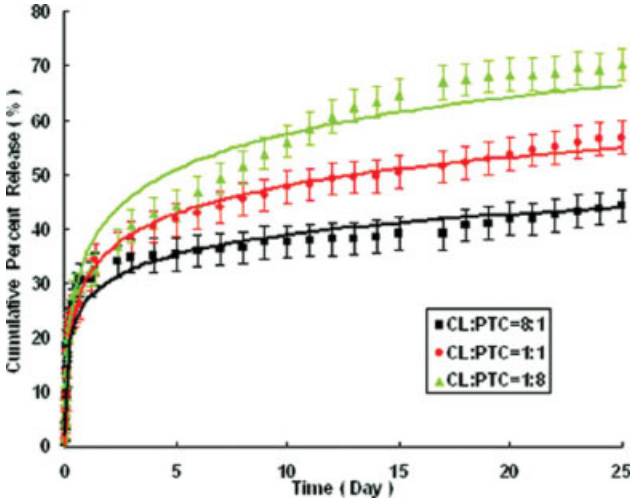

Figure 13 5-Fu release profiles from partly deprotected P(CL-*co*-PTC) copolymers in PBS [polymerization conditions: monomer/catalyst (molar ratio) = 1000; catalyst = $Sn(Oct)_2$; temperature = 180°C; time = 24 h; CL/PTC (monomer feed molar ratio) = 1 : 8, 1 : 1, or 8 : 1 mol/mol]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Thus, the results showed that these two types of copolymers had steady drug-release rates and good controlled-release properties. Moreover, the partly deprotected copolymers had faster drug-release rates than the corresponding unreduced copolymers.

CONCLUSIONS

The copolymers were synthesized by the ring-opening bulk polymerization of CL and PTC with $Sn(Oct)_2$ as the catalyst. These copolymers were further reduced with the Pd/C catalyst to obtain partly deprotected copolymers. The experimental data showed that the copolymerization of monomers CL and PTC was a nonideal copolymerization, and the copolymerization reactivity ratio of monomer CL was higher than that of PTC in the polymerization process. *In vitro* degradation tests indicated that the partly deprotected copolymers possessed faster degradation rates and more hydrophilicity than the copolymers. *In vitro* release profiles of 5-Fu from the copolymers showed that these two types of copolymers had steady drug-release rates and good controlled-release properties. Moreover, the partly deprotected copolymers had faster drug-release rates than the unreduced copolymers.

References

1. Blanco, M. D.; Bernardo, M. V.; Sastre, R. L.; Olmo, R.; Muniz, E.; Teijon, J. M. Eur J Pharm Biopharm 2003, 55, 229.
2. Sinha, V. R.; Bansal, K.; Kaushik, R.; Kumria, R.; Trehan, A. Int J Pharm 2004, 278, 1.
3. Iwasa, N.; Liu, J. Y.; Nomura, K. Catal Commun 2008, 9, 1148.

4. Barbault-Foucher, S.; Grefa, R.; Russo, P.; Guechot, J.; Bochot, A. J Controlled Release 2002, 83, 365.
5. Chawla, J. S.; Amiji, M. M. Int J Pharm 2002, 249, 127.
6. Sun, H.; Mei, L.; Song, C.; Cui, X.; Wang, P. Biomaterials 2006, 27, 1735.
7. Brown, A. H.; Sheares, V. V. Macromolecules 2007, 40, 4848.
8. Fay, F.; Linossier, I.; Langlois, V.; Renard, E.; Vallee-Rehel, K. Biomacromolecules 2006, 7, 851.
9. Hemmrich, K.; Salber, J.; Meersch, M.; Wiesemann, U.; Gries, T.; Pallua, N.; Klee, D. J Mater Sci: Mater Med 2008, 19, 257.
10. Zou, T.; Li, S. L.; Zhang, X. Z.; Wu, X. J.; Cheng, S. X.; Zhuo, R. X. J Polym Sci Part A: Polym Chem 2007, 45, 5256.
11. Barbato, F.; La Rotonda, M. I. Maglio, G.; Palumbo, R.; Quaglia, F. Biomaterials 2001, 22, 1371.
12. Lemmouchi, Y.; Schacht, E.; Lootens, C. J Controlled Release 1998, 55, 79.
13. Matsuo, J.; Aoki, K.; Sanda, F.; Endo, T. Macromolecules 1998, 31, 4432.
14. Liu, Z. L.; Zhang, J. M.; Zhuo, R. X. Chem J Chin Univ 2003, 24, 1730.
15. Jagur-Grodzinski, J. React Funct Polym 1999, 39, 99.
16. Rokicki, G. Prog Polym Sci 2000, 25, 259.
17. Hu, B.; Zhuo, R. X.; Fan, C. L. Polym Adv Technol 1998, 9, 145.
18. Khan, I.; Smith, N.; Jones, E.; Finch, D. S.; Cameron, R. E. Biomaterials 2005, 26, 621.
19. Liu, J.; Zeng, F.; Allen, C. J Controlled Release 2005, 103, 481.
20. Yu, X. H.; Zhuo, R. X.; Feng, J.; Liao, J. Eur Polym J 2004, 40, 2445.
21. Peracchia, M. T.; Gref, R.; Minamitake, Y.; Domb, A.; Lotan, N.; Langer, R. J Controlled Release 1997, 46, 223.
22. Yu, X. H.; Zhuo, R. X.; Feng, J. Macromolecules 2005, 38, 6244.
23. Hu, B.; Yan, G. P.; Zhuo, R. X.; Wu, Y.; Fan, C. L. J Appl Polym Sci 2008, 107, 3343.
24. Mei, L. L.; Yan, G. P.; Yu, X. H.; Cheng, S. X.; Wu, J. Y. J Appl Polym Sci 2008, 108, 93.
25. Xie, Z. G.; Hu, X. L.; Chen, X. S.; Sun, J.; Shi, Q.; Jing, X. B. Biomacromolecules 2008, 9, 376.
26. Krogman, N. R.; Steely, L.; Hindenlang, M. D.; Nair, L. S.; Laurencin, C. T.; Allcock, H. R. Macromolecules 2008, 41, 1126.
27. Allcock, H. R.; Lampe, F. W.; Mark, J. E. Contemporary Polymer Chemistry, 3rd ed.; Science Press/Pearson Education North Asia: Hongkong, China, 2003; p 360.