Synthesis and Properties of Polycarbonate Copolymers of Trimethylene Carbonate and 2-Phenyl-5,5-Bis(hydroxymethyl) Trimethylene Carbonate

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ABSTRACT: The polycarbonate copolymers poly[trimethylene carbonate-*co*-2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate] [P(TMC-*co*-PTC)] were synthesized by the ring-opening polymerization of trimethylene carbonate (TMC) and 2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate (PTC) with tin(II) 2-ethylhexanoate and aluminum isopropoxide as the catalysts. These copolymers were further reduced by a palladium/carbonate (Pd/C; 10%) catalyst to produce partly deprotected copolymers. These two types of copolymers were characterized by ^{1}H-NMR, Fourier transform infrared spectroscopy, UV spectroscopy, gel permeation chromatography, differential scanning calorimetry, and an automatic contact angle meter. The influences of the feed molar ratio of the monomers, the catalyst concentration, the reaction time, and the reaction temperature on the copolymerization process were also studied. The copolymerization of the TMC and PTC monomers was a nonideal copolymerization, and the copolymerization reactivity ratio of TMC was higher than that of PTC. *In vitro* degradation tests indicated that the partly deprotected copolymers possessed faster degradation rates and more hydrophilicity than the corresponding unreduced copolymers. Moreover, the degradation of these two type copolymers increased when the pH value of the buffer solutions decreased. *In vitro* drug-release experiments 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. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 3704–3713, 2012

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

INTRODUCTION

In recent years, biodegradable aliphatic polycarbonates, such as poly(trimethylene carbonate) (PTMC) and poly(5,5-dimethyl trimethylene carbonate) (PDTC), have attracted great interest for their use as biodegradable materials in drug delivery and tissue engineering because of their good medicine permeability, low immunogeneity, low toxicity, good elasticity, good biocompatibility, and degradability of surface erosion.[1–7] Several aliphatic polycarbonates and their copolymers, such as PTMC, PDTC, and poly(L-lactic acid-*co*-trimethylene carbonate), have been investigated extensively for use in drug delivery, soft tissue implants, and tissue regeneration.[8–22]

However, polycarbonates such as PTMC and PDTC have exhibited slow degradation rates because of poor hydrophilicity. For instance, the average weight losses of hydrophobic PTMC were less than 3.40% when PTMC films were incubated in phosphate buffered saline (PBS) solution (0.1 mol/L, pH 7.40, 37°C) for 100 days. Meanwhile, the weight loss of PDTC was only 5.00% after 100 days of degradation in PBS.[23–25] Various modification strategies have been used to enhance the hydrophilicity and reduce the glass-transition temperature (T_g) and crystallinity of aliphatic polycarbonates to improve their biodegradation rates. The average weight losses

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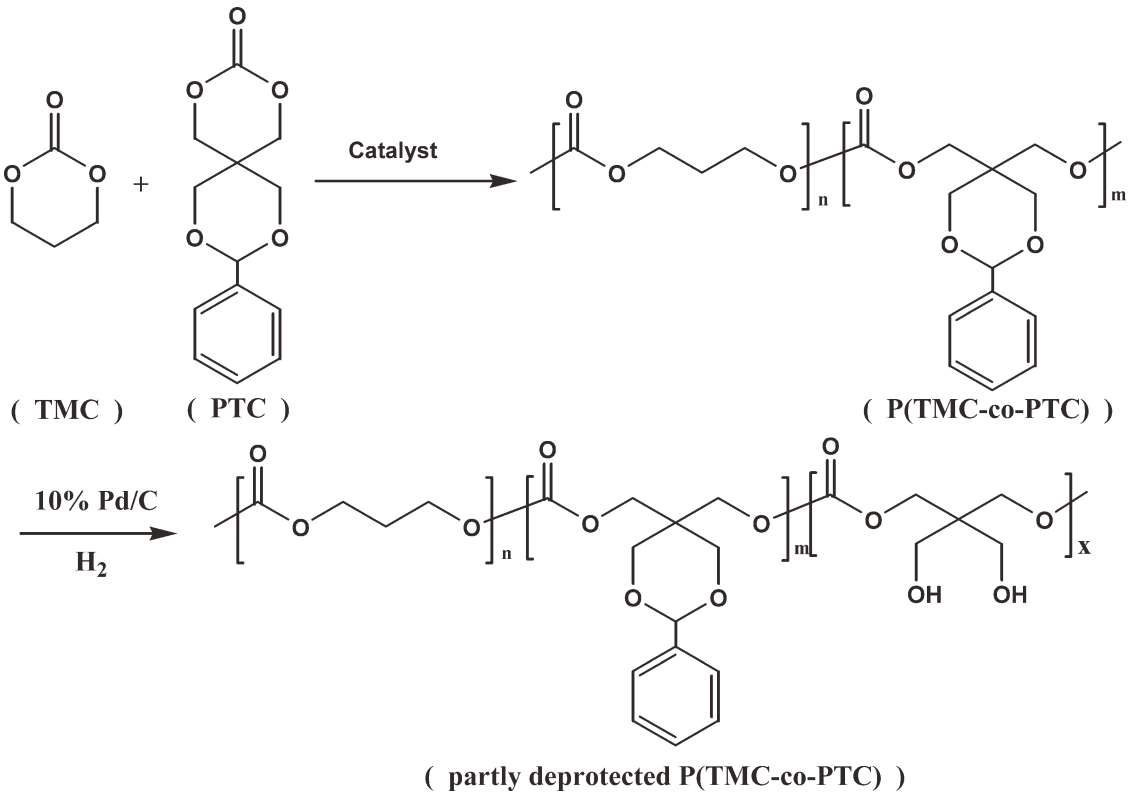

Scheme 1 Synthetic route of copolycarbonates containing hydroxyl groups.

of poly(ethyl glycol)-*b*-poly(5,5-dimethyl trimethylene carbonate) and poly(ethyl glycol)-*b*-poly(trimethylene carbonate) copolymers incubated in the same condition for 6 weeks were 28.90 and 31.40%, respectively; this indicates that the copolymers possessed higher degradation rates than PDTC and PTMC homopolymers, presumably because the hydrophilic poly(ethyl glycol) segments promoted water permeation into the copolymer matrix.[26–28]

Therefore, an increasing number of efforts have focused on the design and preparation of novel polycarbonate copolymers with functional groups. The incorporation of functional pendent groups, such as hydroxyl, carboxyl, and amino groups, into the copolymer backbone would highly affect the properties, such as the hydrophilicity, biocompatibility, biodegradation rates, and drug-release rates, of polycarbonates.[29–32]

2-Phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate (PTC; 9-phenyl-2,4,8,10-tetraoxaspiro-[5,5] undcane-3-one) is a novel, six-membered cyclic carbonate monomer containing potential hydroxyl functional groups after deprotection. In this study, poly [trimethylene carbonate-*co*-2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate] [P(TMC-*co*-PTC)] was synthesized by copolymerization of the six-membered cyclic carbonate monomers trimethylene carbonate (TMC) and PTC. Subsequently, these copolymers were further reduced by a palladium/carbon (Pd/C) catalyst to obtain the partly deprotected P(TMC-*co*-PTC) (Scheme 1). Our aim was not only to increase the hydrophilicity and accelerate the degradation rates of the homopolycarbonates but also to induce chemical modification through hydroxyl groups. The *in vitro* properties were evaluated to prove these two type copolymers as potential polymeric carriers for drug-delivery systems.

EXPERIMENTAL

Instruments and reagents

All chemicals and solvents were analytical grade. Tin(II) 2-ethylhexanoate [$Sn(Oct)_2$], aluminum isopropoxide [$Al(O^iPr)_3$], and ethyl chloroformate were purchased from Sigma-Aldrich (St. Louis, MO) and were purified by redistillation *in vacuo* before use. Toluene and tetrahydrofuran were purified by redistillation over sodium. Triethylamine (Et_3N) was refluxed under phthalic anhydride and dried over calcium hydride (CaH_2) before use. TMC and PTC were prepared, and their structures were confirmed by melting point determination, Fourier transform infrared (FTIR) spectroscopy, ^{1}H-NMR, and UV spectroscopy according to the literature.[29–32]

The copolymers were characterized with a Nicolet IS10 FTIR spectrophotometer (Thermo Fisher Scientific, Inc., Madison, WI), an ultraviolet–visible

spectrophotometer (UV-2800 series, Unico, Shanghai, China), a Varian Mercury-VX300 NMR spectrometer (Varian, Inc., Corp., Palo Alto, CA), and an automatic contact angle meter (SL200A/B/D Series, Solon Technology, Inc., Ltd., Shanghai, China). The number-average molecular weight (M_n) determination was undertaken with gel permeation chromatography (GPC; Waters Corp., Milford, MA; Waters 2965D separations module, Waters 2414 refractive index detector, Shodex K802.5 and K805 and Shodex K-G guard columns). The combined column HR3 molecular weight ranged from 500 to 3 $\times 10^4$. The HR4 molecular weight ranged from 5000 to 5 $\times$ 10^5. The HT5 molecular weight ranged from 5 $\times 10^4$ to 4 $\times$ 10^6. Polystyrene standards were used: M_n = 6520, weight-average molecular weight (M_w)/M_n = 1.04; M_n = 4.42 $\times$ 10^4, M_w/M_n = 1.02; M_n = 1.78 $\times$ 10^4, M_w/M_n = 1.03; M_n = 1.2 $\times$ 10^5, M_w/M_n = 1.05; M_n = 4.19 $\times$ 10^5, M_w/M_n = 1.03; M_n = 7.78 $\times$ 10^5, M_w/M_n = 1.04; M_n = 1.27 $\times$ 10^6, M_w/M_n = 1.02; and M_n = 3.44 $\times$ 10^6, M_w/M_n = 1.18 (Polymer Standards Service—USA, Inc., Warwick, RI). Also used were *N,N*-dimethylformamide solvent, a 1.0 mL/min flow rate, a 323-K column temperature, and a 323-K detector temperature. T_g of the copolymer was determined with differential scanning calorimetry (Netzsch DSC 200 F3, Erich Netzsch GmbH & Co. Holding KG, Gebrüder-Netzsch-Strasse, Selb, Germany) with a 10 K/min heating rate.

Synthesis of the copolymers

TMC (0.51 g, 5.0 mmol) and PTC (1.24 g, 5.0 mmol, 1 equiv) were added to a polymerization tube and then dried by several cycles of argon purging followed by exposure to high vacuum. A solution of $Sn(Oct)_2$ or $Al(O^iPr)_3$ in dry toluene (0.1 mol/L, 100 μL, 1/1000 equiv) was added to the dried mixture via a syringe. After further drying under high vacuum, the tube was sealed and immersed in a thermostatically controlled oil bath at 180°C for 24 h. The resultant solid was dissolved in dichloromethane (5 mL) and then reprecipitated with a mixture of ethanol (50 mL) and *n*-hexane (50 mL). The precipitated solid was filtered, washed with ethanol and diethyl ether (v/v 1 : 1), and dried *in vacuo* for 48 h to yield a white powder of P(TMC-*co*-PTC) (0.73 g, 82%).

^{1}H-NMR ($CDCl_3$, δ, ppm): 7.45–7.25 (m, $C_6\mathbf{H_5}$—), 5.44 [s, C_6H_5—$\mathbf{CH}$—$(O)_2$—], 4.55 [s, —COO—$\mathbf{CH_2}$C$(CH_2O$—$)_2$–CH_2O—], 4.23 [s, —COO—CH_2C($\mathbf{CH_2}$O—$)_2$—CH_2O—], 4.12 (t, —COO—$\mathbf{CH_2}$—CH_2—CH_2—), 4.01 [s, —COO—CH_2C$(CH_2O$—$)_2$—$\mathbf{CH_2}$O—], 3.89 (t, —COO—$\mathbf{CH_2}$—CH_2—CH_2—), 2.04 (m, —CH_2—$\mathbf{CH_2}$—CH_2—). IR (KBr, ν_{max}, cm^{-1}): 3047, 2970, 2865 (—CH_2); 1752 (C=O); 1458 (C—C); 1102 (C—O). UV ($CHCl_3$, λ, nm): 237, 261.

The molecular weight (M_n) was measured by GPC, and the average copolymer compositions of the TMC and PTC repeat units (molar percentage) were determined from ^{1}H-NMR.

The P(TMC-*co*-PTC) copolymers with different average copolymer compositions of TMC and PTC repeat units (molar percentage) were synthesized by the same method described previously under different reaction conditions. Their molecular weights (M_n's) were also measured by GPC, and the average copolymer compositions of the TMC and PTC repeat units (molar percentage) were also determined from ^{1}H-NMR.

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

Pd/C (0.10 g, 10%) catalyst and 30 mL of anhydrous methanol were both added to a solution of P(TMC-*co*-PTC) (0.68 g, 14.0 mmol) dissolved in *N,N*-dimethylformamide (10 mL) and methanol (2 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 a mixture of ethanol (50 mL) and *n*-hexane (50 mL). The precipitated solid was filtered, washed with *n*-hexane, and dried *in vacuo* for 48 h to afford a light yellow powder of partly deprotected P(TMC-*co*-PTC) (0.55 g, 83%).

^{1}H-NMR ($CDCl_3$, δ, ppm): 7.26–7.46 (m, $C_6\mathbf{H_5}$—), 5.44 [s, C_6H_5—$\mathbf{CH}$—$(O)_2$—], 4.60 [s, $\mathbf{HO}CH_2C(CH_2O)_2$—$CH_2\mathbf{OH}$], 4.55 [s, —COO—$\mathbf{CH_2}C(CH_2O$—$)_2$—$CH_2O$—], 4.23 [s, —COO—$CH_2$C($\mathbf{CH_2}$O—$)_2$—$CH_2O$—], 4.12 (t, —COO—$\mathbf{CH_2}$—$CH_2$—$CH_2$—), 4.01 [s,—COO—$CH_2C(CH_2O$—$)_2$—$\mathbf{CH_2}$O—], 3.89 (t, —COO—$\mathbf{CH_2}$—$CH_2$—$CH_2$—), 3.72–3.81 (—$\mathbf{CH_2}$OH), 2.04 (m, —$CH_2$—$\mathbf{CH_2}$—$CH_2$—). IR (KBr, ν_{max}, cm^{-1}): 3450 (—OH); 2970, 2865 (—CH_2); 1750 (C=O); 1458 (C—C); 1102 (C—O). UV ($CHCl_3$, λ, nm): 237, 261. ^{1}H-NMR ($CDCl_3$ + D_2O, δ, ppm): 7.25–7.45 (m, $C_6\mathbf{H_5}$—), 5.44 [s, C_6H_5—$\boldsymbol{CH}$—$(O)_2$—], 4.54 [s, —COO—$\mathbf{CH_2}$C$(CH_2O$—$)_2$—CH_2O—], 4.22 [s, —COO—$\mathbf{CH_2}$C$(CH_2O$—$)_2$—CH_2O—], 4.12 (t, —COO—$\mathbf{CH_2}$—CH_2—CH_2—), 4.01 [s, —COO—CH_2C$(CH_2O$—$)_2$—$\mathbf{CH_2}$O—], 3.89 (t, —COO—$\mathbf{CH_2}$—CH_2—CH_2—), 3.72–3.81 (—$\mathbf{CH_2}$OH), 2.04 (m, —CH_2—$\mathbf{CH_2}$—CH_2—).

The molecular weight (M_n) was measured by GPC, and the average copolymer compositions of TMC, PTC, and deprotected PTC repeat units (molar percentage) were determined from ^{1}H-NMR.

In vitro degradability testing

The copolymers (0.1 g) were pressed in a columned tablet with 0.6 mm thickness and 1.2 cm diameter and then dried *in vacuo* for 24 h. The tablets were

TABLE I
Effect of the Catalyst on the Molecular Weight of the Copolymer

TMC/PTC monomer feed molar ratio (mol/mol)	TMC/PTC repeat unit ratio in the copolymer (mol/mol)[a]	M_n (10^4)[b]	M_w/M_n[b]	M_n (10^4)[c]	M_w/M_n[c]
0 : 1	0 : 1	2.04	1.14	1.28	1.33
0.125 : 1	0.253 : 1	2.21	1.11	1.57	1.09
0.25 : 1	0.520 : 1	2.30	1.12	1.68	1.09
0.5 : 1	0.678 : 1	2.86	1.15	1.72	1.11
1 : 1	1.326 : 1	2.99	1.20	1.83	1.11
2 : 1	2.356 : 1	3.00	1.14	2.04	1.10
4 : 1	4.917 : 1	3.23	1.18	2.24	1.18
8 : 1	9.989 : 1	3.33	1.13	2.66	1.20
1 : 0	1 : 0	3.35	1.12	2.82	1.17

Polymerization conditions: TMC/PTC monomer feed molar ratio = 1 : 1, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalysts: $Sn(Oct)_2$ and $Al(O^iPr)_3$.
[a] The average copolymer compositions of the TMC and PTC repeat units (mol %) were determined from ^{1}H-NMR.
[b] M_w and molecular weight distribution with $Al(O^iPr)_3$ as the catalyst.
[c] M_w and molecular weight distribution with $Sn(Oct)_2$ as the catalyst.

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 from the degradation medium, rinsed with distilled water, and then dried *in vacuo* for 48 h; we calculated the weight loss and molecular weight loss.

In vitro drug-release study

Fluorouracil (5-Fu; 10 mg) and P(TMC-*co*-PTC) or partly deprotected copolymers (100 mg) were dissolved in 20 mL of tetrahydrofuran. 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 produce 5-Fu-incorporated polymeric columned tablets with 0.6 mm thickness and 1.2 cm diameter.

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 times intervals and tested at 256 nm by a high performance liquid chromatography (HPLC). The change of the concentrations of 5-Fu was obtained from curves of the absorption (A) versus the concentration (C) of 5-Fu in PBS on the basis of Lambert–Beer law.

Statistical analysis

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

RESULTS AND DISCUSSION

Synthesis of the copolymers

The P(TMC-*co*-PTC) copolymers were synthesized by the ring-opening copolymerization of PTC and TMC with $Sn(Oct)_2$ and $Al(O^iPr)_3$ as the catalysts. The FTIR spectra of copolymers showed a characteristic peak in 1752 cm^{-1}, which represented the absorption peak of C=O groups. In the ^{1}H-NMR spectra of the copolymers, the typical signals for TMC and PTC repeat units in the backbone of the copolymer structures were observed at 7.25–7.45 ppm (PTC repeat units: —C_6H_5) and 2.04 ppm (TMC repeat units: —$OOCCH_2CH_2CH_2O$—), respectively. Thus, the average copolymer compositions of the PTC and TMC repeat units (molar percentage) could be calculated according to the integration values of the 7.25–7.45-ppm peaks (—C_6H_5) and 2.04-ppm peak (—$OOCCH_2CH_2CH_2O$—). 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 feed molar ratio of the TMC/PTC monomers on the polymerization with $Sn(Oct)_2$ and $Al(O^iPr)_3$ as the catalysts are shown in Table I. The polymerization conditions were as follows: the feed molar ratio of monomer to catalyst ([M]/[C]) was 1000/1, the reaction temperature was 180°C, and the reaction time was 24 h. The molecular weight of P(TMC-*co*-PTC) increased appreciably, whereas the TMC/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1. The repeat unit molar ratio of TMC/PTC in the backbone of the copolymers also increased, whereas the TMC/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1.

TABLE II
Ring-Opening Copolymerization of P(TMC-*co*-PTC) with Al(O^{i}Pr)$_3$ as a Catalyst

TMC/PTC monomer feed molar ratio (mol/mol)	[M]/[C] (mol/mol)	Time (h)	Temperature (°C)	M_n (10^4)	M_w/M_n
0.5 : 1	250	24	180	1.37	1.21
0.5 : 1	500	24	180	1.61	1.24
0.5 : 1	1000	24	180	2.86	1.15
0.5 : 1	2000	24	180	2.16	1.19
0.5 : 1	1000	6	180	1.88	1.23
0.5 : 1	1000	12	180	2.03	1.20
0.5 : 1	1000	36	180	1.97	1.18
0.5 : 1	1000	48	180	1.31	1.32
0.5 : 1	1000	24	170	1.85	1.25
0.5 : 1	1000	24	190	1.11	1.19
0.5 : 1	1000	24	200	0.98	1.31

Polymerization conditions: TMC/PTC monomer feed molar ratio = 0.5 : 1, time = 24 h, [M]/[C] = 1000, catalyst: Al(O^{i}Pr)$_3$.

Moreover, the repeat unit molar ratio of TMC/PTC in the backbone was always larger than the corresponding TMC/PTC monomer feed molar ratio in the polymerization process. Thus, the results indicate that the TMC monomer had a higher reactivity than the PTC monomer.

According to the copolymerization mechanism and the equation of the copolymerization reactivity ratio [eqs. (1)–(5)],[29,30,33] the monomer copolymerization reactivity ratios and the copolymerization characteristic of TMC and PTC could be calculated. In the copolymerization process, the copolymer composition of the repeat unit molar ratio of TMC/PTC in the backbone at the time t could be described by Eq. (1):

$$\frac{-d[\mathrm{M}_1]/dt}{-d[\mathrm{M}_2]/dt} = \frac{d[\mathrm{M}_1]}{d[\mathrm{M}_2]} \tag{1}$$

$$F_1 = \frac{d[\mathrm{M}_1]}{d[\mathrm{M}_1] + d[\mathrm{M}_2]} = 1 - F_2 \tag{2}$$

$$\frac{d[\mathrm{M}_1]}{d[\mathrm{M}_2]} = \frac{[\mathrm{M}_1]}{[\mathrm{M}_2]} \times \frac{r_1[\mathrm{M}_1] + [\mathrm{M}_2]}{r_2[\mathrm{M}_2] + [\mathrm{M}_1]} \tag{3}$$

$$f_1 = \frac{[\mathrm{M}_1]}{[\mathrm{M}_2] + [\mathrm{M}_1]} = 1 - f_2 \tag{4}$$

$$F_1 = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2 f_1 f_2 + r_2 f_2^2} \tag{5}$$

where $[\mathrm{M}_1]$ and $[\mathrm{M}_2]$ are the monomer concentrations of TMC and PTC, respectively, at time t in the polymerization process; $d[\mathrm{M}_1]$ and $d[\mathrm{M}_2]$ are the copolymer molar compositions of the repeat units TMC and PTC, respectively, in the backbone at time t; F_1 and F_2 are the repeat unit TMC and PTC molar composition ratios, respectively, in the copolymer at time t; f_1 and f_2 are the monomer concentration ratios of TMC and PTC, respectively, in the total monomer concentration at time t in the polymerization process; and r_1 and r_2 are the copolymerization reactivity ratios of the monomers TMC and PTC, respectively, in the polymerization process.

The average copolymer compositions of the TMC and PTC repeat units (molar percentage) could be determined from ^{1}H-NMR of the copolymers prepared by the copolymerization of the monomers TMC and PTC with Sn(Oct)$_2$ as a catalyst. The polymerization conditions were as follows: [M]/[C] was 1000/1, the reaction temperature was 180°C, and the reaction time was 24 h. So the relationship curve of F_1 versus f_1 could be worked out as Figure 1. r_1 and r_2 were calculated by eqs. (1)–(5) as follows:

$$r_1 = 1.24 > 1, r_2 = 0.57 < 1, r_1 r_2 = 0.71 < 1$$

This result demonstrates that the copolymerization of the monomers TMC and PTC was a nonideal copolymerization and that r_1 was higher than r_2.

The effects of [M]/[C], reaction temperature, and reaction time are shown in Table II. The polymerization conditions were as follows: the TMC/PTC monomer feed molar ratio was 0.5 : 1 on the polymerization with Al(O^{i}Pr)$_3$ as a catalyst. The molecular weights of the copolymers increased and subsequently decreased with increasing catalyst dosage. The highest molecular weight (M_n) of the copolymer was 2.86×10^4 when [M]/[C] was 1000, the reaction temperature was 180°C, and reaction time was 24 h. This result indicates that the overhigh dosage of the catalyst resulted in the reduction of the molecular weight of the copolymer.

The molecular weights of copolymers changed when the reaction time varied from 6 to 48 h under the polymerization conditions [M]/[C] = 1000 and reaction temperature = 180°C. The molecular weights of the copolymers reached the maximum value ($M_n = 2.86 \times 10^4$) when the reaction time was

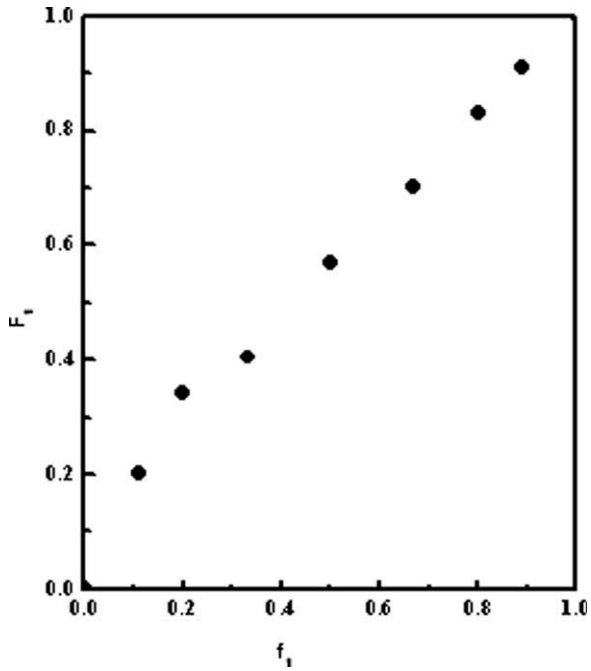

Figure 1 Plot of F_1 versus f_1 for P(TMC-*co*-PTC) copolymers of variable composition [polymerization conditions: temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$].

24 h and then came down rapidly during the more time. The reaction temperature of the copolymerization was chosen above 170°C because the melting point of PTC is 169.5–170.0°C. However, the higher reaction temperature could induce a decrease in the molecular weights of the copolymers. Probably, the long reaction time and high reaction temperature caused the degradation and interchange esterification reaction in the copolymers. The contact angles of the P(TMC-*co*-PTC) copolymers decreased when the TMC/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1. We considered that the hydrophilicities of P(TMC-*co*-PTC) were improved when the TMC/PTC monomer feed molar ratio increased from 1 : 8 to 8 : 1 (Table III).

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

The ^{1}H-NMR and IR spectra showed that the benzene ring and hydroxyl groups all existed in the structures of partly deprotected copolymers, which indicated that parts of the benzene ring groups in the PTC repeat unit of the copolymer 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. In the ^{1}H-NMR spectra of the copolymers, the typical signals for benzene rings (—C_6H_5) were observed at 7.25–7.45 ppm, and the integration values of the peaks decreased. Thus, the average copolymer compositions of TMC, PTC, and partly deprotected PTC repeat units (molar percentage) could be calculated according to the integration values of the 7.25–7.45-ppm peaks (—C_6H_5) and the 2.04-ppm peaks (—$OOCCH_2CH_2CH_2O$—).

Compared to unreduced P(TMC-*co*-PTC), the water contact angles of the partly deprotected copolymers decreased because the hydrophilicity of the copolymers increased when part of benzene ring groups of the repeat unit PTC segments in the copolymers were replaced by hydroxyl groups. Meanwhile, the T_g values of the partly deprotected copolymers fell, probably because of the steric effect elimination and molecular flexibility improvement when the part rigid benzene rings were reduced to hydroxyl groups after deprotection (Table IV).

In vitro degradability test

The *in vitro* degradation of the copolymers and partly deprotected copolymers were measured in the different buffer solutions (0.1 mol/L PBS solution at pH 7.40; 0.1 mol/L carbonate buffer solution at pH 4.00, and 0.1 mol/L acetate buffer solution at pH 10.83 and 37°C). Their degradation rates were denoted by the weight loss (Figs. 2 and 4) and molecular weight loss (Figs. 3 and 5) for 160 days in different buffer solutions at 37°C. The weight loss and molecular weight loss of the unreduced copolymers all decreased when the TMC/PTC monomer feed molar ratio increased from 1 : 4 to 4 : 1. During the degradation process in PBS, the partly deprotected copolymers with different TMC/PTC monomer feed molar ratios on the copolymerization possessed almost the same weight loss and different molecular weight losses as those of the accordingly unreduced copolymers. Moreover, the weight loss and molecular weight loss of the partly deprotected copolymers were all higher than those of the corresponding unreduced copolymers after 160 days of degradation in PBS. For example, the weight loss of

TABLE III
Effect of the Monomer Feed Ratio on the Contact Angle Degree of the Unreduced Copolymers

TMC/PTC monomer feed molar ratio (mol/mol)	Contact angle (°)	Surface free energy (J/m^2)	Adhesion work
0.125 : 1	87.21	30.97	76.35
0.25 : 1	85.66	31.94	78.31
0.5 : 1	80.85	34.95	84.38
1 : 1	72.26	40.31	94.98
2 : 1	71.45	40.82	95.96
4 : 1	65.37	44.57	103.13
8 : 1	64.35	45.20	104.32

Polymerization conditions: temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$.

TABLE IV
Experimental Data Comparison of the Unreduced/Deprotected P(TMC-*co*-PTC) with Different TMC/PTC Monomer Feed Molar Ratios

TMC/PTC monomer feed molar ratio (mol/mol)	TMC/PTC repeat unit ratio in the copolymer (mol/mol)	M_n (10^4)	M_w/M_n	Reduction rate of the repeat unit PTC in the copolymer (mol %)	Contact angle (°)	T_g (°C)
0.25 : 1	4.92 : 1/7.42 : 1	2.235/2.179	1.18/1.15	46.1	85.66/78.65	10.2/−3.0
0.5 : 1	2.36 : 1/4.17 : 1	2.040/1.865	1.14/1.12	45.53	71.45/65.03	33.7/15.7
1 : 1	1.33 : 1/2.11 : 1	1.827/1.654	1.11/1.12	37.03	72.76/64.48	54.0/39.1
2 : 1	0.68 : 1/1.22 : 1	1.716/1.552	1.11/1.08	44.26	80.85/75.02	62.4/42.2
4 : 1	0.52 : 1/0.78 : 1	1.687/1.415	1.09/1.38	33.4	65.37/61.13	67.4/31.5

Polymerization conditions: temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$.

the unreduced P(TMC-*co*-PTC) copolymers (1 : 4, 1 : 1, and 4 : 1 TMC/PTC) were 12.16, 10.21, and 10.07%, respectively, and their molecular weight losses were 12.57, 8.10, and 4.15%, respectively, after 160 days of degradation. Meanwhile, the weight losses of the partly deprotected P(TMC-*co*-PTC) copolymers (1 : 4, 1 : 1, and 4 : 1 TMC/PTC) were 14.70, 12.28, and 10.64%, respectively, and their molecular weight losses were 13.68, 11.17, and 9.73%, respectively, after 160 days of degradation under the same conditions. Therefore, the degradation rates of the partly deprotected copolymers became faster than the corresponding unreduced copolymers, presumably because the hydrophilic hydroxyl groups enhanced the hydrophilicity and promoted water absorption and permeation into the copolymer matrix and improved their biodegradation rates.

The *in vitro* degradation of the same P(TMC-*co*-PTC) copolymer with a TMC/PTC monomer feed molar ratio (mol/mol) of 1 : 1 were also measured in different buffer solutions (0.1 mol/L PBS at pH 7.40, 0.1 mol/L acetate buffer solution at pH 4.00, and 0.1 mol/L carbonate buffer solution at pH 10.83 and 37°C; Figs. 6 and 7). The weight loss and molecular weight loss of the unreduced P(TMC-*co*-PTC) copolymer with a TMC/PTC monomer feed molar ratio of 1 : 1 mol/mol were both increased when the pH value of the buffer solutions decreased. The weight losses of the unreduced P(TMC-*co*-PTC) copolymers with a TMC/PTC monomer feed molar ratio of 1 : 1 mol/mol were 7.49, 10.21, and 12.46%, respectively, and their molecular weight losses were 7.58, 8.10, and 10.3%, respectively, after 160 days of degradation in different buffer solutions of carbonate buffer solution: 0.1 mol/L, pH 10.83, PBS: 0.1 mol/L, pH 7.40; and 0.1 mol/L acetate buffer solution at pH 4.00, respectively, after 160 days of degradation. Therefore, the degradation rates of the copolymers in 0.1 mol/L PBS at pH 7.40 was faster than that in 0.1 mol/L carbonate buffer solution at pH 10.83 and

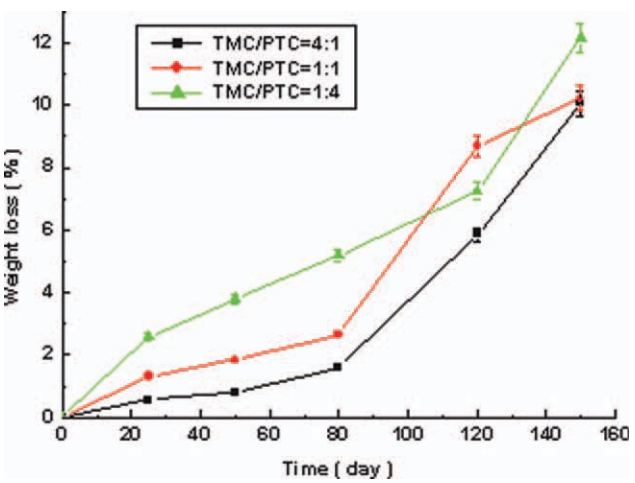

Figure 2 Weight loss (%) of P(TMC-*co*-PTC) in PBS {0.1 mol/L, pH 7.40, 37°C; polymerization conditions: temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

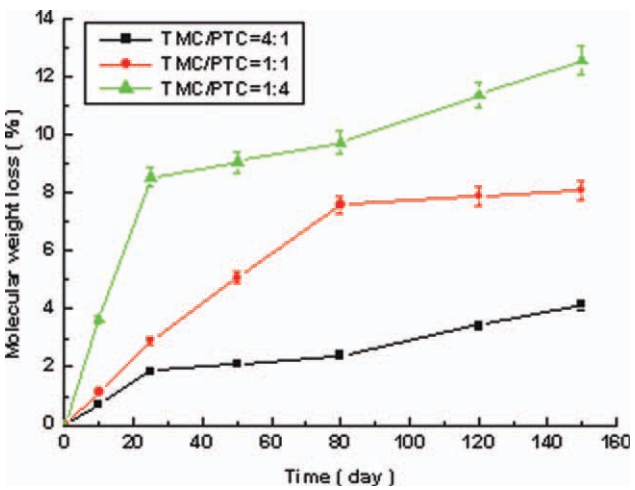

Figure 3 Molecular weight loss (%) of P(TMC-*co*-PTC) in PBS {0.1 mol/L, pH 7.40, 37°C; polymerization conditions: TMC/PTC monomer feed molar ratios = 4 : 1, 1 : 1, and 4 : 1, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

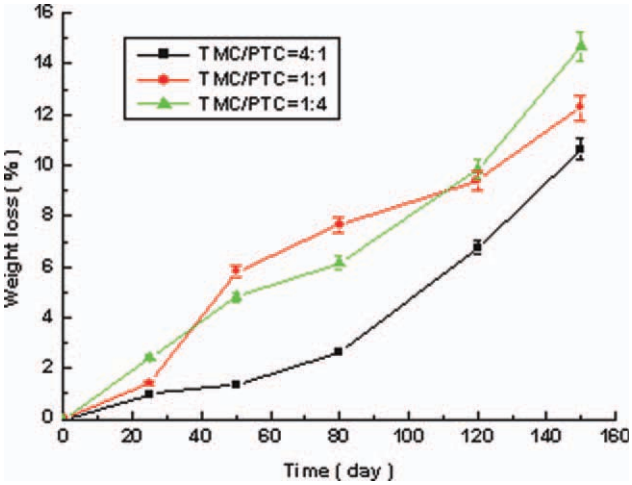

Figure 4 Weight loss (%) of partly deprotected P(TMC-*co*-PTC) in PBS {0.1 mol/L, pH 7.40, 37°C; polymerization conditions: TMC/PTC monomer feed molar ratios = 4 : 1, 1 : 1, and 1 : 4, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

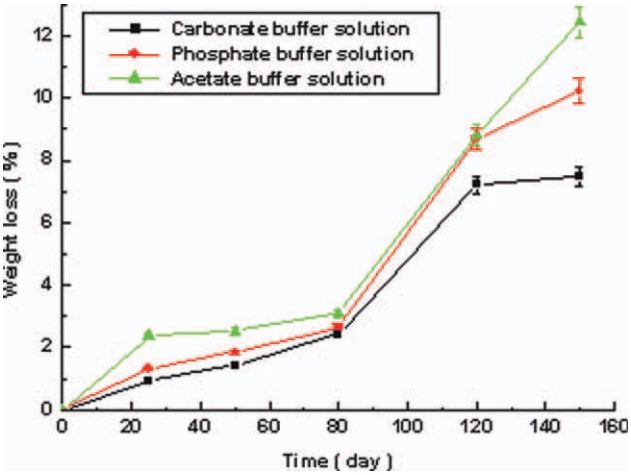

Figure 6 Weight loss (%) of P(TMC-*co*-PTC) in different buffer solutions (0.1 mol/L PBS at pH 7.40, 0.1 mol/L carbonate buffer solution at pH 4.00, and 0.1 mol/L acetate buffer solution at pH 10.83) at 37°C {polymerization conditions: TMC/PTC monomer feed molar ratio = 1 : 1, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

slower than that in acetate buffer solution (0.1 mol/L, pH 4.00). Thus, the results indicate that the acidic solution accelerated the degradation rates of the polycarbonate copolymers.

In vitro drug-release properties of the copolymers

The 5-Fu release profiles of the unreduced polycarbonate copolymers and partly deprotected copolymers are shown in Figures 8 and 9. The substantial release rates of the 5-Fu-incorporated polycarbonate tablets maintained for more than 30 days of measurement. The 5-Fu-incorporated polycarbonate tablets had no obvious phenomenon of abrupt release, and the initial drug release was fast but abated slowly over the period of time of the measurements. The release rate increased when the TMC/PTC monomer feed molar ratio decreased; this was presumably due to the higher degradation rates of P(TMC-*co*-PTC).

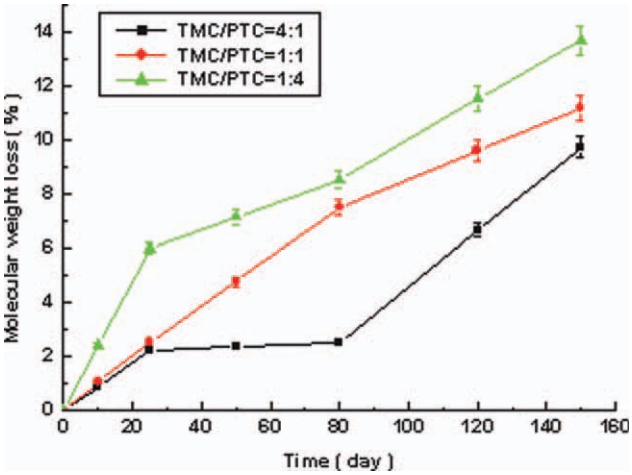

Figure 5 Molecular weight loss (%) of partly deprotected P(TMC-*co*-PTC) in PBS {0.1 mol/L, pH 7.40, 37°C; polymerization conditions: TMC/PTC monomer feed molar ratios = 4 : 1, 1 : 1, and 1 : 4, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

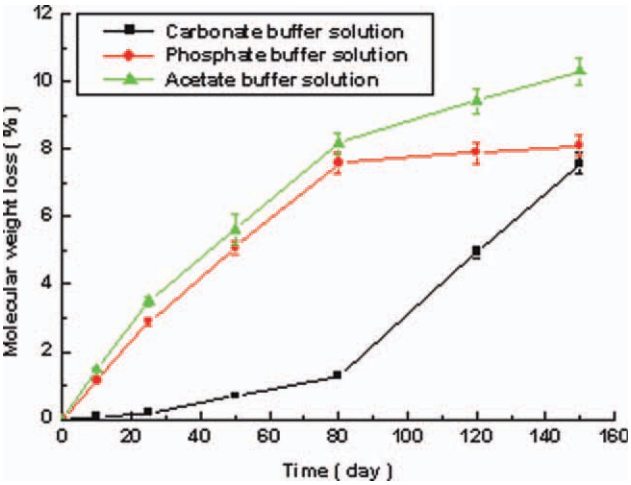

Figure 7 Molecular weight loss (%) of P(TMC-*co*-PTC) during the degradation process in PBS (pH 7.40, 0.1 mol/L), carbonate solution (pH 4.00, 0.1 mol/L), and acetate buffer solution (pH 10.83, 0.1 mol/L) at 37°C {polymerization conditions: TMC/PTC monomer feed molar ratio = 1 : 1, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The release rates of the partly deprotected copolymers were higher than those of the corresponding unreduced copolymers with the same TMC/PTC monomer feed molar ratios. The accumulative percentage release of the unreduced P(TMC-*co*-PTC) with a TMC/PTC monomer feed molar ratio of 1 : 4 mol/mol reached 27.96%, whereas those of the unreduced P(TMC-*co*-PTC) with a TMC/PTC monomer feed molar ratio of 1 : 1 mol/mol and P(TMC-*co*-PTC) with a TMC/PTC monomer feed molar ratio of 4 : 1 mol/mol also reached 21.39 and 17.73%, respectively, after drug controlled release for 30 days. The release rates of the partly deprotected copolymers were higher than those of the corresponding unreduced copolymers with the same TMC/PTC monomer feed molar ratios. The accumulative percentage release of the partly deprotected P(TMC-*co*-PTC) with a TMC/PTC monomer feed molar ratio of 1 : 4 mol/mol reached 55.53%, whereas those of the partly deprotected P(TMC-*co*-PTC) with a TMC/PTC monomer feed molar ratio of 1 : 1 mol/mol and the partly deprotected P(TMC-*co*-PTC) with a TMC/PTC monomer feed molar ratio of 4 : 1 mol/mol also reached 44.00 and 39.78%, respectively, after drug controlled release for 30 days. This indicated that the hydrophilic hydroxyl groups enhanced the hydrophilicity and biodegradation rates and promoted the water absorption and drug diffusion coefficient. Thus, these results show 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.

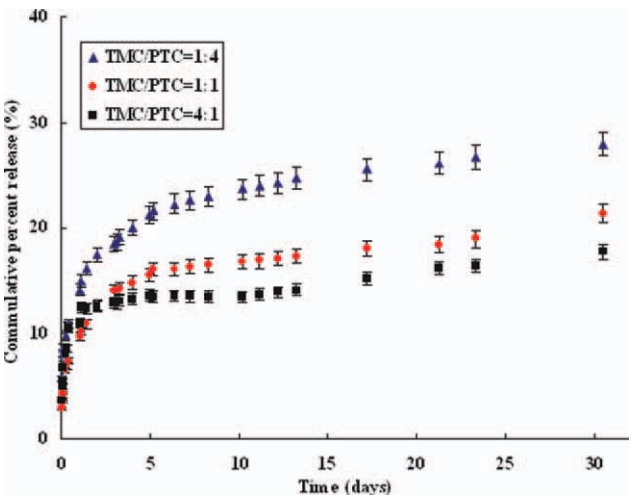

Figure 8 Release profile of 5-Fu from unreduced polycarbonate copolymers {polymerization conditions: TMC/PTC monomer feed molar ratios = 4 : 1, 1 : 1, and 1 : 4, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

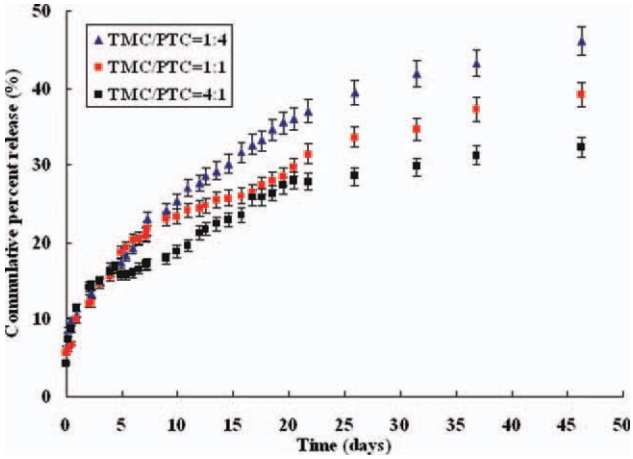

Figure 9 Release profile of 5-Fu from partly deprotected polycarbonate copolymers {polymerization conditions: TMC/PTC monomer feed molar ratios = 4 : 1, 1 : 1, and 1 : 4, temperature = 180°C, time = 24 h, [M]/[C] = 1000, catalyst: $Sn(Oct)_2$}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSIONS

P(TMC-*co*-PTC)s and their corresponding partly deprotected copolymers were synthesized in this work. The experimental data showed that the copolymerization of the monomers TMC and PTC was a nonideal copolymerization and that r_1 was higher r_2. The partly deprotected copolymers possessed faster degradation rates and more hydrophilicity than the corresponding unreduced copolymers. The degradation of the copolymers increased when the pH value of the buffer solution decreased. *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.

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