Ring-Opening Copolymerization and Properties of Polycarbonate Copolymers

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ABSTRACT: A series of polycarbonate copolymers were synthesized by the ring-opening bulk polymerization of 2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate (PTC) and 5,5-dimethyl trimethylene carbonate (DTC) with tin(II) 2-ethylhexanoate and aluminum isopropoxide as initiators. The copolymers obtained were characterized by ^{1}H-NMR, Fourier transform infrared, and ultraviolet. The influence of the molar ratio of the monomers, the initiators, and their concentrations, the reaction time, and the reaction temperature on the copolymerization was also studied. The copolymerization of monomers DTC and PTC was a nonideal copolymerization, and the copolymerization reactivity ratio of the monomer DTC was higher than that of PTC in the copolymerization process. *In vitro* release profiles of fluorouracil from the copolymers showed that the copolymer had a steady drug-release rate and good controlled-release property. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 108: 93–98, 2008

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

INTRODUCTION

In recent years, aliphatic polycarbonates have attracted interest as biodegradable biomedical materials and environmentally degradable materials. Biodegradable polycarbonates, such as homopolymers and copolymers of 1,3-dioxan-2-one [trimethylene carbonate (TMC)] and 5,5-dimethyl-1,3-dioxan-2-one [5,5-dimethyl trimethylene carbonate (DTC)], have been widely used in drug delivery, soft tissue implantation, and tissue regeneration because of their good biodegradation, biocompatibility, elasticity, and low toxicity.[1–4]

Basically, there are five methods reported to synthesize poly(alkylene carbonate)s: (1) the reaction of aliphatic diols with phosgene, (2) the copolymerization of epoxides with carbon dioxide in the presence of organometallic catalysts, (3) the ring-opening polymerization of cyclic carbonate monomers, (4) carbonate interchange reactions between aliphatic diols and dialkyl carbonates, and (5) the direct condensation of diols with CO_2 or alkali metal carbonates. Only methods 2 and 3 can be used to prepare aliphatic polycarbonates with high molecular weights.[5–7]

In the ring-opening polymerization process, five- and six-membered cyclic carbonates are the most commonly used monomers. However, decarboxylation has appeared during the polymerization process of five-membered cyclic carbonates such as ethylene carbonates[8] and 1,2-propylene carbonate,[9] whereas a loss of CO_2 has accompanied the polymerizations, resulting in ether linkages along the backbone of polycarbonates. Then, the molar fractions of ethylene carbonate or 1,2-propylene carbonate repeat units in the structures of polycarbonates have been less than 0.5.[8] The cationic polymerization of six-membered cyclic carbonates has also been accompanied by decarboxylation, yielding mixed-linkage polycarbonates containing ether bonds.[10] For example, polycarbonates containing ether linkages have been reported in the ring-opening polymerization of TMC and neopentylene carbonate with BF_3OEt_2, $BC1_3$, and BBr_3 as catalysts.[11]

It is well known that no decarboxylation has been observed in the anionic polymerization of six-membered cyclic carbonates. A number of Sn-based catalysts are the preferred catalysts for the ring-opening polymerization of TMC without decarboxylation. Poly(trimethylene carbonate) with a weight-average molecular weight (M_w) of about 2.5×10^5 and 87.5% monomer conversion has been reported with

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$BuSnC1_3$ as the catalyst. Therefore, the anionic polymerization of six-membered cyclic carbonates has been widely adopted for producing aliphatic polycarbonates at present.[10,11]

The biodegradation rate of aliphatic polycarbonates mostly depends on the structure of the polycarbonates. The biodegradation of poly(ethylene carbonate) pellets in the peritoneal cavity in rats was apparent within 2 days of implantation and was nearly completed within 2 weeks. However, less than 3% weight loss resulted from a poly(5,5-dimethyl trimethylene carbonate) (PDTC) film incubated in a buffer solution (pH 7.4, 37°C) for 100 days because hydrophobic PDTC has a relatively high glass-transition temperature (27°C) and crystallinity (melting temperature = 108°C, standard molar enthalpy of formation of crystallinity (ΔH_f) = 20 J/g).[12]

Therefore, various modification strategies must be employed to enhance the hydrophilicity and reduce the glass-transition temperature and crystallinity of aliphatic polycarbonates to improve their biodegradation rates.[13] Thus, the approach to copolymerization and graft polymerization with other cyclic carbonates has the obvious advantage of easy accessibility to the targets. PDTC was grafted to hydrophilicity groups of poly{α,β-[*N*-(2-hydroxyethyl)-L-aspartamide]} (PHEA) to make PDTC-*g*-PHEA copolymers. The average weight losses of PDTC-*g*-PHEA under the same degradation conditions were more than 40%, indicating that the rate of degradation of PDTC-*g*-PHEA was faster than that of PDTC.[13] Two amphiphilic copolymers [poly(PEG-*b*-DTC) and poly(PEG-*b*-TMC)] were synthesized by the polymerization of DTC and TMC with the hydroxyl end group of methoxy-terminated poly(ethylene glycol) (PEG) as the initiator under the catalysis of tin(II) 2-ethylhexanoate [$Sn(Oct)_2$].[14] Compared with the polycarbonate homopolymers of DTC and TMC,[15] the average weight losses of poly(PEG-*b*-DTC) and poly(PEG-*b*-TMC) after 6 weeks were 28.9 and 31.4%, respectively, in a phosphate buffer solution (PBS) at 37°C, indicating that the copolymers possessed higher rates of degradation, presumably because the hydrophilic PEG segments promoted water permeation into the copolymer matrix.[16]

2-Phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate (PTC) is a novel six-membered cyclic carbonate monomer that contains potential functional groups. The aim of a molecular sign is to produce poly[2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate-*co*-5,5-dimethyl trimethylene carbonate] [P(PTC-*co*-DTC)] copolymers by the anionic copolymerization of PTC and DTC and to obtain subsequently polycarbonate copolymers containing some of the side-chain hydroxyl groups after the deprotection. This will not only increase the hydrophilicity and accelerate the degradation rates but also be conducive to chemical modification with the introduction of hydroxyl groups.

In this work, we report the preparation and copolymerization of six-membered cyclic carbonate monomers including PTC and DTC. P(PTC-*co*-DTC) polycarbonate copolymers were characterized with ^{1}H-NMR, Fourier transform infrared (FTIR), and ultraviolet (UV). The influence of the feed molar ratio of the monomers, the initiators, and their concentrations, the reaction time, and the reaction temperature on the copolymerization were investigated. The drug-release property *in vitro* of the copolymers was also evaluated.

EXPERIMENTAL

Instruments and reagents

The compounds prepared were characterized with a Spectrum One infrared spectrophotometer (Perkin-Elmer, Waltham, MA) and a Varian Mercury-VX300 NMR spectrometer (Varian, Columbia, MD). The molecular weight was measured by gel permeation chromatography [GPC; Waters 2965D separations module, Waters 2414 refractive-index detector, Shodex K802.5 and K805 with a Shodex K-G guard column, polystyrene standard, dimethylformamide (DMF) as the solvent, 1.0 mL/min flow rate, 323 K column temperature, and 318 K detector temperature] (Waters, Milford, MA).

All chemicals and solvents were analytical-grade. $Sn(Oct)_2$, aluminum isopropoxide [$Al(O^iPr)_3$], and ethyl chloroformate were purchased from Sigma–Aldrich and purified by redistillation *in vacuo* before use. Toluene and tetrahydrofuran (THF) were purified by redistillation over sodium. Triethylamine (Et_3N) was refluxed under phthalic anhydride and dried over calcium hydride (CaH_2) before use. DTC, PTC, PDTC, and poly[2-phenyl-5,5-bis(hydroxymethyl) trimethylene carbonate] were prepared according to the literature.[17–19]

Synthesis of the copolymers

DTC (0.52 g, 4.0 mmol) and PTC (1.0 g, 4.0 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 (15 mL) and then reprecipitated with ethanol (80 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(PTC-*co*-DTC) (1.22 g, 80%).

^{1}H-NMR ($CDCl_3$, δ, ppm): 7.48–7.27 (m, $\mathbf{C_6H_5}$—), 5.49 [s, C_6H_5—$\mathbf{CH}$—$(O)_2$—], 4.57 [s, —COO—$\mathbf{CH_2}$

$C(CH_2O—)_2—CH_2O—$], 4.15 [t, —COO—$CH_2C(\mathbf{CH_2}$ O—)$_2$ —$CH_2O—$], 4.05 [s, —COO—$CH_2C(CH_2O—)_2$ —$\mathbf{CH_2}$O—], 3.09 [s, —$C(CH_3)_2—\mathbf{CH_2}—O—$], 1.01 (s, $\mathbf{CH_3}$). IR (KBr, cm^{-1}): 3036, 3065 (C—H), 1749 (C=O), 1473–1406 (CH_3), 1259 (C—O—C=O), 1111–1033 (C—O). UV ($CHCl_3$, λ, nm): 253–262.

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

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

In vitro drug-release study

Fluorouracil (5-Fu; 10 mg) and P(PTC-*co*-DTC) (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(PTC-*co*-DTC) tablets.

The tablet was suspended in 10 mL of PBS (pH 7.4) 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 220 nm with a Lambda Bio 40 ultraviolet–visible spectrophotometer (PerkinElmer, Waltham, MA). The changes in the concentrations of 5-Fu were obtained from curves of absorption rate A versus concentration C for 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 the t test, with $P < 0.05$ being considered a significant difference.

RESULTS AND DISCUSSION

Preparation and characterization

The cyclic carbonate monomer PTC was prepared by two-step reactions from pentaerythritol (Fig. 1). The purity and structure of PTC and DTC were confirmed by the melting point, FTIR, ^{1}H-NMR, and UV according to the reported literature (Figs. 2 and 3).[17–19]

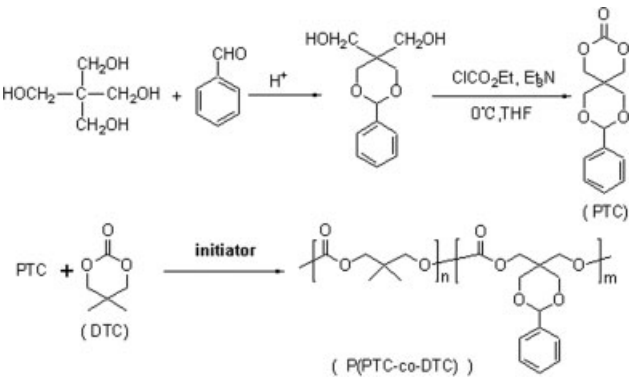

Figure 1 Synthetic route of P(PTC-*co*-DTC) polycarbonate copolymers.

The P(PTC-*co*-DTC) copolymers were synthesized by the anionic ring-opening copolymerization of PTC and DTC with $Sn(Oct)_2$ and $Al(O^iPr)_3$ as the initiators. P(PTC-*co*-DTC) 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 1750 cm^{-1}, which represented the absorption peak of C=O groups. In the ^{1}H-NMR spectra of the copolymers, the typical signals for PTC and DTC repeat units in the backbone of the copolymer structures could be observed at 7.37–7.48 (PTC repeat units: —$\mathbf{C_6H_5}$) and 1.01 ppm (DTC repeat units: —$\mathbf{CH_3}$). Thus, the average copolymer compositions of PTC and DTC repeat units (mol %) could be calculated according to the integration values of the 7.37–7.48 ppm (—$\mathbf{C_6H_5}$) peaks and the 1.01 ppm (—$\mathbf{CH_3}$) peak. The effects of the polymerization conditions, including the molar ratio of the monomers, varieties of the initiators, monomer/catalyst molar ratio, reaction time, and temperature, on the molecular weights of the copolymers are listed in Tables I–III.

The effects of the monomer feed molar ratio of DTC to PTC on the polymerization with $Sn(Oct)_2$ and $Al(O^iPr)_3$ as the initiators are shown in Tables I and II. The polymerization conditions were listed as follows: the feed molar ratio of the monomers to the initiator was 1000/1, the reaction temperature was 180°C, and the reaction time was 24 h. Both the molecular weight of P(PTC-*co*-DTC) and the repeat unit molar ratio of DTC to PTC in the backbone of the polycarbonate copolymers increased when the monomer feed molar ratio of DTC to PTC increased from 1 : 8 to 8 : 1. Moreover, the repeat unit molar ratio of DTC to PTC in the backbone was always larger than the monomer feed molar ratio of DTC to PTC in the polymerization process correspondingly. Thus, the results suggested that the DTC monomer had more reactivity than the PTC monomer and that the content of DTC repeat units in the backbone of P(PTC-*co*-DTC) was larger than that of PTC repeat units.

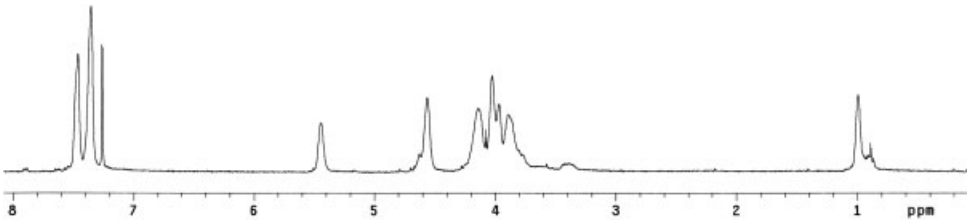

Figure 2 ^{1}H-NMR spectrum of the P(PTC-*co*-DTC) polycarbonate copolymer [polymerization conditions: PTC/DTC (monomers) = 1 : 1, monomers/initiator (molar ratio) = 1000, initiator = Al(O^{i}Pr)$_3$, temperature = 180°C, time = 24 h].

According to the copolymerization mechanism and the equations of the copolymerization reactivity ratio [eqs. (1)–(5)],[20] the monomer copolymerization reactivity ratios and the characteristics of the copolymerization of DTC and PTC can be determined. In the copolymerization process, the copolymer composition of the repeat unit molar ratio of DTC to PTC in the backbone at time t can be described by eq. (1):

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

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

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

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

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

where $[M_1]$ and $[M_2]$ are the monomer concentrations of DTC 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 DTC and PTC in the backbone at time t, respectively; F_1 and F_2 are the molar composition ratios of repeat units DTC and PTC in the copolymer at time t, respectively; f_1 and f_2 are the monomer concentration ratios of DTC 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 DTC and PTC in the polymerization process, respectively.

The average copolymer compositions of PTC and DTC repeat units (mol %) can be measured from ^{1}H-NMR. The polymerization conditions were listed as follows: the initiator was Al(O^{i}Pr)$_3$, the feed molar ratio of the monomers to the initiator 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 4. r_1 and r_2 were calculated with eqs. (1)–(5) as follows: $r_1 = 1.080$, $r_2 = 0.565$, and $r_1 r_2 = 0.610 < 1$. This result demonstrated that the copolymerization of monomers DTC and PTC was a nonideal copolymerization and that r_1 was higher than r_2 in the polymerization process.

The effects of the feed molar ratio of the monomers to the initiator, reaction temperature, and reaction time are shown in Table III. The polymerization conditions were listed as follows: the monomer feed molar ratio of DTC to PTC was 1 : 1 for the polymerization with Sn(Oct)$_2$ as the initiator. The molecular weights of the polycarbonate copolymers increased and subsequently decreased with the increase in the

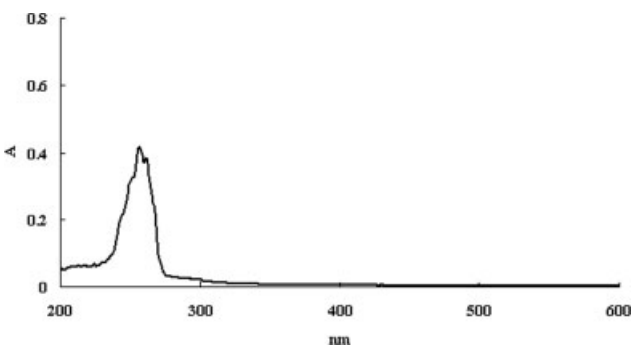

Figure 3 UV curve of the P(PTC-*co*-DTC) polycarbonate copolymer in chloroform [polymerization conditions: PTC/DTC (monomers) = 1 : 1, monomers/initiator (molar ratio) = 1000, initiator = Al(O^{i}Pr)$_3$, temperature = 180°C, time = 24 h].

TABLE I
Effect of the DTC/PTC Feed Ratio on the Copolymerization with Al(O^{i}Pr)$_3$ as an Initiator

Monomer DTC/PTC feed ratio (mol/mol)	Repeat unit DTC/PTC ratio in the copolymer (mol/mol)	M_n (10^4)	M_w/M_n
0.125 : 1	0.232 : 1	1.47	1.22
0.25 : 1	0.429 : 1	1.48	1.17
0.5 : 1	0.935 : 1	1.60	1.05
1 : 1	1.111 : 1	2.28	1.20
2 : 1	2.115 : 1	2.85	1.23
4 : 1	4.545 : 1	4.47	1.03
8 : 1	9.259 : 1	4.58	1.12

TABLE II
Effect of the DTC/PTC Feed Ratio on the Copolymerization with $Sn(Oct)_2$ as an Initiator

Monomer DTC/PTC feed ratio (mol/mol)	Repeat unit DTC/PTC ratio in the copolymer (mol/mol)	M_n (10^4)	M_w/M_n
0.125 : 1	0.236 : 1	2.20	1.17
0.25 : 1	0.453 : 1	2.59	1.20
0.5 : 1	0.898 : 1	2.85	1.34
1 : 1	1.083 : 1	4.05	1.19
2 : 1	2.610 : 1	4.13	1.23
4 : 1	4.025 : 1	4.16	1.20
8 : 1	11.346 : 1	4.22	1.17

TABLE III
Effects of the Initiator Concentration, Reaction Time, and Reaction Temperature on the Copolymerization with $Sn(Oct)_2$ as an Initiator

[M]/[I][a]	Time (h)	Temperature (°C)	M_n (10^4)	M_w/M_n
250	24	180	1.26	1.34
500	24	180	6.68	1.25
1000	24	180	4.05	1.19
2000	24	180	2.54	1.18
1000	8	180	2.48	1.25
1000	16	180	3.05	1.34
1000	36	180	4.50	1.16
1000	48	180	0.87	1.21
1000	24	170	3.10	1.12
1000	24	190	3.39	1.33
1000	24	200	0.89	1.22

[a] Feed molar ratio of the monomers to the initiator.

initiator dosage. The highest M_n value of the copolymer was 6.68×10^4 when the feed molar ratio of the monomers to the initiator was 500, the reaction temperature was 180°C, and the reaction time was 24 h. This result indicated that the overly high dosage of the initiator resulted in the reduction of the molecular weight of the copolymer.

The molecular weights of the polycarbonate copolymers changed while the reaction time varied from 8 to 36 h under the polymerization conditions (the feed molar ratio of the monomers to the initiator was 1000, and the reaction temperature was 180°C.). The molecular weights of the polycarbonate copolymers reached the maximum value ($M_n = 4.50 \times 10^4$) when the reaction time was 36 h and then came down rapidly as more time elapsed. 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, the higher reaction temperature induced the molecular weights of the polycarbonate copolymers to decrease. The long reaction time and high reaction temperature probably led to the degradation and interchange esterification reaction of the copolymers.

In vitro drug-release property of the copolymers

The overall process of drug release from polymeric tablets is mostly controlled by drug diffusion, drug dissolution, and polymeric degradation.[21–25] The 5-Fu release profiles of the copolymers are shown in Figure 5. A substantial release rate of the 5-Fu-incorporated P(PTC-*co*-DTC) tablets could be maintained for more than 500 h of measurement. Compared to the tablets made from the polycarbonate homopolymers and copolymer of DTC and TMC,[15] the 5-Fu-incorporated P(PTC-*co*-DTC) tablets released the

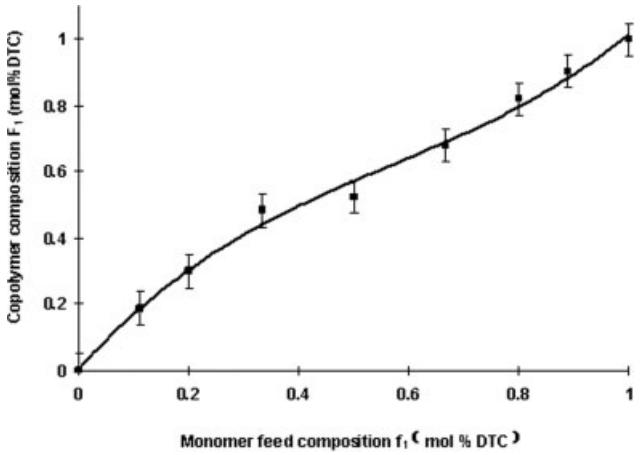

Figure 4 F_1 as a function of f_1 [polymerization conditions: monomers/initiator (molar ratio) = 1000, initiator = $Al(O^iPr)_3$, temperature = 180°C, time = 24 h].

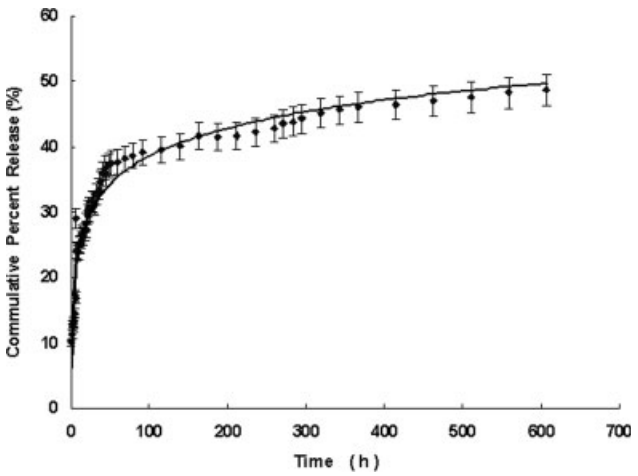

Figure 5 5-Fu release profiles from the polycarbonate copolymers [polymerization conditions: PTC/DTC (monomers) = 1 : 1, monomers/initiator (molar ratio) = 1000, initiator = $Al(O^iPr)_3$, temperature = 180°C, time = 24 h].

drug faster, presumably because of the different copolymer structures, the higher rate of degradation of P(PTC-*co*-DTC), and the increased drug diffusion coefficient. The copolymer P(PTC-*co*-DTC) structures containing the phenyl groups probably resulted in the bigger size of the microhole in the 5-Fu-incorporated copolymer tablets in comparison with those of the polycarbonate homopolymers and copolymer of DTC and TMC, thus leading to 5-Fu being released readily from the P(PTC-*co*-DTC) tablets.

CONCLUSIONS

P(PTC-*co*-DTC) polycarbonate copolymers were synthesized by ring-opening bulk polymerization with $Sn(Oct)_2$ and $Al(O^iPr)_3$ as initiators. The copolymers obtained were characterized with ^{1}H-NMR, FTIR, and UV. The effects of the molar ratio of the monomers, the initiators, and their concentrations, the reaction time, and the reaction temperature on the copolymerization were also studied. The experimental data showed that the copolymerization of monomers DTC and PTC was a nonideal copolymerization and that the copolymerization reactivity ratio of monomer DTC was higher than that of PTC in the polymerization process. *In vitro* release profiles of 5-Fu from the copolymers showed that the copolymers had a steady drug-release rate and good controlled-release property.

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