Polym. Bull. (2014) 71:47–56
DOI 10.1007/s00289-013-1044-7

ORIGINAL PAPER

Syntheses and properties of novel copolymers of polycaprolactone and aliphatic polycarbonate based on ketal-protected dihydroxyacetone

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Received: 28 August 2012 / Revised: 13 July 2013 / Accepted: 22 August 2013 /
Published online: 12 September 2013

Abstract The random copolymers of ε-caprolactone (CL) and 2,2-ethylenedioxy propane-1,3-diol carbonate (EOPDC) were synthesized in bulk at 120 °C using $Sn(Oct)_2$ as a catalyst. The poly(EOPDC-co–CL)s obtained were characterized by FT IR, ^{1}H NMR, ^{13}C NMR, GPC and DSC. The copolymers were obtained with yield of 84.2–97.8 %. The number-average molecular weight of the copolymer is 2.75–7.76 × 10^4 with a polydispersity of 1.52–1.68. The properties of the copolymer including the enzymatic degradation by Pseudomonas Cepacia lipase and drug-controlled release property were also investigated. The results showed that the copolymers are degradable at physiological conditions, and their degradation rate and release of Tegafur in the copolymers increase with increasing CL content in the copolymers.

Keywords Ring-opening polymerization · ε-Caprolactone · 2,2-Ethylenedioxy-1,3-propanediol carbonate · Degradation

Introduction

Biodegradable polymers belong to the class of the most attractive biomaterials because of their wide applications in biomedical fields [1]. Most of the synthetic biodegradable polymers are aliphatic polyesters, among them, ε-polycaprolactone

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(PCL) is one of the most important biodegradable polymers due to its biodegradability, biocompatibility, non-toxicity and good permeability to drug [2]. However, PCL has slow degradation rate because of its poor hydrophilicity and high crystallinity that limit its applications in the biomedical fields. To satisfy the requirements of industrial, agricultural and specific medical applications, many modification strategies have been chosen to optimize certain properties of the biomaterials. Modification via copolymerization is an effective way to obtain the materials with desirable properties, a lot of copolymers of ε-caprolactone (CL) with other monomers such as lactide (LA) [3] and glycolide [4, 5], 5-methyl-5-benzyloxycarbonyl-1,3-dioxane-2-one (MBC) [6, 7], trimethylene carbonate (TMC) [8–11], 2,2-dimethyl trimethylene carbonate (DTC) [12–14], 1,4-dioxane-2-one [15] and poly(ethylene glycol) (PEG) [16–18] have been extensively investigated to improve their physical or chemical properties and further expand applications of PCL.

Aliphatic polycarbonates represent one family of bioresorbable materials used for biomedical applications because of their good biocompatibility, low toxicity, and biodegradability [19, 20]. Recently, increasing attention has been paid to the synthetic aliphatic polycarbonates bearing functional groups, such as alkyl [21], allyl [22], OH [23, 24], NH_2 [25], COOH [26], COOR [27] and ketone carbonyl group [28], because these functional groups can be used to regulate hydrophilicity/hydrophobicity, permeability, bioresorption and mechanical properties to obtain biodegradable polymers with improved properties.

In our pervious studies[29, 30], poly(2,2-ethylenedioxy propane-1,3-diol carbonate) (PEOPDC) is a novel biodegradable aliphatic polycarbonate based on dihydroxyacetone with ethylene ketal-protected carbonyl group, which possess good biocompatibility and biodegradation in comparison with poly(2, 2-dimethyl trimethylene carbonate) (PDTC).

As part of our continuing efforts in the study of novel biodegradable polycarbonates homopolymers or copolymers, in this paper, syntheses and characterization of novel polycaprolactone and aliphatic polycarbonate aliphatic polycarbonate copolymers by random ring-opening copolymerization of CL and 2,2-ethylenedioxy-1,3-propanediol carbonate (EOPDC) was described, and the properties of the copolymer including enzymatic degradation properties and preliminary drug-controlled release property were also investigated.

Experimental

Materials

Toluene was dried over Na before use. Stannous octanoate (95 %) and ε-caprolactone were purchased from Aldrich. Pseudomonas Cepacia lipase (40 U/mg) was purchased from Fluka. The initiator $Sn(Oct)_2$ was purified by distillation under reduced pressure and then dissolved in dry toluene. ε-Caprolactone was dried over CaH_2 and purified by distillation under reduced pressure prior to use. 5-Fluoro-1-(tetrahydro-2-furyl)uracil (Tegafur) was recrystallized with ethanol. Magnesium

sulfate, chloroform, Tris, NaN_3, THF and ethyl acetate (Shanghai Chemical Reagent Co., China) were of analytical grade and used as received. Cyclic monomers, EOPDC, were synthesized as described in literature [29].

Measurements

IR spectra (in KBr pellets) were recorded on Perkin Elmer-2 spectrometer. UV spectra were recorded on Perkin-Elmer Lambda Bio 40 UV/Vis Spectrophotometer. ^{1}H NMR analysis was performed on a Mercury VX-300 spectrometer using $CDCl_3$ as a solvent. ^{13}C NMR spectra were recorded on a Mercury VX-300 spectrometer at 62.5 MHz using $CDCl_3$ as a solvent. The concentration of Tegafur was determined by Shimadzu UV-240. Molecular weight was determined by a gel permeation chromatographic (GPC) system (2690D, Waters) with a 2410 refractive-index detector, and Shodex K803 and K805 columns. Chloroform was used as the eluent at a flow rate of 1.0 ml/min. The glass transition temperatures of polymers were measured by differential scanning calorimeter (DSC) (Perkin-Elmer Pyris-1). Samples were heated from −25 °C to 200 °C at a heating rate of 20 °C/min.

Synthesis of copolymer of EOPDC and CL

Prescribed amounts of EOPDC and CL with $Sn(Oct)_2$ as a catalyst were put into polymerization tubes. The tubes were purged with nitrogen three times, and then sealed under vacuum and placed in an oil bath under certain conditions. After the reaction, the products were dissolved in CH_2Cl_2, and precipitated with CH_3OH. The precipitated poly(EOPDC-co–CL) was dried in vacuum at 50 °C for 24 h.

Enzymatic degradation

The polymer films were prepared by solution-casting method, and the size and weight of the films used were about 10 × 10 mm^2 and 10–15 mg, respectively. Enzymatic degradation experiments was performed at 37 °C by immersing copolymer films in 5 ml Tris–HCl buffer solution (0.1 M, pH 8.6) in the presence of 1 mg Pseudomonas Cepacia lipase and 1 mg sodium azide, and the buffer-enzymatic solution was changed every 24 h to maintain the enzymatic activity. These films were taken out from the solution over predetermined time intervals, then washed with distilled water and dried to a constant weight in vacuum. The degradation rate was determined by the weight loss. Weight loss is defined as: weight loss (%) $= [(W_i - W_t)/W_i] \times 100$ %, where W_i is initial weight and W_t is weight after degradation at different time intervals.

In vitro drug-controlled release

A mixture of 50 mg polymer and 5 mg Tegafur was dissolved in 1 ml CH_2Cl_2, then the solution was cast onto Teflon board at room temperature, the film was dried to constant weight in vacuum. The sample was immersed in 50 ml phosphate buffer solution (pH 7.4, 0.1 M) at 37 °C, 10 ml solution was taken off for released Tegafur

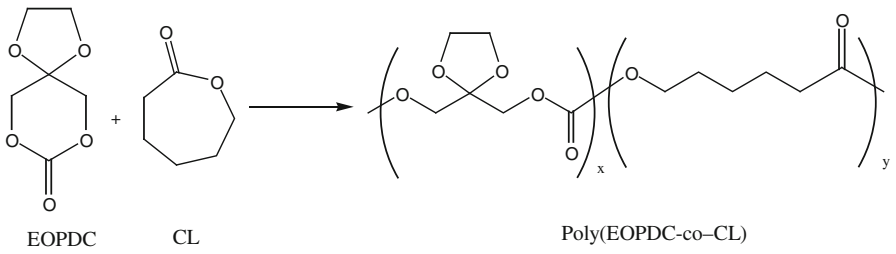
content measurement and the same volume of fresh buffer solution was added at predetermined time intervals. The concentration of Tegafur was determined by UV spectroscopy at maximal absorption wavelength ($\lambda_{max} = 270.8$ nm). The rate of controlled drug release was measured by accumulatively released weight of Tegafur according to the calibration curve of Tegafur.

Results and discussion

Synthesis and characterization of the copolymers

Novel biodegradable copolymers were synthesized by ring-opening polymerization of EOPDC and CL, using $Sn(Oct)_2$ as catalyst in bulk (Scheme 1). By varying the comonomer feed ratio, the copolymerization was carried out at 120 °C for 24 h when the [monomer]/[catalyst] was 1,000. The effects of different molar feed ratios of EOPDC/CL on yield and number-average molecular weight (Mn) of the copolymers were investigated. The results of the copolymerization are shown in Table 1. It can be seen that the molar ratio of EOPDC in the corresponding copolymers is almost the same as that in feeds, which indicates that EOPDC has the same polymerization reactivity as CL in the copolymerization, but the influence of the feed molar ratio of EOPDC/CL on Mn and yield of the copolymers obtained was not obvious. GPC results show that all of the polymers obtained have unimodal molecular weight distributions, so it can be preliminarily concluded that the two monomers of EOPDC and CL have copolymerized.

The copolymers were characterized by FTIR, ^{1}H NMR and ^{13}C NMR. In the FTIR spectra, there were four ester carbonyl absorption peaks at about 1,750 cm^{-1}. The characteristic bands around 1,755, 1,748 cm^{-1} was due to polycarbonate ester C=O stretch, whereas 1,739, 1,733 cm^{-1} was due to polycaprolactone ester C=O stretch, and the characteristic absorption band at 1,253, 1,189, 1,043 cm^{-1} was due to the C–O–C stretching vibration in copolymers, which might indicate the formation of random copolymers. The ^{1}H NMR spectrum of the copolymer with the molar feed ratio of EOPDC/CL (50/50) is presented in Fig. 1. As the EOPDC unit was symmetric, the chemical shifts of two methylene protons in 5-membered ring ($OC\underline{H}_2C\underline{H}_2O$) ($^{a}H$) were at the same site $\delta = 4.01$ ppm, and the chemical shifts of other two methylene protons link to carbonate ester groups ($C\underline{H}_2OCOC\underline{H}_2$) ($^{b}H$)



Scheme 1 Synthesis of polycarbonate copolymer from EOPDC and CL

Table 1 Syntheses of poly(EOPDC-co–CL) with different compositions

Entry	$f_{EOPDC/CL}$[a]	$F_{EOPDC/CL}$[b]	Mn[c]	Mw/Mn[c]	Yield (%)
1	100/0	100/0	150,800	1.67	99.0
2	90/10	90/10	77,600	1.58	97.4
3	70/30	70/30	27,500	1.75	88.9
4	50/50	50/50	43,900	1.62	97.8
5	30/70	30/70	41,900	1.58	87.0
6	10/90	9/91	54,200	1.58	84.2
7	0/100	0/100	56,000	1.59	86.7

$Sn(Oct)_2$ as catalyst, molar ratio of monomer to catalyst $[M]/[I] = 1{,}000$, 120 °C, 24 h

[a] Monomer feed ratio in mmol/mmol

[b] Molar composition in the copolymer was determined by ^{1}H NMR

[c] Number-average molecular weight and molecular weight distribution determined by GPC

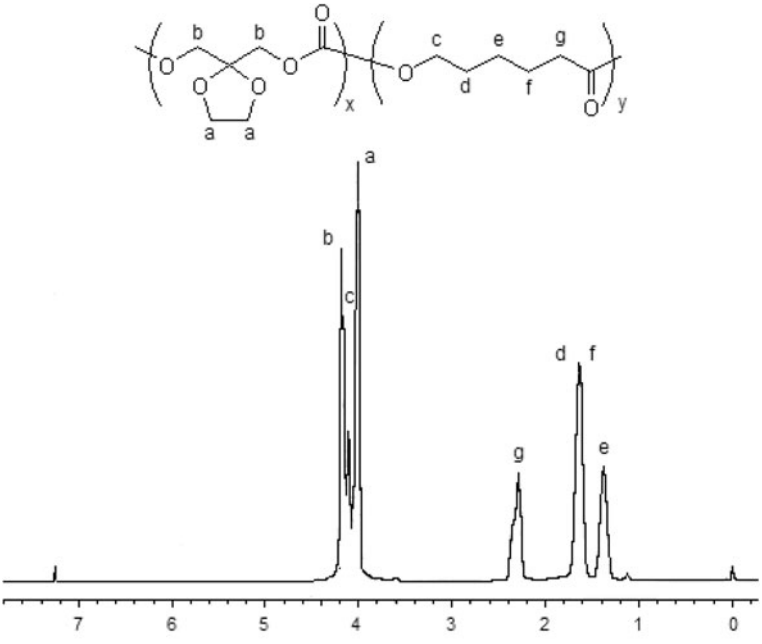


Fig. 1 ^{1}H NMR spectrum of copolymer of EOPDC and CL (50/50)

were at the same site $\delta = 4.18$ ppm [29]. The chemical shift at 4.06 ppm belonged to the characteristic peaks of ($COCH_2CH_2CH_2CH_2C\underline{H}_2O$)(^{c}H) of CL units, 2.31 ppm to ($COC\underline{H}_2CH_2CH_2CH_2CH_2O$) (^{g}H), and 1.39 ppm to ($COCH_2CH_2C\underline{H}_2CH_2CH_2O$) (^{e}H) of CL units, and 1.66 ppm to ($COCH_2C\underline{H}_2CH_2C\underline{H}_2CH_2O$) (^{d}H and ^{f}H)of CL units. ^{1}H NMR was also used to measure the copolymer compositions

by comparing the relative areas of peaks corresponding to the protons of the EOPDC and CL repeat units. It can be found that the molar ratio of EOPDC in the corresponding copolymers is hardly the same as that in feeds. The ^{13}C NMR spectrum of the copolymer with the molar feed ratio of 50/50 EOPDC/CL is shown in Fig. 2. Signals from the EOPDC units and the CL units can be clearly observed. The detailed assignments are shown in Fig. 2. It can be seen, comparing with corresponding carbon resonance of homopolymer, the carbonyl carbon resonance of the EOPDC in the copolymer splits into two peaks at about 154 ppm (^{d}C), and the carbonyl carbon resonance of CL units was two peaks at about 173 ppm (^{j}C), whereas carbon resonance of ^{b}C and ^{e}C also splits into two peaks effected by copolymerization, which is due to the different chemical environments caused by the different sequences in the copolymer chain. Therefore, from the ^{13}C NMR spectra, we can further confirm that the two comonomers are copolymerized by random copolymerization.

Thermal properties of copolymers

The DSC curves of poly(EOPDC-co–CL) were measured and the results are shown in Fig. 3. It can be seen that a endothermic peaks at 62 °C which corresponded to the melting of the PCL, but melting temperature of the copolymer decrease with increasing EOPDC content. When the molar ratio of in feed is more than 50 %, the melting peak is not observed. It is probably because that the PCL regular structure is disturbed, and its crystallization is retarded by introducing the amorphous PEOPDC units into the PCL main chain.

Enzymatic degradation of copolymers

The enzymatic degradation properties of poly(EOPDC-co–CL) copolymers were evaluated by the weight loss at different degradation time, the results are presented

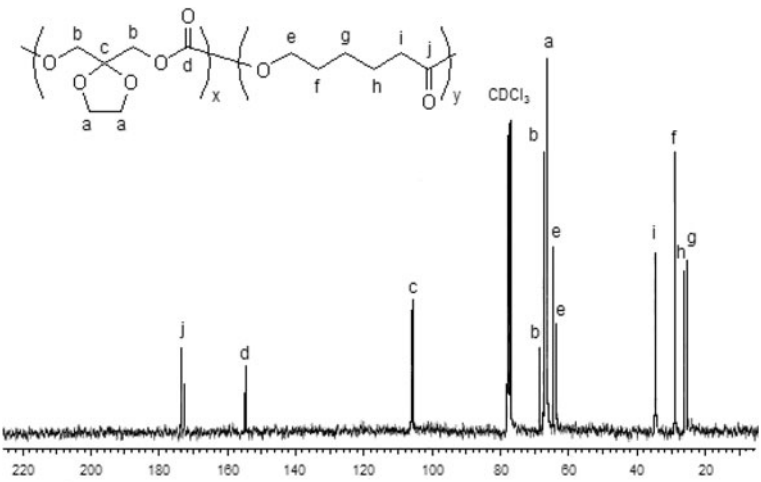


Fig. 2 ^{13}C NMR spectrum of copolymer of EOPDC and CL (50/50)

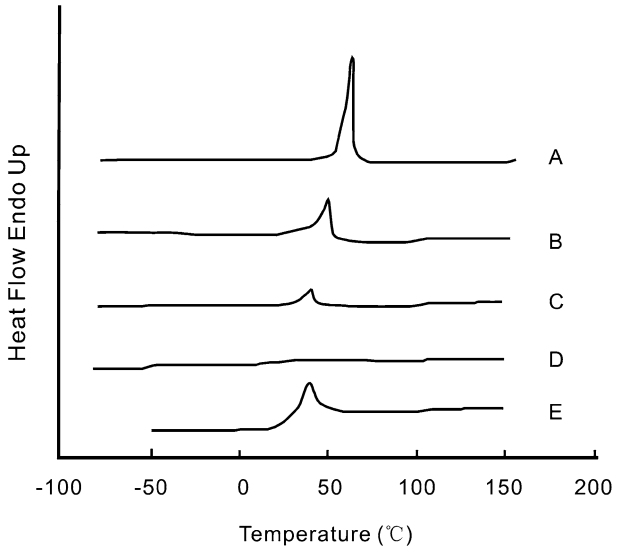


Fig. 3 DSC curves of copolymers of EOPDC and ε-CL. *A* PCL, *B* poly(EOPDC/CL) (10/90), *C* poly(EOPDC/CL) (30/70), *D* poly(EOPDC/CL) (50/50), *E* PEOPDC

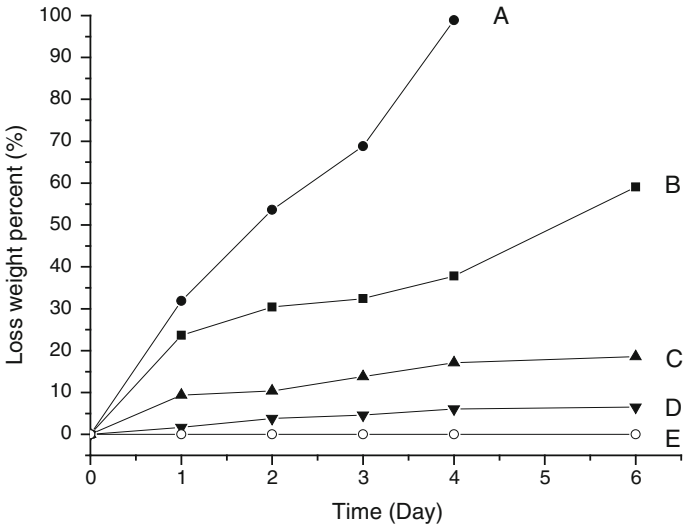


Fig. 4 Enzymatic degradation of copolymers of CL and EOPDC. *A* PCL, *B* poly(EOPDC/CL) (10/90), *C* poly(EOPDC/CL) (50/50), *D* poly(EOPDC/CL) (90/10), *E* PEOPDC

in Fig. 4. It can be seen from Fig. 4 that the degradation rate increases greatly with increasing the molar content of PCL. Thus, the copolymer degradation properties can be adjusted by varying the comonomer feed ratio to adapt to the different applications.

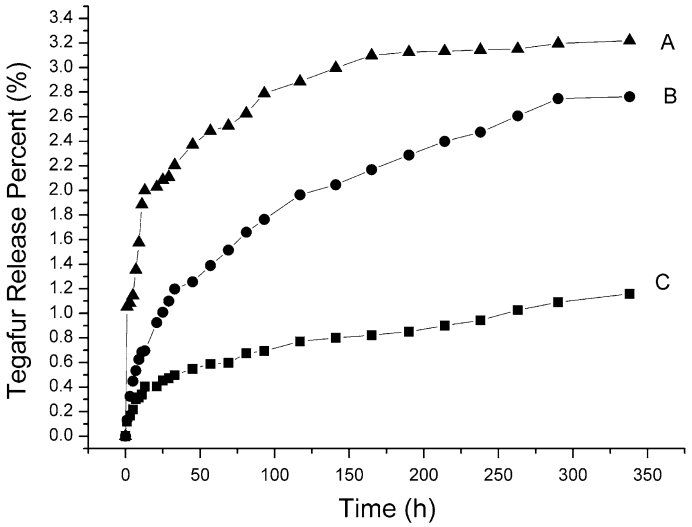


Fig. 5 Tegafur release profiles of copolymers of EOPDC and CL. *A* copolymer with molar ratio of EOPDC/CL (10:90), *B* copolymer with molar ratio of EOPDC/CL (50:50), *C* copolymer with molar ratio of EOPDC/CL (90:10)

In vitro-controlled drug release of copolymers

Anti-tumor drug Tegafur was selected as a model drug to investigate the in vitro-controlled drug release property of the poly(EOPDC-co–CL) copolymers. The release rate was monitored by determining the concentration of accumulatively released Tegafur. The preliminary results are shown in Fig. 5. It can be seen that the rate of controlled drug release from three copolymers was very slow because mainly these copolymers had slow degradation rate in PBS, and that the initial burst release was obvious when CL content reach 90 %. Whereas rate of drug release maintain very slow increasing when CL content reach 50 %. It demonstrates that the behavior of release drug can be controlled by varying the content of EOPDC incorporated into the CL main chain.

Conclusions

Novel biodegradable copolymers of EOPDC and CL with high molecular weight were synthesized under different conditions by ring-opening polymerization. The results show that EOPDC has almost the same polymerization reactivity as CL. The thermal properties can be adjusted by varying the composition of the copolymers. The enzymatic degradation rate increases greatly with increasing the molar content of PCL. The behavior of release drug can be controlled by varying the content of EOPDC incorporated into the CL main chain.

Acknowledgments The authors are grateful for the financial support of national key basic research and development program (G1999064703) and natural science foundation of China (Grant No. 20174029).

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