

Random Copolymers Based on Trimethylene Carbonate and ϵ -Caprolactone for Implant Applications: Synthesis and Properties

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ABSTRACT: Random copolymers of trimethylene carbonate (TMC) and ϵ -caprolactone (CL) have been synthesized by ring-opening polymerization of TMC and CL in the presence of stannous octoate. The effects of feeding dose, reaction temperature and polymerization time, and effect of catalyst content on the copolymerization were investigated. The results showed that the composition of the copolymers was in good agreement with the feeding dose, and the molecular weight of the copolymers decreased firstly with increasing CL content and then increased. The decrease in the reaction temperature, polymerization time and catalyst content would increase the molecular weight of the copolymers. Furthermore, the

feeding dose affected the thermal and mechanical properties of the copolymer largely, and the possessing different properties of random copolymers could be obtained by adjusting the copolymer compositions. This work could optimize the polymerization conditions to achieve the copolymers with controlled properties for implant applications. © 2011 Wiley Periodicals, Inc. *J Appl Polym Sci* 124: 3714–3720, 2012

Key words: biomaterials; trimethylene carbonate; ϵ -caprolactone; random copolymers; ring-opening polymerization; molecular weight; thermal properties; mechanical properties

INTRODUCTION

Worldwide potential demands for biodegradable polymeric materials are quite significant from biomedical and clinical viewpoints. Hence biodegradable polymers with excellent properties have attracted much keen attentions in recent years.^{1–15} Among the biodegradable polymers, homopolymer of trimethylene carbonate (TMC) possesses nontoxicity, biocompatibility, and biodegradability, has been used in clinic applications approved by FDA. However, poly(trimethylene carbonate) (PTMC) is a rubbery polymer that can not be applied as a implanted material due to its poor dimensional stability, tackiness, and inadequate mechanical properties.¹⁶ The incorporation of other monomers containing stiff and tough units into the PTMC chain have been proved to be a successful method of modifying its physical properties.^{17–23} Poly(ϵ -caprolactone) (PCL) is a tough semicrystalline polymer with a low glass transition temperature (approximately -60°C), which degrades very slowly and is most suitable for

long patency applications. Therefore, copolymerization of TMC with CL is a direct method to enhance the properties of PTMC to meet the requirements for the preparation of the implanted devices.

The objectives of this work are: (a) to prepare a series of biodegradable copolymers of TMC and CL [abbreviated as P(TMC-co-CL)] by bulk ring-opening copolymerization using stannous octoate ($\text{Sn}(\text{Oct})_2$) as the catalyst, (b) to investigate the influence of reaction conditions (feeding dose, polymerization time, and reaction temperature) on copolymerization and performance of the copolymers and (c) to discuss the effect of the molar ratio of monomers to catalyst M/C (i.e., the catalyst content) on the molecular weight and its distribution of P(TMC-co-CL). The structure of the resulting copolymers was verified by Fourier transform infrared spectroscopy (FTIR), carbon-13 nuclear magnetic resonance ($^{13}\text{C-NMR}$), and proton nuclear magnetic resonance ($^1\text{H-NMR}$), molecular weight and its distribution were tested by gel permeation chromatography (GPC), thermal properties were performed on differential scanning calorimetry (DSC) and thermogravimetric analyzer (TGA).

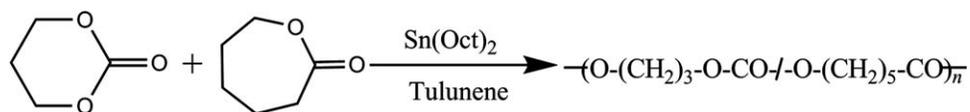
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EXPERIMENTAL

Materials

Polymer grade trimethylene carbonate ($m_p = 45.0^{\circ}\text{C}$) was purchased from Daigang Biomaterial Co., Ltd,



Scheme 1 Synthetic route of copolymers of TMC and CL in the presence of Sn(Oct)_2 .

recrystallized three times in anhydrous ethyl acetate and dried to constant weight prior to use; ϵ -caprolactone (99%), was purchased from Sigma-Aldrich, freshly distilled over CaH_2 under reduced pressure before use; Stannous octanoate (Sn(Oct)_2) (95%) was used as received from Sigma-Aldrich. All other solvents and reagents used were of analytical grades and purified by standard methods.

Measurements

FTIR spectra were measured on a PerkinElmer Spectrum One (B) spectrometer (PerkinElmer, USA) over the wave number range of $400\text{--}4000\text{ cm}^{-1}$. The testing samples were cast as thin films on the KBr plates; The copolymer composition and structure were determined by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ analysis with a Bruker ARX 300 spectrometer (Bruker, Swiss) using solutions of polymer in CDCl_3 solution with tetramethylsilane as an internal reference; The molecular weight (M_w and M_n) and the molecular weight distribution (M_w/M_n) of the products were determined by GPC (WATERS, USA) with a Waters Model 1515 isocratic high-performance liquid chromatography (HPLC) pump, a Waters Model 2414 differential refractive index detector and a Waters Styragel HT4 chromatographic column, using THF as eluent running at a flow rate of 1 mL/min at 35°C . Molecular weight and molecular weight distributions were calculated using polystyrene as standard. The phase behaviors were determined with a Netzsch DSC 200 F3 (Netzsch, Germany) equipped with a liquid nitrogen cooling system under nitrogen atmosphere. The samples were run at a heating rate of 10°C/min from -100 to 100°C to eliminate the thermal history and then a second scan was recorded, the glass transition temperature (T_g) was measured from the second heating cycle. The thermal stability of the polymers under nitrogen atmosphere was carried out by a Netzsch TGA 209 F3 (Netzsch, Germany) with Al_2O_3 crucible and the samples were heated from room temperature to 600°C at a heating rate of 10°C/min .

Copolymers preparation

Copolymerization reaction was carried out in glass ampoules and purged with dry nitrogen. According to the experimental designs, a mixture of dried trimethylene carbonate and distilled ϵ -caprolactone

were added to glass ampoules under nitrogen atmosphere, respectively, and Sn(Oct)_2 was added as a solution in anhydrous toluene. The ampoules were purged three times with dry nitrogen and heat-sealed under vacuum. The ampoules were conditioned in an oil bath preheated at the polymerization temperature and vigorously shaken to obtain a homogeneous mixture of the monomers and the catalyst. All copolymerization were carried out for a period of 24 h at $130 \pm 2^\circ\text{C}$, unless mentioned otherwise. After the reaction time the ampoules were quenched to room temperature and the polymers were discharged. The products were dissolved in CHCl_3 , precipitated in excess methanol, washed with methanol, and dried under reduced pressure at 37°C until constant weight.

RESULTS AND DISCUSSION

Polymers synthesis

The synthetic route of P(TMC-co-CL) was accomplished via ring-opening polymerization in the melt, using Sn(Oct)_2 as the catalyst (Scheme 1), and the results of the copolymerization are given in Table I. Under the applied polymerization conditions the monomer conversion was almost complete and the obtained copolymer compositions agree with the feeding dose well.

The effect of factors such as the feeding dose, reaction temperature and polymerization time on the copolymerization was studied. In Table I, it is shown that when the polymerization conditions were at 130°C for 24 h, the TMC contents in the obtained copolymers were in good agreement with the feeding dose. However, the variation of the temperature and polymerization time would change the compositions. For example, in No.12, when the polymerization temperature was 110°C , the TMC content in the copolymer was lower than that in the feeding dose, and in No.14, when the polymerization time was 48 h, the TMC content in the copolymer was higher than that in the feeding dose. Moreover, it is obvious that under the applied polymerization conditions, The M_n of all the prepared copolymers was high ($>200,000$). The highest molecular weight was obtained after 24 h of polymerization at 110°C . Comparing the molecular weights of the copolymers, it could be concluded that the molecular weight firstly decreased and then increased with increasing CL content (Fig. 1), which was similar to the change

TABLE I
Ring-Opening Copolymerization of TMC and CL in the Bulk With $\text{Sn}(\text{Oct})_2$

No.	TMC content (mol %)		<i>M</i> / <i>C</i>	<i>T</i>	<i>t</i>	TMC conv. ^b	CL conv. ^b	<i>M_w</i> ^c	<i>M_n</i> ^c	PDI ^c	[η] ^d
	Feeding	Polymer ^a		°C	h	%	%	$\times 10^5$	$\times 10^5$		dl·g ⁻¹
1	100	100	5000	130	24	99.0	–	3.09	2.85	1.08	5.45
2	90	90.1	5000	130	24	99.3	99.3	2.94	2.66	1.10	4.47
3	80	78.9	5000	130	24	99.2	99.3	2.88	2.60	1.11	3.92
4	70	67.5	5000	130	24	100	99.6	2.79	2.51	1.11	3.54
5	60	62.3	5000	130	24	100	99.7	2.83	2.55	1.11	3.53
6	50	50.0	5000	130	24	99.2	99.7	2.81	2.53	1.11	3.47
7	40	39.4	5000	130	24	100	100	2.65	2.36	1.12	2.98
8	30	30.3	5000	130	24	99.3	99.2	2.65	2.34	1.13	3.00
9	20	21.0	5000	130	24	98.5	99.2	2.75	2.46	1.11	3.21
10	10	10.3	5000	130	24	99.2	99.9	2.78	2.50	1.11	3.28
11	0	0	5000	130	24	–	100	3.02	2.80	1.08	3.78
12	80	77.8	5000	110	24	98.9	99.2	3.01	2.78	1.08	4.08
13	80	81.1	5000	150	24	100	100	2.49	2.17	1.15	2.90
14	80	81.7	5000	130	48	100	100	2.47	2.14	1.15	2.70
15	80	81.0	5000	130	72	100	100	2.42	2.07	1.17	2.68

^a Determined by $^1\text{H-NMR}$.

^b Determined by $^1\text{H-NMR}$.

^c Calculated from GPC analysis.

^d Derived from ubbelohde viscometer with tetrachloroethane in room temperature.

tendency of the viscosity (Fig. 2). Furthermore, if the feeding doses were the same, the copolymers reacted at lower temperature with the same polymerization time showing higher molecular weight (with the comparison of No. 3, 12, and 13), and M_n decreased with longer polymerization times at the same polymerization temperatures (with the comparison of No. 3, 14, and 15). This may be related to thermal degradation that can occur at higher polymerization temperatures and prolonged polymerization periods.^{24–26} Therefore, feeding dose, reaction temperature and polymerization time seriously affect the molecular weight when designing copolymer materi-

als for implant applications and should be taken into account.

The molar ratio of monomers to catalyst M/C (i.e., catalyst content) also has an important influence on the molecular weight when the monomers feed dose was constant. The general trend is that M_n was increased with increasing the value of M/C (Fig. 3), namely, M_n was increased with decreasing the catalyst content in feed, which was attributed to the reduction of the active centers caused by reducing the catalyst consumption. In that case, the polymer would form a long chain in good conditions for copolymerization that results in a rapid increase of

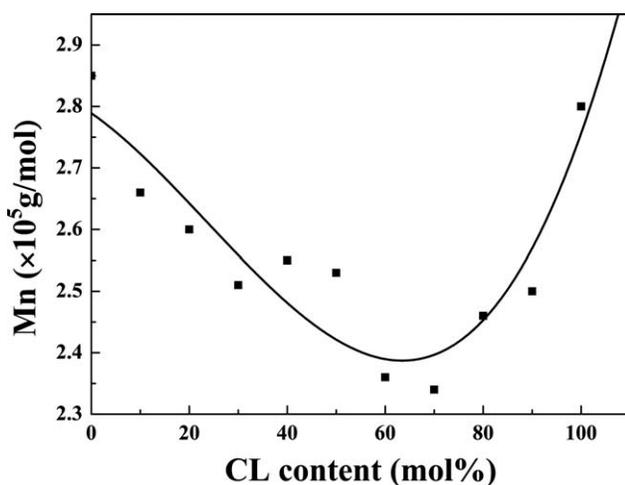


Figure 1 The average molecular weight of the polymers as a function of the CL content.

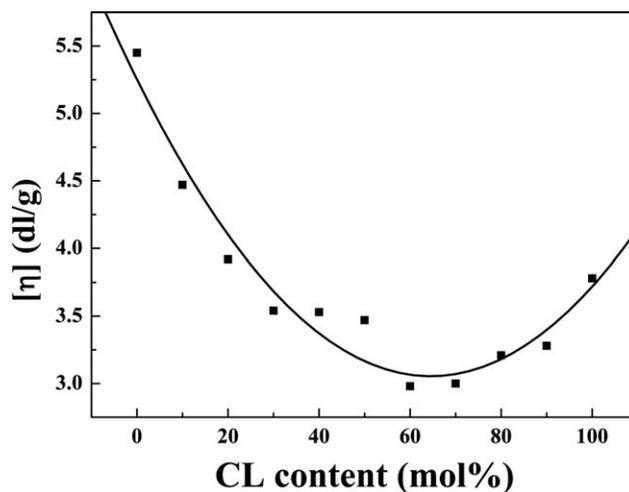


Figure 2 Inherent viscosities of the polymers as a function of the CL content.

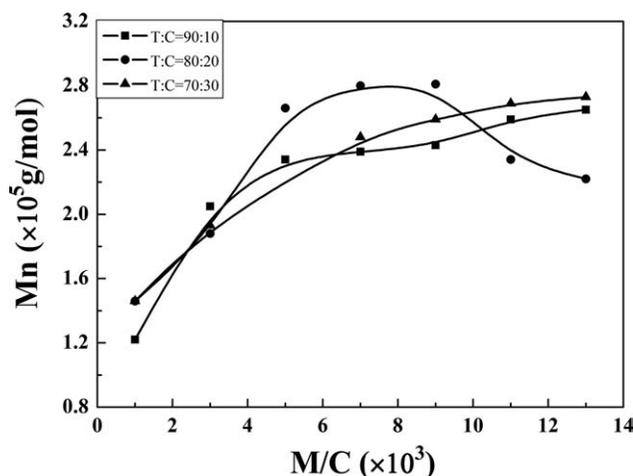


Figure 3 The average molecular weight of the copolymers as a function of the catalyst content with different monomers feed ratio.

the average molecular weight. The results indicate that the average molecular weight of the final polymers could be controlled by adjusting the content of catalyst used in copolymerization.

Meanwhile, the copolymers with the variation of the comonomers composition gained under the copolymerization conditions had a narrow molecular weight distribution (M_w/M_n) with polydispersity indexes of 1.08–1.17, which is important to accurately regulate the degradable speed of the polymers in biomedical applications.

Copolymers characterization

The chemical structure of copolymers was characterized by FTIR, which was in agreement with the expected. The IR spectrum of P(TMC-co-CL) (Fig. 4) showed characteristic stretching bands at about 2963

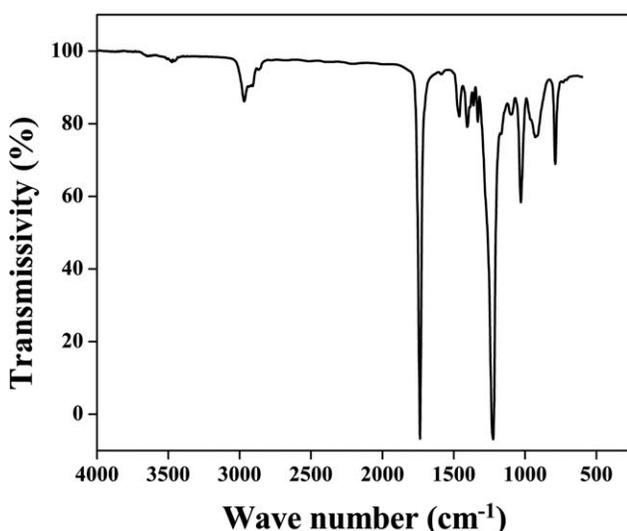


Figure 4 FTIR spectrum of a copolymer of TMC and CL (Table I, no. 3).

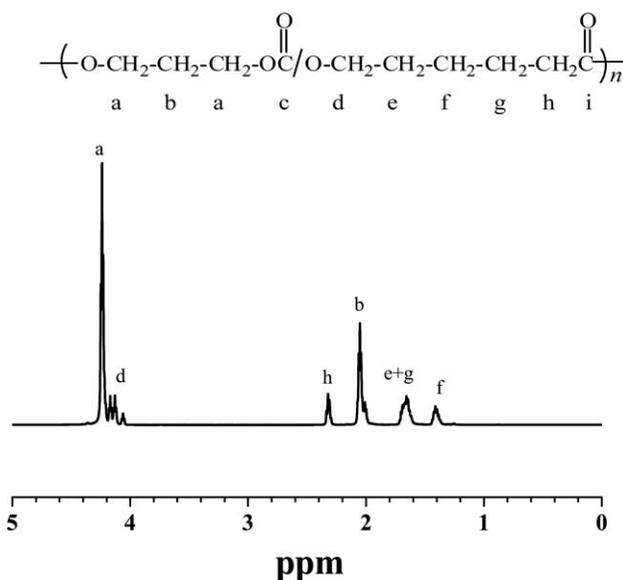


Figure 5 $^1\text{H-NMR}$ spectrum of a copolymer of TMC and CL (Table I, no. 12).

cm^{-1} attributed to $-\text{CH}_2-$, 1736 cm^{-1} attributed to ester $\text{C}=\text{O}$ and the unique ester $\text{C}=\text{O}$ indicates that there is no block structure in the products and copolymers are random prepared in our research.

The copolymer composition was characterized by $^1\text{H-NMR}$ spectrum (Fig. 5). The area of the signal of $[\text{CH}_2-\text{CH}_2-\text{CH}_2]$ group of TMC unit at 2.05 ppm and the signals of $[\text{CH}_2\text{O}]$ group of ϵ -CL unit at 2.3 ppm were employed to calculate the composition of the copolymers. According to the two characteristic resonances in their $^1\text{H-NMR}$ spectra respectively, the mole compositions of the copolymers were in agreement with the monomers feed ratio (See Table I). This demonstrated that both monomers were incorporated into the copolymers.

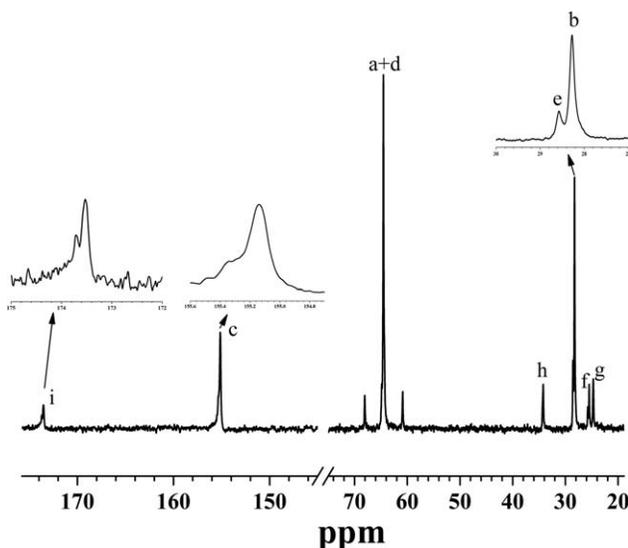


Figure 6 $^{13}\text{C-NMR}$ spectrum of a copolymer of TMC and CL (Table I, no. 12).

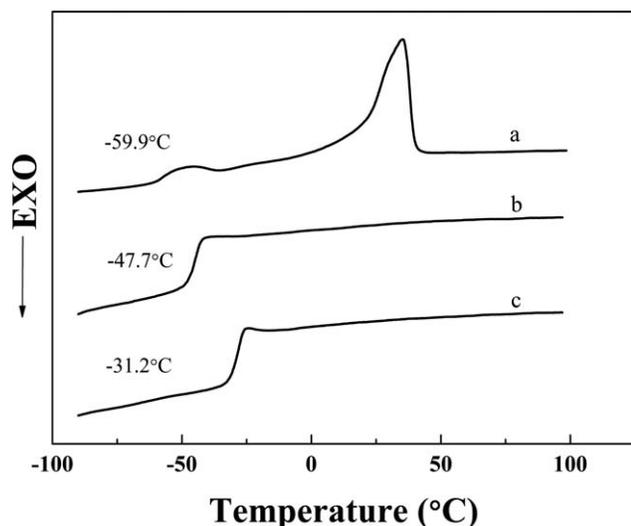


Figure 7 DSC curves of copolymers of TMC and CL. The molar ratio of TMC to CL was (a) 20:80; (b) 50:50; (c) 80:20.

Figure 6 shows the ^{13}C -NMR spectrum of the copolymer. It has been demonstrated that there are no signals at 68.0 and 60.8 ppm, and the signals of carbonyl carbon of TMC and CL units do not split in the ^{13}C -NMR spectrum of the block copolymer of TMC with CL. Therefore, the signals at 68.0 and 60.8 ppm, as well as signal splitting of the carbonyl carbon of TMC and CL units in Figure 6, indicate that the copolymer of TMC and CL catalyzed by $\text{Sn}(\text{Oct})_2$ is not block, but rather a highly random copolymer, which was in a good agreement with the result proved by FTIR spectrum.

Thermal properties

The thermal properties of the copolymers of TMC and CL were investigated with DSC. The characteristic DSC curves, as examples, are shown in Figure 7.

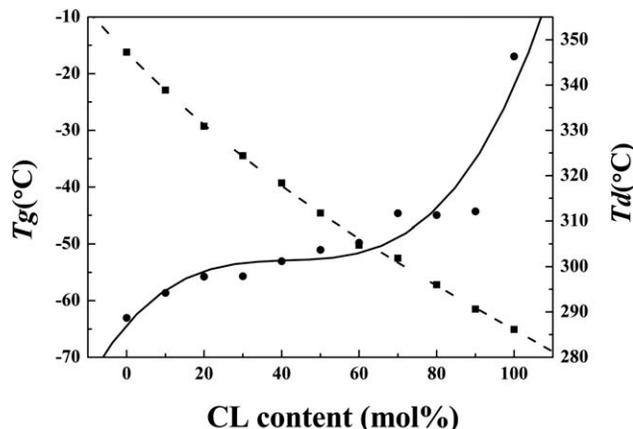


Figure 8 Thermal properties of TMC-CL copolymers as a function of the CL content. (■) Experimental glass transition temperature (T_g); (...) Fox equation; (●) Thermal degradation temperature (T_d).

The copolymer structure can be further verified by DSC analysis. According to the DSC test, all the copolymers showed a single glass transition temperature ranging from -65.1°C for PCL to -16.2°C for PTMC, confirming the random nature of the copolymers because block copolymer has two T_{gs} .²⁷ Besides, the general tendency is that the glass transition temperature (T_g) decreased while increasing the content of CL unit, according to Figure 8.

The glass transition temperature is an important parameter in connection with structures and properties, which is related to the molecular structure and motion. Copolymerization could endue the copolymers with distinct performances result from the respective homopolymers; For random copolymers, Fox derived the following equation that allows the estimation of the glass transition temperature of a copolymer based on the glass transition temperatures of the respective homopolymers²⁸:

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}}$$

Here W_1 and W_2 refer to the weight fraction of the two comonomers and T_{g1} and T_{g2} refer to the glass transition temperatures of the two corresponding homopolymers.

The good agreement of the experimental results with the model (Fig. 8) also indicates that the range of compositions of the copolymers agreed with the monomers feed ratio.

The polymerization conditions such as reaction temperature and time had an important influence on the thermal properties of the copolymers. The thermal properties data of the copolymers synthesized under different conditions are integrated in Table II. It is clear that the T_g of the copolymers, obtained at higher temperature with the same reaction time, was high. This result implied that the reactivity of TMC was higher at 150°C than that at 110°C , and TMC entered the polymeric chains preferentially to form long PTMC segments and resulted in higher glass

TABLE II
The Glass Transition Temperature of the Copolymers Obtained at Different Reaction Temperatures and Polymerization Times

No.	TMC content (mol %)		M/C	T	t	T_g
	Feeding	Polymer ^a		$^\circ\text{C}$	h	$^\circ\text{C}$
3	80	78.9	5000	130	24	-31.2
12	80	77.8	5000	110	24	-32.2
13	80	81.1	5000	150	24	-29.4
14	80	81.7	5000	130	48	-28.5
15	80	81.0	5000	130	72	-29.8

^a Determined by ^1H -NMR.

TABLE III
Mechanical Properties of the TMC-CL Copolymers^a

No.	T/C monomer	M_n	M_w/M_n	E^b	σ_m^c	ϵ_m^d	σ_b^e	ϵ_b^f
	mol %	$\times 10^5$		MPa	MPa	%	MPa	%
1	100 : 0	2.85	1.08	9.50	18.08	941.64	10.41	915.71
2	90 : 10	2.66	1.10	9.17	2.98	1325.80	2.14	1326.1
3	70 : 30	2.51	1.11	4.51	1.00	116.57	0.85	157.73
4	50 : 50	2.53	1.11	2.75	0.58	86.32	0.43	125.80
5	30 : 70	2.34	1.13	2.26	0.37	55.28	0.03	1267.49
6	10 : 90	2.50	1.11	143.16	23.91	1029.10	20.22	1209.56
7	0 : 100	2.80	1.08	261.61	27.67	825.93	25.17	826.56

^a The experimental conditions of synthesis are reported in Table I and the copolymers were compression molded into 2 mm thick films at 130°C.

^b E = Young's modulus.

^c σ_m = tensile stress.

^d ϵ_m = tensile strain.

^e σ_b = tensile stress at break.

^f ϵ_b = tensile strain at break.

transition temperature. The effect of copolymerization time was nearly the same as that of reaction temperature.

The crystalline state of the copolymers depends on their compositions. When the content of TMC unit in the copolymer is high, e.g., above 20 mol %, the copolymers are amorphous and there is no melting temperature (T_m) appears, whereas at lower contents they are semicrystalline and T_m increased while decreasing TMC content. This may be because the introduction of TMC in the copolymer destroyed the regularity of the PCL chain, and thus resulted in the variation of the T_m .

The thermal stabilities of copolymers were detected with TGA. The results show that the temperatures at which the initial weight loss occurred (T_d) were greater than 280°C and T_d increased gradually while increasing CL unit, indicating that all the polymers had good thermal stabilities (Fig. 8).

Mechanical properties

The mechanical properties of compression-molded specimens of the prepared TMC and CL copolymers as well as those of the corresponding homopolymers are listed in Table III. What is particularly worth mentioning is that thermal processing did not have a significant effect on the polymer molecular weights and none of the polymers suffered thermal degradation under the applied processing conditions.

All the copolymers containing TMC content above 20 mol % had a low Young's modulus because of their low T_g and amorphous nature, and the values of the initial Young's modulus as well as the tensile stress of the copolymers decrease with increasing TMC content. This effect is explained by a partial decrease in the crystallinity of the copolymer.²⁹ The copolymers with TMC content between 30 and 70

mol % are weak, having very low strengths and deform irreversibly at very low stresses.

CONCLUSIONS

Random copolymers of TMC and CL were synthesized in the presence of $\text{Sn}(\text{Oct})_2$, verified by FTIR and ^{13}C -NMR. The effects of feeding dose, polymerization temperature and time on the molecular weight and properties of the copolymers were investigated. The compositions of the copolymers were perfectly controlled by the reaction conditions and in agreement with the monomers feed dose. High molecular weight copolymers were prepared and narrow M_w/M_n was obtained by adjusting the monomers feed dose and changing catalyst content in feed, which would affect the molecular weight and distribution of copolymers in a great degree. The obtained results showed that the thermal and mechanical properties of the polymers are strongly determined by the molar composition. Therefore, copolymers of TMC and CL with different thermal behaviors can be obtained by adjusting the copolymer compositions. These random copolymers, with special properties under the control of their molecular weights, are expected to have potential application as implanted devices. The degradability in *vitro/vivo*, release behaviors using gestodene as model and the suitability of the copolymers based on trimethylene carbonate and ϵ -caprolactone for the preparation of biomedical implants are being investigated in our group.

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