

## STUDIES ON THE DEGRADATION OF POLY(L-LACTIDE-*r*-TRIMETHENE CARBONATE) COPOLYMERS\*

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**Abstract** Biodegradable poly(L-lactide-*r*-trimethene carbonate) copolymers (P(LLA-*co*-TMC)) with different compositions were synthesized. The degradation of the copolymers was carried out in phosphate buffer saline solutions (pH = 7.4) at 37 °C. The compositions, structure and properties of the copolymers in degradation were characterized with <sup>1</sup>H-NMR, DSC, XRD, GPC, and SEM. The weight loss of the P(LLA-*co*-TMC) 50/50 was much faster than that of P(LLA-*co*-TMC) 85/15 and PLLA homopolymer. Interestingly, though the molecular weight of the copolymers decreased greatly during degradation, the compositions were rarely varied. After long time degradation, the PLLA segments were induced to crystallize in the P(LLA-*co*-TMC) 85/15 copolymer. The SEM observation of the surface and cross-section of P(LLA-*co*-TMC) 85/15 copolymer films found it was similar to the bulk degradation of PLLA homopolymer.

**Keywords:** Copolymer; Poly(L-lactide-*r*-trimethene carbonate); Degradation; Crystallization.

### INTRODUCTION

In the past decades, biodegradable polymers have been attracted much interest to chemists and biomaterials scientists due to their great therapeutic performances in medical applications such as suture, drug carriers and tissue engineering scaffolds<sup>[1–6]</sup>. Polylactide (PLLA) is one of the most commonly used biodegradable polymers for its excellent properties in biocompatibility, biodegradability, non-immunogenicity and mechanical properties<sup>[7, 8]</sup>. However, PLLA was stiff and degraded slowly due to its high crystallinity, which limited its medical applications.

Copolymerization is an important strategy to modify the stiffness and degradation time of PLLA. Lactones were reported to copolymerize with L-lactide (LLA) to result in flexible and degradation tunable PLLA based copolymers<sup>[9–11]</sup>. Aliphatic polycarbonates are amorphous, elastic and biodegradable polymers, which are preferable for the modification of PLLA to increase the flexibility and avoid the acidity in degradation products. The aliphatic polycarbonates were usually synthesized by the ring-opening polymerization of trimethylene carbonate (TMC) and its derivatives<sup>[12–17]</sup>. Albertsson synthesized the copolymers of LLA and TMC and the copolymers were successfully shaped porous scaffolds for tissue engineering<sup>[18–21]</sup>. Feijen studied the *in vivo* behaviors of PTMC and the copolymers of PTMC and PDLLA, the results demonstrated that PTMC and its

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copolymers were suitable for fabricating degradable devices for short- and long-term applications in soft tissue engineering<sup>[22, 23]</sup>.

Considering the degradation mechanisms of PLLA and PTMC, they were very different. Pitt studied the hydrolysis of PLLA in details and defined the degradation of PLLA as “bulk degradation mechanism”<sup>[24]</sup>. The ester bonds in the backbones were cleaved under the attack of water, and thus the polymers were degraded. The polycarbonates could not be hydrolyzed but degraded *via* “enzyme-catalyzed” mechanism<sup>[25, 26]</sup>, they could only be degraded in the presence of enzymes. For PLLA-polycarbonate copolymers, what the degradation behaviors of the copolymers would be? How the polycarbonate segments affected the degradation of PLLA in hydrolysis? To our best knowledge, there was rare degradation study on PLLA-polycarbonate copolymers.

In our previous work<sup>[5]</sup>, we synthesized the random copolymers of P(LLA-*r*-TMC) *via* ring-opening polymerization. The copolymers were fabricated into cell scaffolds and the introduction of TMC in PLLA was favorable for cell proliferation. In this paper, the degradation of P(LLA-*r*-TMC) copolymers with different compositions was investigated. The weight loss of the copolymers was tested. The compositions, structure and properties of the copolymers during degradation were characterized with <sup>1</sup>H-NMR, DSC, XRD, GPC, and SEM.

## EXPERIMENTAL

### Materials

L-lactide (LLA) was purchased from Bright China Industrial Co. Ltd (Shenzhen, China) and recrystallized in anhydrous toluene for three times. Trimethylenecarbonate (TMC) was synthesized according to the method previously reported<sup>[5]</sup>. Stannous octanoate (Sn(Oct)<sub>2</sub>) was purchased from Aldrich and used as received. Dichloromethane and other chemicals were analytical pure reagents from Kelong Chemical Co. (Chengdu, China) and used as received.

### Measurements

<sup>1</sup>H-NMR spectra were performed on a Bruker Avance II NMR spectrometer at 400 MHz using CDCl<sub>3</sub> as a solvent with 0.5% tetramethylsilane as the internal standard. Differential scanning calorimetry (DSC) measurements were recorded on a TA DSC Q2000. The measurement procedure was conducted as follows: the samples were cooled from room temperature to −80 °C at a rate of 5 K/min and held at −80 °C for 5 min, the samples were then heated to 200 °C at a rate of 5 K/min. X-ray diffraction (XRD) measurements were recorded on a Philips X'Pert Pro MPD XRD analyzer with a Cu Kα ( $\lambda = 0.154$  nm) radiation source, supplied voltage and current were set to 40 kV and 25 mA, respectively. The samples were scanned with a step size of 0.06° from 2° to 40°. The molecular weight ( $M_n$  and  $M_w$ ) and the molecular weight distribution ( $M_w/M_n$ ) of the copolymers were determined by GPC (a Waters 1515 Isocratic HPLC Pump and a 2414 Refractive Index Detector) with respect to polystyrene standards; the samples were analyzed at 25 °C with CHCl<sub>3</sub> as an eluent at a flow rate of 1.0 mL/min. The samples' surface and cross-section morphologies were observed by using a HITACHI S-4800 scanning electron microscope (SEM).

### The Synthesis of P(LLA-*r*-TMC) Copolymers

The purified monomers of L-LA and TMC were mixed with different ratios and put into polymerization tubes. Sn(Oct)<sub>2</sub> was used as the catalyst, the content of Sn(Oct)<sub>2</sub> was 0.05 wt% to the total weight of monomers. The polymerization tubes were purged with nitrogen and degassed to remove oxygen and trace water. The tubes were sealed under vacuum and placed in an oil bath under 130 °C for 24 h. After polymerization, the products were dissolved in CHCl<sub>3</sub>, concentrated and precipitated with CH<sub>3</sub>OH. The precipitates were dried in vacuum at room temperature for 2 days.

### The Preparation of Films for Degradation

The P(LLA-*r*-TMC) copolymers, PLLA and PTMC homopolymers were dissolved in CH<sub>2</sub>Cl<sub>2</sub>, the solutions were cast onto glass plates. After the solvent was evaporated, the films were dried in vacuum at room temperature for 2 days. The thickness of the films was about 0.2 mm. The films were cut into small pieces with approximate

sizes of 10 mm × 10 mm for degradation, and the weight of each piece was recorded.

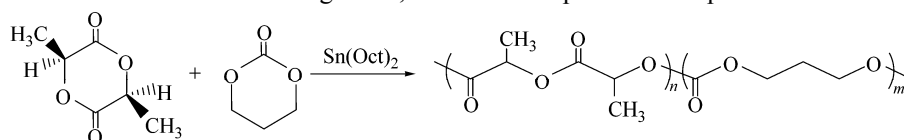
The degradation pieces of the P(LLA-*r*-TMC) copolymers, PLLA and PTMC homopolymers films were put in PE tubes with the capacity of 5 mL distilled water. The degradation study was performed in a phosphate buffer saline (PBS) solution with pH = 7.4 at 37 °C, 4 mL of PBS solution in the tubes was replaced by fresh PBS solution every week. The degraded film pieces in each time interval were washed with distilled water for three times and dried in vacuum at room temperature to constant weight. All the degradation samples were carried out in triplicate to ascertain the reproducibility. The mass loss of the degradation samples was calculated according to the following formula.

$$\text{Mass loss (\%)} = (1 - W_t/W_0) \times 100\%$$

$W_0$ : the initial weight of the degraded specimen,  $W_t$ : the final weight of the degraded specimen.

## RESULTS AND DISCUSSION

The synthesis of the P(LLA-*r*-TMC) copolymers was presented in Scheme 1. The copolymerization was carried out in the presence of stannous octoate as catalyst. PLLA and PTMC homopolymers and two copolymers with the TMC contents of 15% and 50% in the copolymers were synthesized. The degradation behavior of the two copolymers together with the two homopolymers of PLLA and PTMC was investigated. The compositions of the copolymers were consistent with the feeding doses, which were reported in our previous research<sup>[5]</sup>.



**Scheme 1** The synthetic route of poly(L-lactide-*r*-trimethene carbonate) copolymer

Mass loss is an important parameter to demonstrate the degradation of polymers. The mass losses of the four specimens were weighted and presented in Fig. 1. It was clear that the mass losses of the copolymers were faster than those of PLLA and PTMC homopolymers. Nearly no mass loss was observed in PTMC specimens. The PTMC specimens seemed to keep the constant weight during degradation. In the early period (within the first 40 days), the mass losses of all the four specimens were not obvious, which were lower than 5%. With the degradation time elongated, the mass losses of PLLA, P(LLA-*r*-TMC) 85/15 and P(LLA-*r*-TMC) 50/50 were accelerated. The P(LLA-*co*-TMC) 50/50 specimen showed significantly higher degradation rate than the other three samples, and in the subsequent degradation time, the mass losses of the P(LLA-*r*-TMC) 50/50 specimens degraded for 140, 215 and 309 days were  $(7.3 \pm 0.8)\%$ ,  $(18.0 \pm 1.9)\%$  and  $(38.2 \pm 4.9)\%$ .

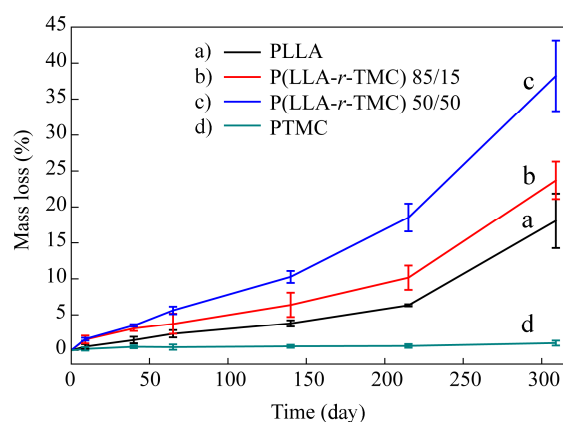


**Fig. 1** The weight loss of PLLA, P(LLA-*r*-TMC) 85/15, P(LLA-*r*-TMC) 50/50 and PTMC in the degradation process

For biodegradable copolymers, the composition variation is a necessary parameter to learn the degradation behaviors. The  $^1\text{H}$ -NMR spectra were used to measure the compositions of the P(LLA-*r*-TMC) copolymers. The  $^1\text{H}$ -NMR spectra of P(LLA-*co*-TMC) 85/15 copolymers in different degradation time were presented in Fig. 2. There were two distinct peaks of the protons in the PLLA segments. The chemical shifts of  $\text{CH}$  and  $\text{CH}_3$  in LLA units appeared at  $\delta = 5.2$  and 1.6, respectively. There were also two peaks of proton signals in the PTMC segments, the chemical shifts of  $\text{OCH}_2$  and  $\text{CH}_2\text{O}$  in TMC units were at the same site of  $\delta = 4.2$ , the peak at  $\delta = 2.0$  was assigned to the protons in  $\text{CH}_2\text{CH}_2\text{CH}_2$ . The compositions of the copolymers were determined from the integration ratio between the protons of  $\text{CH}_2\text{O}$  in TMC units at  $\delta = 4.2$  and those of  $\text{CH}$  in LLA units at  $\delta = 5.2$ . The calculated results were presented in Table 1.

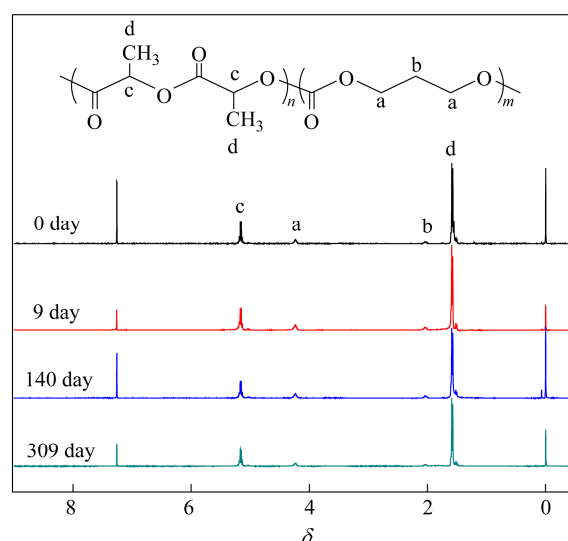


**Fig. 2** The  $^1\text{H}$ -NMR spectra of P(LLA-*r*-TMC) 85/15 copolymer degraded for 9, 140 and 309 days

**Table 1.** The composition variations of degraded P(LLA-*r*-TMC) copolymers

| Sample | Compositions (LLA %) |       |        |        |         |         |         |
|--------|----------------------|-------|--------|--------|---------|---------|---------|
|        | 0 day                | 9 day | 40 day | 65 day | 140 day | 215 day | 309 day |
| 85/15  | 84.6                 | 83.1  | 83.6   | 83.4   | 83.7    | 83.5    | 85.1    |
| 50/50  | 49.4                 | 50.3  | 49.8   | 49.5   | 49.2    | 46.3    | 45.1    |

The composition variation of the P(LLA-*r*-TMC) copolymers was very interesting, the compositions of the degraded copolymers were varied little in both the copolymers with 85% and 50% LLA contents. For the P(LLA-*r*-TMC) 85/15 copolymer, the LLA contents in different time intervals were ranged from 83.1% to 85.1%. The LLA contents in the P(LLA-*r*-TMC) 50/50 copolymers were around 50% whenever the degradation time was 9 days or 140 days. It was very different from the composition variation of other biodegradable copolymers which were composed of polyesters<sup>[27]</sup>. The compositions in copolymers were nearly the same as those in feeding doses (Table 1), it implied that the reactivity of the two monomers was comparable in the ring-opening polymerization. The TMC units were dispersed in PLLA segments homogeneously. During degradation, the copolymers were degraded into oligomers, whose compositions were the same as those of the copolymers. The oligomers were dissolved in degradation medium to result in the weight loss, as TMC units were homogeneously dispersed in the oligomers, thus the compositions of the copolymers were not changed during degradation.

GPC was used to test the molecular weight variation of the copolymers. The GPC curves of the four polymers are presented in Fig. 3. The molecular weights of PLLA, P(LLA-*r*-TMC) 85/15 and P(LLA-*r*-TMC) 50/50 were decreased when the degradation time was elongated to 309 days. The polydispersity of the three

copolymers was widened too. For PTMC polymer, both the peak shape and elution time were nearly the same, it implied that the degradation of PTMC was not a hydrolysis process.

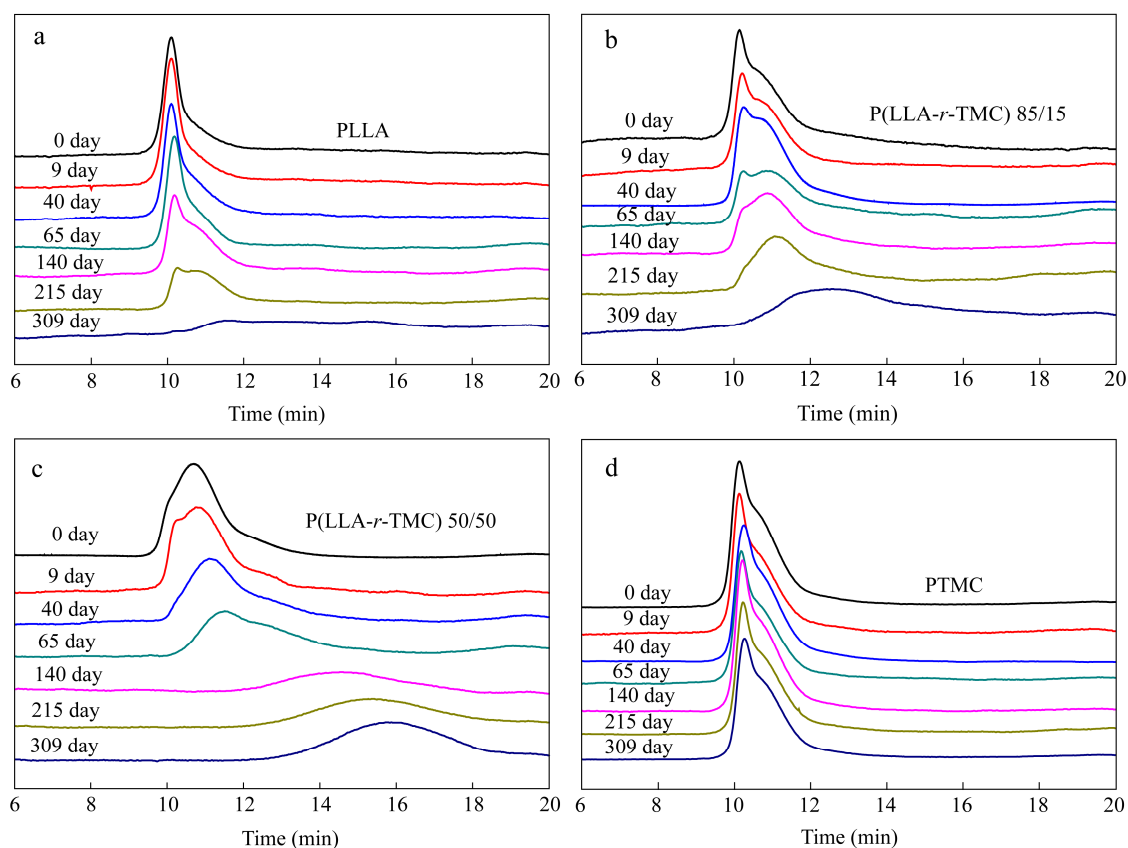


**Fig. 3** The GPC curves of PLLA, P(LLA-*r*-TMC) 85/15, P(LLA-*r*-TMC) 50/50 and PTMC after different degradation for different days

The calculated molecular weights and the polydispersities of the copolymers are summarized in Table 2. The molecular weights of PLLA, P(LLA-*r*-TMC) 85/15 and P(LLA-*r*-TMC) 50/50 decreased from  $10.5 \times 10^4$ ,  $9.6 \times 10^4$  and  $8.9 \times 10^4$  to  $3.9 \times 10^4$ ,  $3.3 \times 10^4$  and  $0.4 \times 10^4$  when the degradation time was 309 days. The molecular weight of the P(LLA-*r*-TMC) 50/50 copolymer decreased the fastest. The decrease of molecular weight demonstrated that the degradation was happened in the PLLA and copolymers. The polydispersities of the three polymers of PLLA, P(LLA-*r*-TMC) 85/15 and P(LLA-*r*-TMC) 50/50 widened from 1.25, 1.20 and 1.11 to 2.83, 2.30 and 2.03. As PTMC was not degraded in PBS solution, its molecular weight and polydispersity were fixed. They were kept at around  $9.3 \times 10^4$  and 1.08, respectively.

**Table 2.** The molecular weights and polydispersities of the copolymers in degradation

| Sample | 0 day                |      | 9 day                |      | 40 day               |      | 65 day               |      | 140 day              |      | 215 day              |      | 309 day              |      |
|--------|----------------------|------|----------------------|------|----------------------|------|----------------------|------|----------------------|------|----------------------|------|----------------------|------|
|        | $M_n \times 10^{-4}$ | PDI  | $M_n \times 10^{-4}$ | PDI  | $M_n \times 10^{-4}$ | PDI  | $M_n \times 10^{-4}$ | PDI  | $M_n \times 10^{-4}$ | PDI  | $M_n \times 10^{-4}$ | PDI  | $M_n \times 10^{-4}$ | PDI  |
| PLLA   | 10.5                 | 1.25 | 10.5                 | 1.27 | 10.2                 | 1.31 | 10.0                 | 1.30 | 9.3                  | 1.47 | 8.7                  | 1.63 | 3.9                  | 2.83 |
| 85/15  | 9.6                  | 1.20 | 9.5                  | 1.22 | 9.4                  | 1.30 | 8.7                  | 1.42 | 6.5                  | 1.53 | 4.9                  | 1.74 | 3.3                  | 2.30 |
| 50/50  | 8.9                  | 1.11 | 8.4                  | 1.12 | 5.7                  | 1.28 | 4.3                  | 1.34 | 1.1                  | 1.35 | 0.7                  | 1.61 | 0.4                  | 2.03 |
| PTMC   | 9.5                  | 1.09 | 9.4                  | 1.07 | 9.4                  | 1.13 | 9.3                  | 1.07 | 9.3                  | 1.08 | 9.3                  | 1.08 | 9.2                  | 1.11 |

The degradation of polyesters usually induced crystallization. X-ray diffraction (XRD) was used to examine the crystalline structure of the copolymers. As we knew that the copolymerization would destroy the regularity of PLLA chains and thus the crystalline capability of PLLA was reduced. The degradation of PLLA was mainly occurred in amorphous zones. The amorphous zones were more accessible to water to hydrolyze the ester bonds in the backbones. The XRD spectra of P(LLA-*r*-TMC) 85/15 copolymers in different degradation time are shown in Fig. 4. As shown in Fig. 4, the P(LLA-*r*-TMC) 85/15 copolymer was initially amorphous before degradation. When the copolymer was degraded for 215 days, a weak crystal peak of PLLA was appeared in the XRD spectrum. The PLLA crystal peaks were strengthened when the degradation time was elongated to 309 days. A strong diffraction was detected at  $16.8^\circ$  and a weak one at  $19.2^\circ$ , they were the characteristic diffraction peaks of PLLA crystals.

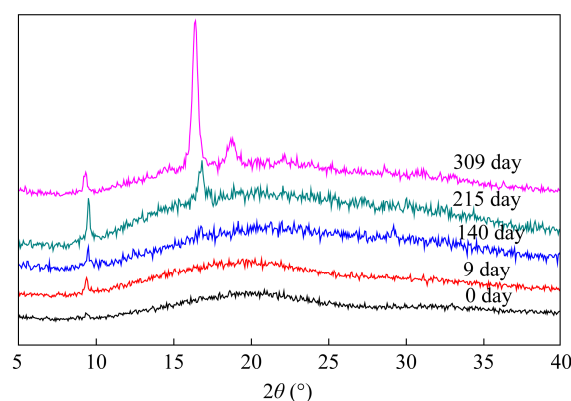


**Fig. 4** The XRD spectra of P(LLA-*r*-TMC) 85/15 degraded for 9, 140, 215 and 309 days

DSC was used to evaluate the thermal property changes in degradation. The DSC curves of P(LLA-*r*-TMC) 85/15 copolymers degraded for 9, 140 and 309 days are presented in Fig. 5. The thermal properties of the P(LLA-*r*-TMC) 85/15 copolymers degraded for different time are shown in Table 3. It was clear that the glass transition temperature ( $T_g$ ) of the copolymer decreased with increasing degradation time. The  $T_g$  of original copolymer was around  $50.0^\circ\text{C}$ , and that of copolymer degraded for 309 days was  $44.1^\circ\text{C}$ . The cold crystalline temperature ( $T_c$ ) of the copolymers exhibited the same variation trend as the  $T_g$ s. Interestingly, the melting temperature ( $T_m$ ) of the degraded copolymer was changed little, and it was around  $158^\circ\text{C}$ .  $\Delta H$  is an important parameter to characterize the capability of polymer crystallization. The original P(LLA-*r*-TMC) 85/15 copolymer was amorphous. The  $\Delta H_s$  of the degraded copolymers were 0.3, 0.5, 1.0, 1.7, 2.6 and  $3.5\text{ J/g}$  when the degradation time was 9, 40, 65, 140, 215 and 309 days. The increase of  $\Delta H$  demonstrated that the crystallization capability of PLLA segments was enhanced. The degradation led to shorter PLLA chain lengths in the copolymers, which promoted the mobility of PLLA segments and resulted in high crystallinity<sup>[27]</sup>.

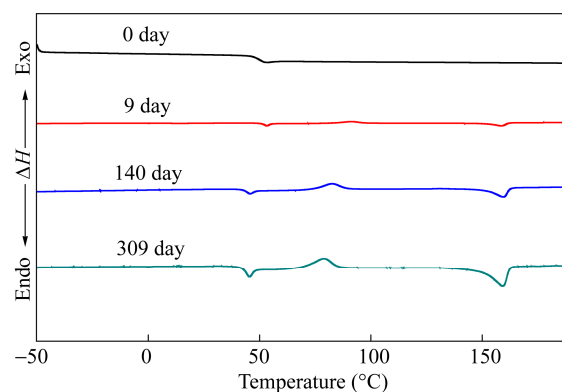
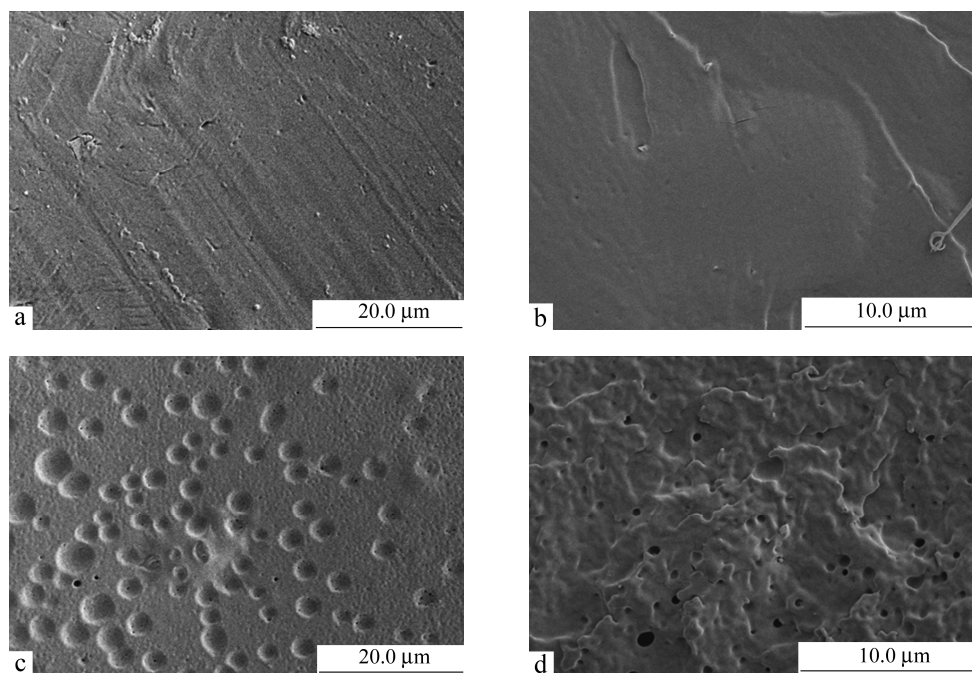


**Fig. 5** The DSC curves of P(LLA-*r*-TMC) 85/15 degraded for 9, 140 and 309 days

**Table 3.** The thermal properties of P(LLA-*r*-TMC) 85/15 in degradation process

| Time (day) | $T_g$ (°C) | $T_c$ (°C) | $T_m$ (°C) | $\Delta H$ (J/g) |
|------------|------------|------------|------------|------------------|
| 0          | 50.0       | —          | —          | —                |
| 9          | 49.2       | 91.2       | 158.7      | 0.3              |
| 40         | 47.3       | 86.2       | 158.6      | 0.5              |
| 65         | 46.4       | 84.5       | 158.6      | 1.0              |
| 140        | 44.6       | 82.7       | 158.9      | 1.7              |
| 215        | 44.4       | 79.0       | 157.9      | 2.6              |
| 309        | 44.1       | 69.8       | 157.5      | 3.5              |

**Fig. 6** The SEM photographs of P(LLA-*r*-TMC) (85/15) films in degradation process: (a) surface degraded for 9 days, (b) cross-section degraded for 9 days, (c) surface degraded for 309 days and (d) cross-section degraded for 309 days

The morphologies of the degraded P(LLA-*r*-TMC) 85/15 copolymer films were observed by SEM (Fig. 6). In the photographs of the copolymers degraded for 9 days, both the surface and cross-section were smooth. After degraded for 309 days, the surface of the film was not smooth, low-lying areas were observed. The cross-section became rough and many small cavities appeared in the cross-section. In the copolymers, PTMC segments were not degraded, only the PLLA segments could be hydrolyzed during the degradation. The degradation mechanism of PLLA was “bulk degradation”. The phenomena of the P(LLA-*r*-TMC) 85/15 copolymer films were conformed to bulk degradation processes.

## CONCLUSIONS

P(LLA-*r*-TMC) copolymers were synthesized by ring-opening polymerization of L-lactide and trimethene carbonate in the presence of stannous octoate as catalyst. The degradation of the copolymers was studied in phosphate buffer saline solutions at 37 °C. The weight loss, composition and molecular weight variations, thermal properties and morphology of the degradation copolymer films were characterized. The weight loss of the P(LLA-*co*-TMC) 50/50 copolymer was much faster than that of P(LLA-*co*-TMC) 85/15 and PLLA homopolymer. Though the molecular weight of the copolymers decreased greatly during the degradation, however, the compositions were rarely changed. PLLA segments were induced to crystallize in the P(LLA-*co*-

TMC) 85/15 copolymer during degradation. The surface and cross-section morphology observation of P(LLA-co-TMC) 85/15 copolymer films demonstrated that the degradation of copolymers were conformed to the bulk degradation mechanism.

## REFERENCES

- 1 Drumright, R.E., Gruber, P.R. and Henton, D.E., *Adv. Mater.*, 2000, 12: 1841
- 2 Tyson, T., Finne-Wistrand, A. and Albertsson, A.C., *Biomacromolecules*, 2009, 10: 149
- 3 Wistrand, A.F. and Albertsson, A.C., *Chinese J. Polym. Sci.*, 2007, 25(2): 113
- 4 Pego, A.P., Vanluyn, M., Brouwer, L.A., Van Wachem, P.B., Poot, A.A., Grijpma, D.W. and Feijen, J., *J. Biomed. Mater. Res.*, 2003, 67A: 1044
- 5 Ji, L.J., Lai, K.L., He, B., Wang, G., Song, L.Q., Wu, Y. and Gu, Z.W., *Biomed. Mater.*, 2010, 5: 045009
- 6 Pego, A.P., Poot, A.A., Grijpma, D.W. and Feijen, J., *J. Control. Release*, 2003, 87: 69
- 7 Wang, L., Cai, C. and Dong, C.M., *Chinese J. Polym. Sci.*, 2008, 26(2): 161
- 8 Wei, J.C., Sun, J.S., Wang, H.J., Chen, X.S. and Jing, X.B., *Chinese J. Polym. Sci.*, 2010, 28(4): 499
- 9 He, B., Bei, J.Z. and Wang, S.G., *Polymer*, 2003, 44: 989
- 10 Lai, K.L., He, B. and Gu, Z.W., *Chinese J. Polym. Sci.*, 2008, 26(2): 177
- 11 He, B., Wan, Y.Q., Bei, J.Z. and Wang, S.G., *Acta Polymerica Sinica (in Chinese)*, 2004, (5): 693
- 12 Artham, T. and Doble, M., *Macromol. Biosci.*, 2008, 8: 14
- 13 Wang, X.L., Zhuo, R.X., Liu, L.J., He, F. and Liu, G., *J. Polym. Sci. A: Polym. Chem.*, 2002, 40: 70.
- 14 Wang, X.L., Zhuo, R.X., Huang, S.W., Liu, L.J. and He, F., *Macromol. Chem. Phys.*, 2002, 203: 985
- 15 He, F., Wang, Y., Feng, J., Zhuo, R.X. and Wang, X., *Polymer*, 2003, 44: 3215
- 16 Lai, K.L., Ji L.J., Long, C.Y., Li, L., He, B., Wu, Y. and Gu, Z.W., *J. Appl. Polym. Sci.*, 2012, 123: 2204
- 17 Long, C.Y., Sheng, M.M., He, B., Wu, Y., Wang, G. and Gu, Z.W., *Chinese J. Polym. Sci.*, 2012, 30(3): 387
- 18 Odelius, K., Plikk, P. and Albertsson, A.C., *Biomacromolecules*, 2005, 6: 2718
- 19 Stridsberg, K. and Albertsson A.C., *J. Polym. Sci. Part A: Polym. Chem.*, 2000, 38: 1774
- 20 Andronova, N. and Albertsson, A.C., *Biomacromolecules*, 2006, 7: 1489
- 21 Odelius, K. and Albertsson, A.C., *J. Polym. Sci. Part A: Polym. Chem.*, 2008, 46: 1249
- 22 Pego, A.P., Grijpma, D.W. and Feijen, J., *Polymer*, 2003, 44: 6495
- 23 Song, Y., Kamphuis, M.M.J., Zhang, Z., Sterk, L.M., Vermes, I., Poot, A.A., Feijen, J. and Grijpma, D.W., *Acta Biomaterialia*, 2010, 6: 1269
- 24 Pitt, C.G. and Gu, Z.W., *J. Control. Release*, 1987, 4: 283
- 25 Zhang, Z., Kuijer, R., Bulstra, S.K., Grijpma, D.W. and Feijen, J., *Biomaterials*, 2006, 27: 1741
- 26 Zhang, Z., Zou, S., Vancso, G.J., Grijpma, D.W. and Feijen, J., *Biomacromolecules*, 2005, 6: 3404
- 27 He, B., Bei, J.Z. and Wang, S.G., *Polym. Adv. Technol.*, 2003, 14(9): 645