

Synthesis and Thermal Properties of Novel Biodegradable ABCBA Pentablock Copolymers from Poly (Ethylene glycol), L-Lactide and p-Dioxanone

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ABSTRACT: *In this work, new biodegradable ABCBA type pentablock copolymers with different mole ratio of L-lactide and PPDO-b-PEG-b-PPDO triblock copolymer were synthesized and characterized. In the first step, PPDO-b-PEG-b-PPDO triblock copolymer was synthesized via a ring-opening polymerization of P-Di Oxanone (PDO) monomer with Poly (Ethylene Glycol) (PEG) using stannous octoate (Sn(Oct)₂) as the catalyst. In the second step, L-lactide monomers (60 or 80 mole ratio) as the end blocks were added to the resulting prepolymer in presence of stannous octoate (Sn(Oct)₂) catalyst. In the first step, Poly (Ethylene Glycol) (PEG) and, in the second step, triblock copolymer acts as the macro-initiator. The obtained pentablock copolymers were identified by ¹H and ¹³CNMR spectroscopy. Intrinsic viscosity of the resulting copolymers was measured via dilute solution viscometry in chloroform as the solvent. The thermal properties (such as melting points, melting enthalpy and crystallinity) and thermal degradation behavior were studied by Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA). From the obtained results, it was seen that the poly (L-lactide) end blocks show similar crystallization behavior like poly (L-lactide) homopolymer and also melting temperature of pentablock copolymers rise with an increase in L-lactide content.*

KEY WORDS: *Biocompatibility, Biodegradability, Pentablock copolymer, Ring-opening polymerization, Copolymerization.*

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INTRODUCTION

Biodegradable aliphatic polyesters constitute a most important field in polymer science that has been widely applied to make various types of medical devices such as, pharmacological (biodegradable controlled-release drug delivery systems) [1], multi and monofilament surgical sutures [2], absorbable nerve guides [3] and other biomedical applications. These materials can be degraded into biocompatible components in vivo [4]. In the family of aliphatic polyesters, poly (L -lactide) (PLLA) and poly (p-dioxanone) (PPDO) have attracted the attention of many researchers. They have excellent tissue compatibility which can be used in living body satisfactory [5], and be decomposed to none-toxic inorganic components (CO_2 and H_2O) [6]. It has been reported that poly (L -lactide) (PLLA) has good biocompatibility and physical properties. However, low deformation at break and high modulus has limited the applications of poly (L -lactide) (PLLA) [7]. Poly (1, 4-dioxan-2-one) (PPDO) is a semi-crystalline biodegradable poly (ether-ester) with good mechanical and degradation properties that can be used for general applications [8]. Biodegradability is the main advantage of poly (p-dioxanone) (PPDO), and the presence of an ether bond and additional methylene unit in its molecular structure endows great flexibility and hydrophilicity to poly (p-dioxanone) (PPDO), but also causes marked hydrolysis [9]. Poly (ethylene glycol) (PEG) is the polyether with outstanding physicochemical and biological properties including the solubility in water and organic solvents, hydrophilic properties, and lack of toxicity, which allow PEG to be used for many biomedical applications [10].

Although, homopolyesters widely are used in making biomedical devices, but their applications are limited by their inherent brittleness, low mechanical properties, water insolubility, and no uniform degradation rate. Hence, their properties can be significantly enhanced and broadened by modification via copolymerization. In particular, block copolymerization may offer a broader spectrum of mechanical and degradation properties to meet the demands of various applications [11]. Numerous triblock copolymers from L -lactide (L-LA), poly (p-dioxanone) (PPDO) and Poly (ethylene glycol) (PEG) such as PPDO-b-PEG-b-PPDO [12-14]; PLA-ran-PPDO-b-PEG-b-PLA-ran-PPDO [15-17]; have been synthesized that above mentioned undesirable properties

of each homopolymer were modified via block copolymerization, but a few studies on the preparation of pentablock copolymers have been reported.

For the evaluating effects of individual segments in general properties of copolymer, tri and pentablock copolymers from Poly (ethylene glycol) (PEG), p-dioxanone (PDO) and L -lactide (L-LA) were prepared and characterized in this study. In the first step, PPDO-b-PEG-b-PPDO triblock copolymer was synthesized and used as two functional groups macro-initiator for the preparation of pentablock copolymers by reaction with further L -lactide (L-LA). The structures of the block copolymers were characterized using ^1H and ^{13}C NMR spectroscopy. Thermal properties of the copolymers were investigated by DSC and TGA thermograms. In these block copolymers, each block individually insert its properties in resulting copolymers, which improve thermal and mechanical properties of copolymers. These materials with resulting properties may have been potential medical device applications as carriers for controlled drug delivery, absorbable surgical suture, absorbable surgical clips and staples where improved toughness and ductility are desirable.

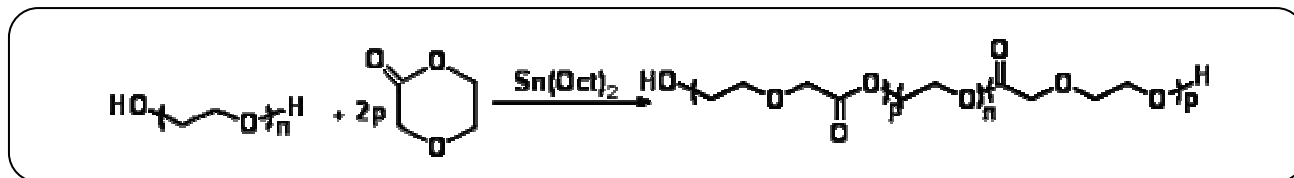
EXPERIMENTAL SECTION

Materials

The stannous octoate ($\text{Sn}(\text{Oct})_2$, Sigma, ST. Louis, MO) was used as received. P-dioxanone (PDO) was purchased from Biopolytech (Korea) company and dried over CaH_2 for 48h, distilled under reduced pressure just before polymerization. Poly (ethylene glycol) (PEG, $\bar{M}_n = 15000$), was purchased from Merck (Germany) and used without any further purification. All chemicals or solvents were reagent grade (Merck Inc.) and dried or purified according to the established procedure [18]. L -lactide (L-LA) was prepared from 90% L-lactic acid solution (Merck Inc.), according to *Gilding* [19].

Measurement

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained with a Bruker-DRX-500 spectrometer at room temperature, using CDCl_3 , as solvent and Tetra Methyl Silane (TMS) as internal reference. Differential Scanning Calorimetry (DSC) measurements were carried out on a differential scanning calorimeter (TA) DSC-60 at the heating rate of $10^\circ\text{C}/\text{min}$,



Scheme 1

in range of the ambient temperature to near the degradation temperature of any homo and copolymers. Thermogravimetric measurements (TG/DTG) were conducted with a TGA Q50 V6.3 TA instruments thermogravimetric analyzer in platinum pans at the heating rate of 10°C/min, until percent weight be decreased to zero under a steady flow of nitrogen. The PLA/PPDO/PEG molar ratios in copolymers were characterized by ¹H-NMR spectra, and TGA thermograms. Intrinsic viscosities of homo and copolymers were measured at 30°C, with C= 0.5g/dL in CHCl₃ using an Ubbelohde viscometer.

Methods

Synthesis of PPDO-b-PEG-b-PPDO prepolymer

In the first-step reaction, synthesis of a 46/54 mole% (PPDO-b-PEG-b-PPDO) prepolymer was performed in a polymerization tube under a vacuum condition with magnetic stirrer. Certain amount of poly (ethylene glycol) (PEG) and Sn(Oct)₂, in chloroform solution were charged into a polymerization tube and kept under vacuum at 70°C, for 1h to remove all volatiles. Then calculated amount of fresh distilled p-dioxanone (PDO) monomer was added and kept under vacuum at 70°C, for 2h. Polymerization tube was sealed under vacuum and located in silicon oil bath at 100°C, for 20h and at 80°C for 48h. Subsequently, tube was broken and contents dissolved in chloroform, and precipitated in methanol. At final, resulting triblock copolymers were dried under vacuum at 50°C, for 24h, and used as central segment in synthesis of pentablock copolymers.

Synthesis of pentablock copolymer from L-LA and PPDO-b-PEG-b-PPDO

The preparation of pentablock copolymers was similar to the previously discussed triblock copolymerization. Predetermined amount of dried triblock copolymer (prepolymer) with Sn(Oct)₂ after mixing in chloroform solution, was charged into a glass polymerization tube and kept

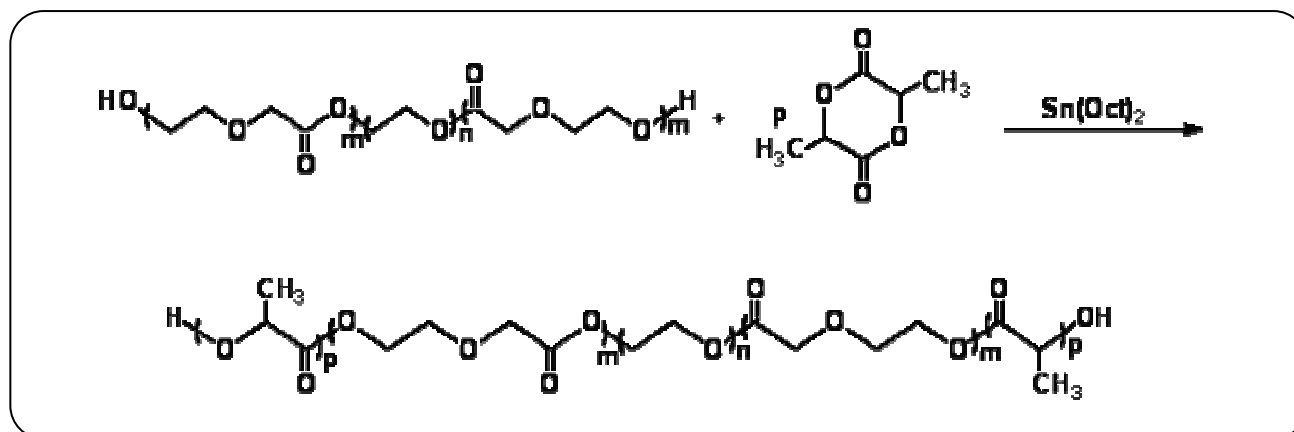
under vacuum at 70°C, for 1h. Under nitrogen atmosphere, the calculated amount of fresh recrystallized L-lactide (L-LA) (60 or 80% mole ratio) was added into the tube content and pentablock copolymer (60 or 80% mole ratio of L-LA) was obtained. Prepolymer easily was dissolved in L-lactide (L-LA) monomer, and homogenous system was obtained in low temperature. Mixture kept under vacuum at 80°C for 2h. Under vacuum condition, glass tube was sealed and immersed in an oil bath at 110°C, for 48h. At final, glass tube was broken and content was dissolved in chloroform, and then precipitated in n-Hexane. The copolymer was dried in vacuum at ambient temperature for 24h.

RESULTS AND DISCUSSION

Hydroxyl-containing materials act as initiator for the ring-opening block copolymerization of various lactones. In this work, the general procedure reported in previous articles [13, 14] was used for block copolymerization of p-dioxanone (PDO) with poly (ethylene glycol) (PEG). The PPDO-b-PEG-b-PPDO triblock copolymer was successfully synthesized and subjected to further polymerization with L-lactide (L-LA) as two end blocks. The copolymerization reaction is given in Scheme 1.

With Sn(Oct)₂ as catalyst, pentablock copolymers (60 or 80 mole ratio of L-LA) were synthesized via ring-opening polymerization by changing the feed proportion of L-lactide (L-LA) and prepolymer. The copolymerization reaction is given in Scheme 2.

Theoretically, two hydroxyl end groups of triblock copolymer would initiate the polymerization with L-lactide (L-LA), and ABCBA type block copolymers could be obtained. Some articles [20-22], have proposed an initiation mechanism for block copolymerization of ring lactones with poly (ethylene glycol) PEG as macro-initiator. This mechanism can be applied for preparation of block copolymerization from L-lactide (L-LA) with triblock copolymer, since the block copolymerization of L-lactide (L-LA) and triblock copolymer by Sn(Oct)₂



Scheme 2

catalyst can proceed via a similar activated complex. In present work, triblock copolymer was added into glass tube, and $\text{Sn}(\text{Oct})_2$ was added after all of the triblock copolymer was melted. When, prepolymer macro-initiator was formed, L -lactide (L-LA) was added. It can effectively avoid producing poly (L -lactide) (PLLA) by this way. Biodegradable aliphatic polyester can be synthesized in melt or in solution. Due to the competitive reactions (chain growth and degradation) in high temperature, molecular weight initially is low. For minimizing the competitive reactions, all the polymerization reactions were carried out at low concentration of catalyst (mole of reacting monomer/ mole of catalyst=3000-5000), low temperature and high reaction time. It can be expected that the molecular weight and intrinsic viscosity be raised under this conditions.

Spectral Characterization

The ^1H NMR spectra shown in Fig. 1, are attributed to typical copolymers with different mole ratio of L -lactide (L-LA) and prepolymer (a: 80/20, b: 60/40). The resonance signals belonging to the two kinds of methine and methyl protons in the repeating PLLA units were observed at 5.20 ppm (f) and 1.60 ppm (a), respectively [23, 24]. The signal occurring at 3.66 ppm (b) was assigned to the methylene protons of poly (ethylene glycol) (PEG). The signals occurring at 3.71 ppm (c), 4.15 ppm (d), and 4.23 ppm (e), can be reasonably assigned to the different methylene protons of PPDO blocks [17]. Copolymers compositions, the ratio of L -lactide /prepolymer, could be calculated from the integrated signals at 5.20 ppm (f), 3.66 ppm (b) and one of the methylene triplets attributed

to the p -dioxanone (PDO) units in the 3.71-4.23 ppm range. As shown in Table 1, the mole fraction of L -lactide (L-LA) in the copolymers was nearly equal to the mole fraction of L -lactide (L-LA) in crude feed, showing that the compositions of resulting pentablock copolymers could be adjusted by varying the feed composition.

Monomer sequencing and block structural of copolymer were determined from ^{13}C NMR spectra. The ^{13}C NMR spectra of two pentablock copolymers are shown in Fig 2. The peaks at 17.03 (a), 69.59 (e) and 169.98 (g) ppm were assigned to the PLLA blocks and the peak at 71.24 (f) ppm was attributed to the poly (ethylene glycol) (PEG) block. The peaks appeared at 64.11 (b), 68.54 (c), and 70.90 (d) ppm were attributed to three methylene units of p -dioxanone (PDO) and also the peak at 170 (h) ppm was assigned to carbonyl carbons of p -dioxanone (PDO) in pentablock copolymers [17]. No peaks due to the random LLA-PDO sequence appeared in expanded carbonyl carbon region, which demonstrated that the block copolymers were free of any random sequence.

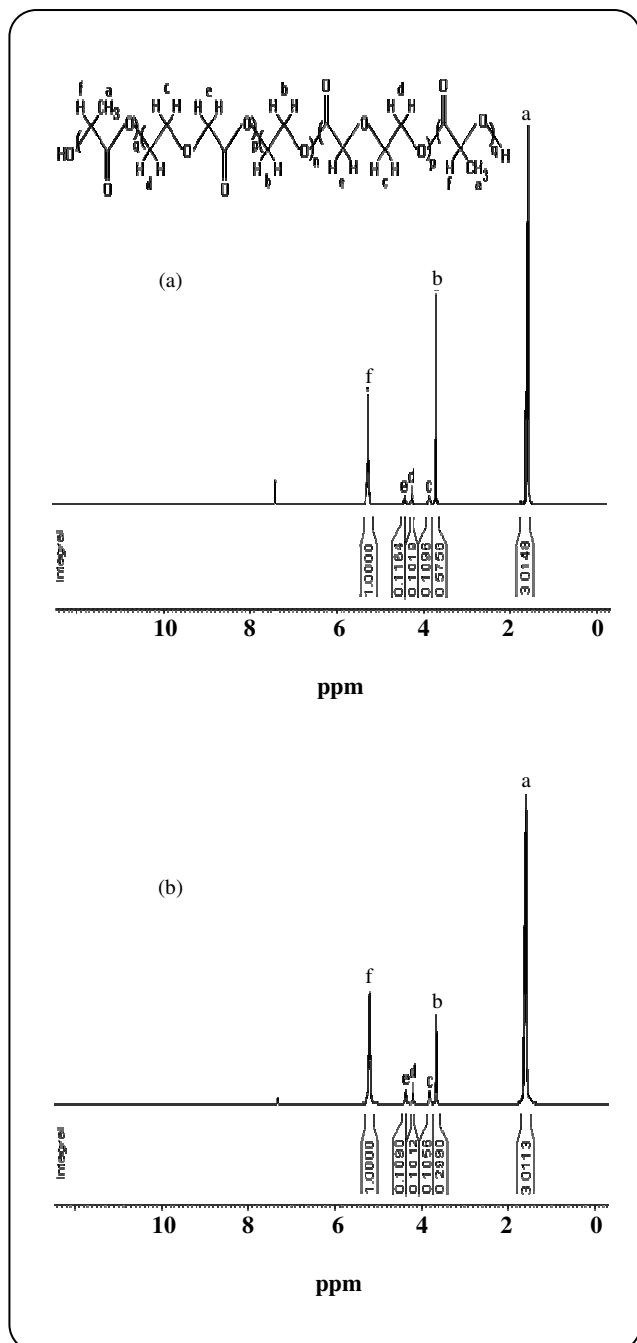
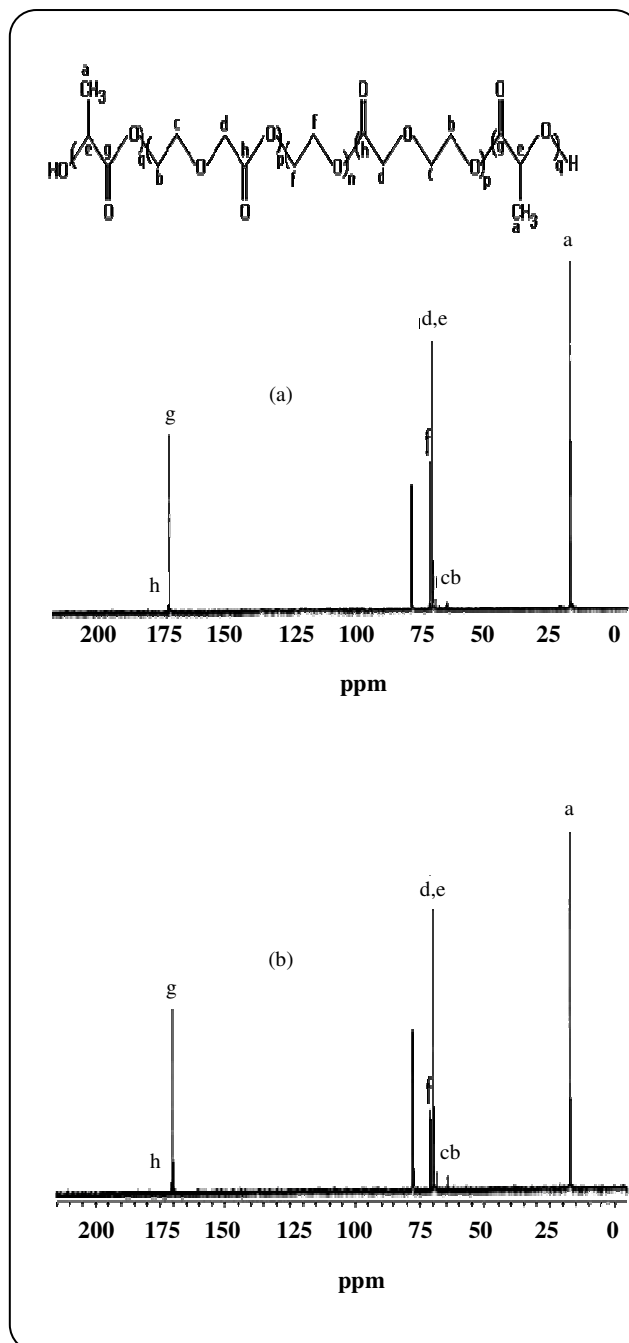
Fig 2 shows that by increasing the mole ratio of L -lactide (L-LA) in copolymer composition, the length of peaks corresponded to the PPDO and PEG is decreased.

Physical Properties

The measured viscosity of homo and copolymers and mole ratio of each monomer (calculated from ^1H NMR) was reported in Table 1. Comparing the intrinsic viscosities of two pentablock copolymers showed that by increasing the L -lactide content, intrinsic viscosity raised.

Table 1: Characterization of tri and pentablock copolymers.

Polymer	PEG (Mn)	$[\eta]$	Mole ratio in crude feed L-LA/PDO/PEG	Mole ratio calculated from ^1H NMR L-LA/PDO/PEG
Triblock	15000	0.6513	0/46.3/53.7	0/54.5/45.5
Pentablock1	15000	0.8185	60.4/18.3/21.3	83.4/4.5/12.0
Pentablock2	15000	0.8978	81.4/8.6/10	88.8/4.7/6.4

Fig. 1: Comparison of ^1H NMR spectra: (A) L -lactide /Prepolymer; 80/20, (B) L -lactide / Prepolymer; 60/40.Fig. 2: Comparison of ^{13}C NMR spectra: (A) L -lactide /Prepolymer; 80/20, (B) L -lactide / Prepolymer; 60/40.

Thermal Properties

DSC thermograms of poly (L -lactide), tri and pentablock copolymers are presented in Figs. 3 and 4. In the DSC thermogram of prepolymer, two melting peaks were detected at 46.8 and 101.6°C, which suggested the both poly (ethylene glycol) (PEG) and poly (p-dioxanone) (PPDO) blocks crystallized and formed two different crystal domains in prepolymer. DSC thermogram of pentablock copolymer(L-LA 60%), showed three melting points at 45.95, 86.99 and 145.1°C, that are attributed to the melting points of poly (ethylene glycol) (PEG), poly (p-dioxanone) (PPDO) and poly (L -lactide) (PLLA) blocks, respectively. The presence of PLLA end blocks attached to triblock prepolymer decreased the melting temperature of corresponding PEG and PPDO blocks. The DSC thermogram of pentablock copolymer (L-LA 80%), showed one melting point that it is attributed to poly (L -lactide) (PLLA) blocks. In fact, by increasing the L -lactide (L-LA) content, melting temperature and ΔH_m of PLLA blocks were raised, also two melting endotherms belong to poly (ethylene glycol) (PEG) and poly (p-dioxanone) (PPDO) segments were eliminated. All the information obtained from DSC data could further prove that the resulting copolymers contained three kinds of blocks, PEG, PPDO and PLLA blocks. From DSC thermograms, T_m and ΔH_m was obtained that are shown in Table 2. According to the relationship between ΔH_m and crystallinity, which higher ΔH_m is attributed to the higher crystallinity, by increasing the L -lactide (L-LA) content in these copolymers, T_m and crystallinity was raised and consequently thermal properties of PLLA end blocks to come near to the thermal properties of PLLA homopolymer.

TGA and DTGA thermograms of PLLA, tri and pentablock copolymers are shown in Figs. 5 and 6. The thermal degradation behavior of resulting pentablock copolymers were studied by TGA/DTGA methods. For these copolymers, the thermal degradation behavior was mainly determined by L -lactide (L-LA) content. According to the Table 3 and Fig.5, the initial and final decomposition temperatures (T_i , T_f) increased with increasing the L -lactide (L-LA) content. In random copolymers single-step weight loss is observed, while TGA of block copolymers showed several inflection points, which is dependent to the number kinds of blocks.

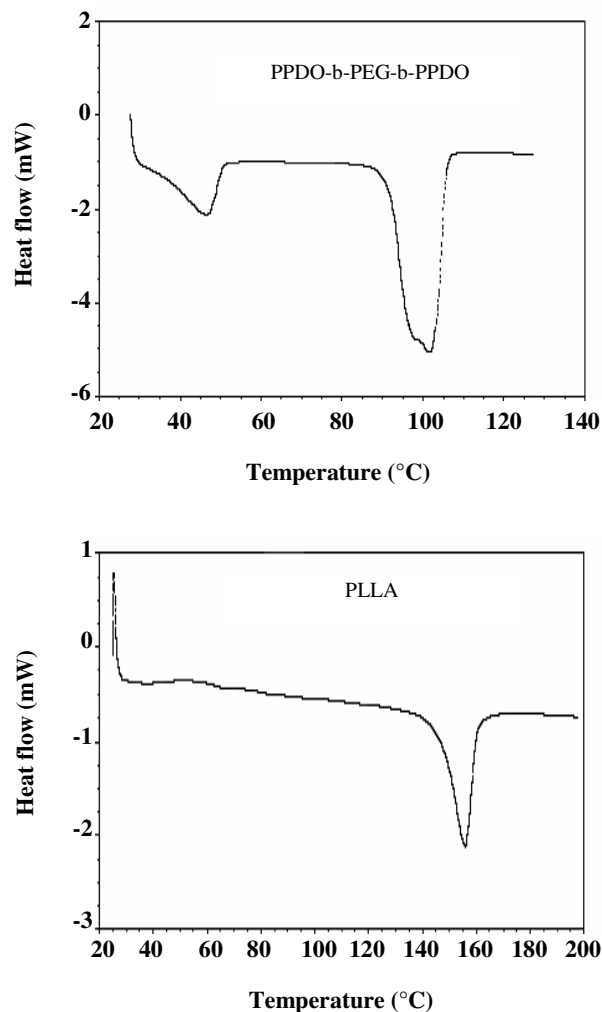


Fig. 3: DSC thermograms of PLLA and triblock copolymers.

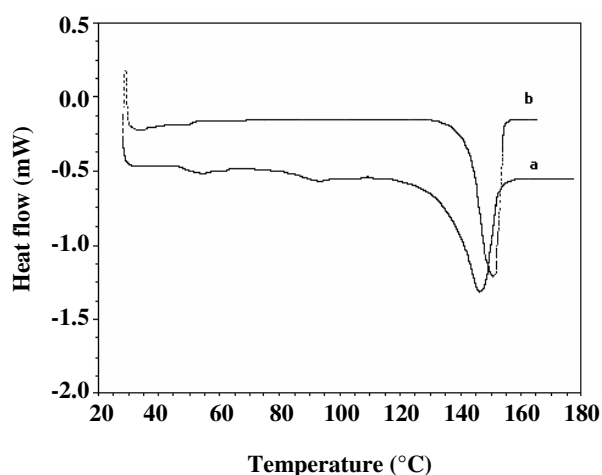


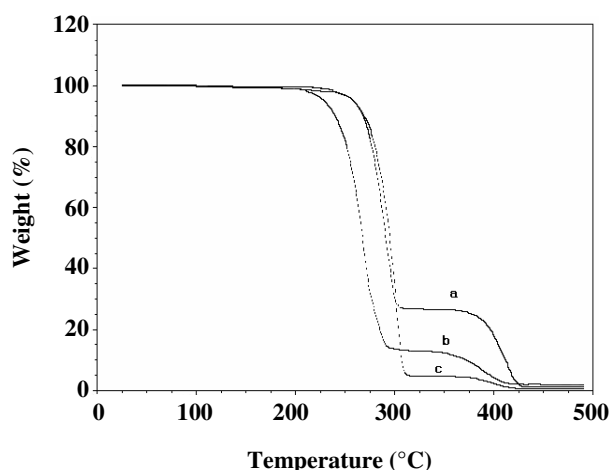
Fig. 4: DSC thermograms of pentablock copolymers (A); pentablock 1, (B); pentablock 2.

Table 2: Thermal properties of homo and block copolymers (DSC data).

Polymer	T _m °C	ΔH _m j/g	Weight percentage in crude feed L-LA/PDO/PEG
PLLA	156.0	35.27	100/0/0
Triblock	46.8, 101.6 (PEG and PPDO)	26.6, 110.1 (PEG and PPDO)	0/66.6/33.3
Pentablock 1	145.1	26.13	75.5/16.27/8.13
Pentablock 2	149.9	30.86	98.88/6.74/3.4

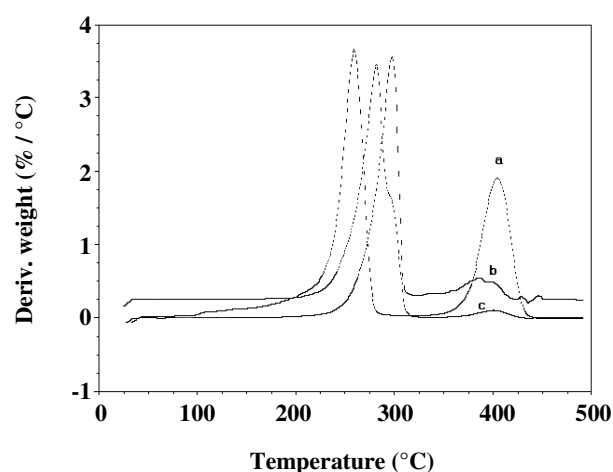
Table 3: Thermal degradations of homo and block copolymers (TGA data).

Polymer	Mole ratio L-LA/PDO/PEG	T _i , T _f °C (PEG)	T _i , T _f °C (PDO)	T _i , T _f °C (L-LA)
PLLA	100/0/0	-	-	263.9-315.3
PPDO	0/100/0	-	251.4-305.8	-
triblock	0/46.3/53.7	381.8-419.5	236.7-269.1	-
Pentablock 1	60.4/18.3/21.3	366.3-409.1	-	250.1-289.8
Pentablock 2	81.4/8.6/10	379.2-415.4	-	261.5-314.6

**Fig. 5: TGA thermograms of block copolymers (A); triblock, (B); pentablock1, (C); pentablock 2.**

From TGA thermograms, the weight percentages of each block in polymer composition obtained that was listed in Table 4.

In the triblock copolymer (PPDO-b-PEG-b-PPDO), two degradation processes were detected. In attention to degradation temperature of poly (ethylene glycol) (PEG) (upper than 380°C), can be suggested that the first degradation step is due to the poly (p-dioxanone) (PPDO) block and second step corresponded to the poly (ethylene glycol) (PEG) block. Weight percentage of each block that obtained from TGA curves was compatible with weight percentage of components in crude feed.

**Fig. 6: DTG thermograms of block copolymers (A); triblock, (B); pentablock1, (C); pentablock2.**

In pentablock copolymers ABCBA type (PLLA-b-PPDO-b-PEG-b-PPDO-b-PLLA), we have expected that three inflection points must be seen in TGA curves, but inflection point of PPDO was not observed, because overlapping the degradation temperature domain of poly (p-dioxanone) (PPDO) with poly (L-lactide) (PLLA), and because the low weight percentage of poly (p-dioxanone) (PPDO).

From Fig.6, the DTGA thermograms show one small peak attributed to poly (p-dioxanone) (PPDO) block that justified the overlapping of poly (L-lactide) (PLLA) and poly (p-dioxanone) (PPDO) inflection points in TGA

Table 4: Composition of polymer in comparing with the crude feed.

Polymer	Weight percentage calculated from TGA L-LA/PDO/PEG	Weight percentage in crude feed L-LA/PDO/PEG
Triblock	0/64.1/35.0	0/66.6/33.3
Pentablock 1	66.9/22.0/11.1	75.5/16.3/8.2
Pentablock 2	89.0/7.4/3.6	89.9/6.7/3.4

thermograms. As can be seen from the results obtained by the DSC, TGA, and DTGA thermograms, the crystallization rate of copolymers increased with increasing weight fraction of poly (L-lactide) (PLLA) blocks.

CONCLUSIONS

PLLA-b-PPDO-b-PEG-b-PPDO-b-PLLA copolymers with different L-lactide (L-LA) content were synthesized in presence of Sn(Oct)₂ as catalyst. All the copolymerization reactions were carried out in low temperature and long reaction time, to minimize the competitive reactions (chain growth and degradation) and in low concentration of catalyst to obtaining high molecular weight copolymers. The structures of copolymers were confirmed by means of ¹HNMR and ¹³CNMR spectroscopy. Weight percentage of monomers (obtained from TGA thermograms) and mole ratio of any component (calculated from ¹HNMR spectra) confirmed that polymerization performed with high yield. The intrinsic viscosities of the pentablock copolymers increased compared with the triblock prepolymer. According to the ¹³CNMR spectra, DSC and TGA thermograms, block structure of obtained copolymers were justified, and also TGA thermograms showed by increasing the L-lactide (L-LA) content thermal stability of resulting copolymers increased. All the results suggested that degradation behaviors and crystallinity rate could be controlled by adjusting weight fraction of poly (L-lactide) (PLLA) to prepolymer. This may be good for the solidification and molding after melt processability required in biomedical applications, such as absorbable surgical suture, absorbable surgical clips and staples.

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