

# Synthesis and thermal properties of novel multiblock biodegradable copolymers derived from polyethylene glycol, $\epsilon$ -caprolactone and p-dioxanone

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**ABSTRACT:** Multiblock copolymers from polyethylene glycol (PEG),  $\epsilon$ -caprolactone (CL), and p-dioxanone (PDO) were synthesized and characterized. Triblock copolymers were first synthesized from PEG with number-averaged molecular weights ( $M_n$ ) of 3000, 4000, and 15000 Daltons, and  $\epsilon$ -caprolactone in the presence of  $\text{Sn}(\text{Oct})_2$ .  $^1\text{H-NMR}$  spectra of these copolymers were recorded. Thermal behaviour and thermal stability of these copolymers were evaluated by differential scanning calorimetry (DSC) and TGA thermograms, respectively. These triblock copolymers with two hydroxyl functional groups were subjected to further block copolymerization with PDO in the presence of  $\text{Sn}(\text{Oct})_2$  as catalyst. Thermal behaviours of these copolymers were evaluated by DSC and TGA thermograms. For comparison of block and random copolymer thermal behaviour, random triblock copolymer from PEG, CL, and PDO was prepared and its thermal behaviour was characterized by DSC and TGA.

**KEYWORDS:** Polyethylene glycol, p-dioxanone,  $\epsilon$ -caprolactone, multiblock copolymer

## INTRODUCTION

Synthetic bioresorbable polymers are of interest for a variety of biomedical, pharmaceutical, and industrial applications. Polylactides, polyglycolide, poly( $\epsilon$ -caprolactone) (PCL), poly(p-dioxanone) (PPDO) and their copolymers are widely used in various fields ranging from surgical sutures to controlled drug delivery systems<sup>1-3</sup>.

Poly(1,4-dioxan-2-one) or poly(p-dioxanone) is a well known as an easily hydrolysable material that has been used to make monofilament sutures with good tenacity and knotting<sup>4</sup>. The presence of an ether bond and an additional  $-\text{CH}_2-$  in its molecular structure gives PPDO greater flexibility compared to polyglycolide and polylactide<sup>5</sup>. Furthermore, PPDO shows slower degradation by hydrolysis, due to the lower concentration of ester groups, as compared to the lactide-glycolide copolymers. PPDO is now considered a candidate not only for medical uses, but also for universal uses, such as film, moulded products, laminates, foams, non-woven material, adhesives, and coatings<sup>6</sup>.

Poly ( $\epsilon$ -caprolactone) is a biodegradable polymer with a slow rate of biodegradation in human tissues<sup>7</sup>. From a mechanical point of view, it is classified as a brittle material with a high elastic modulus. But because of the presence of five methylene

moieties in the polymer backbone the modulus is lower than that of polylactide<sup>8,9</sup>.

Unique properties of polyethylene glycol include: solubility in water and many organic solvents, lack of solubility in hexane and ethyl ether, lack of toxicity, FDA approval for internal consumption, rapid clearance from the body, lack of immunogenicity, and high mobility and large exclusion volume in water. Because of these features, a new family of triblock copolymers based on polyethylene glycol have attracted the attention of investigators<sup>10</sup>. When coupled to another molecule, many of these properties are transferred to the conjugate product. It has been shown that by appropriate selection of the co-monomers a wide variety of materials with a broad range of properties can be obtained. Block copolymerization may offer a broader spectrum of mechanical and degradation properties to meet the demands of various applications.

Many copolymers were synthesized from PEG, CL, and PDO. Recently, Kim<sup>11</sup> and his coworkers, synthesized and characterized ABA type random triblock copolymers, poly(PDO-co-CL)-block-poly(ethyleneoxide)-block-poly(PDO-co-CL) by the random insertion of a PCL segment. PPDO-b-PEG-b-PPDO was modified into a semi-crystalline and highly flexible state. Also polymeric nanoparticles were prepared from these polymers. A series of

ABA triblock copolymers with different length of PEG blocks were synthesized *via* the initiated polymerization of PDO by using different molecular weights of PEG as macroinitiators in the presence of Sn(Oct)<sub>2</sub> as a catalyst. The molecular weight and content have a great effect on the thermal and the crystalline behaviours, the thermal stability, and the water absorption of the copolymers<sup>12</sup>.

The morphology, crystallization, and self-nucleation behaviour of double crystalline diblock copolymers of PPDO and PCL with different compositions have been studied<sup>13</sup>.

By use of PEG as macroinitiator and Sn(Oct)<sub>2</sub> as catalyst, ABA type (PDO-co-LLA)-b-PEG-b-(LLA-co-PDO) block copolymers were synthesized in bulk by polymerization of PDO and LLA with dihydroxyl-terminated PEG. Thermal and aqueous solution properties of these triblock copolymers were studied extensively<sup>14–16</sup>.

In this article, we describe a two-step synthesis and characterization of some new ABCBA pentablock copolymers, where the C block is PEG and B and A blocks are PCL and PPDO, respectively. In the first step, a triblock copolymer of PEG and  $\epsilon$ -caprolactone was synthesized, and then this copolymer carrying two-hydroxyl functionality was used for the synthesis of pentablock copolymer in the presence of PDO. Spectral and thermal behaviours of these new copolymers were also investigated. These copolymers have potential applications as carriers for controlled drug delivery and other biomedical applications.

## MATERIALS AND METHODS

### Materials

$\epsilon$ -Caprolactone was from Merck (Germany) and used without any further purification. P-dioxanone purchased from Biopolytech (Korea) and distilled over CaH<sub>2</sub> at reduced pressure just before polymerization. Polyethylene glycol ( $M_n = 3000, 4000, \text{ and } 15000$  Daltons) was purchased from Merck (Germany) and used without any further purification. The catalyst, tin-2-ethyl hexanoate (Sigma, St. Louis, USA) was purified by vacuum distillation. All other chemicals or solvents were reagent grade (Merck, Darmstadt, Germany) and, if necessary, were purified according to established procedures<sup>17</sup>.

### Preparation of PCL-b-PEG-b-PCL prepolymer

Appropriate amounts of PEG and Sn(Oct)<sub>2</sub> were placed into a polymerization tube and kept under a vacuum at 70 °C, for 1 h. Then, a calculated amount of  $\epsilon$ -Caprolactone was added and kept under vacuum

at 50 °C, for 2 h, until all volatiles were removed. The tube was then sealed under vacuum and placed in a silicon oil bath at 160 °C, for 5 h. Subsequently, the tube was broken, the contents dissolved in chloroform, and reprecipitated in methanol. Finally, the resulting triblock copolymers were dried under vacuum at 50 °C for 24 h, and used as the central segment in the synthesis of pentablock copolymers. All of the polymerization reactions were performed at a low concentration of catalyst (mole of reacting monomer/ mole of catalyst = 3000–5000).

### Preparation of pentablock PPDO-PCL-b-PEG-b-PCL-PPDO copolymer

The preparation of the pentablock copolymers was similar to the previously discussed triblock copolymer. Predetermined amounts of dried prepolymer and Sn(Oct)<sub>2</sub> with a magnetic stirrer was placed in a polymerization tube and kept under vacuum at 80 °C for 2 h. Then, a calculated amount of fresh distilled p-dioxanone was added under a nitrogen atmosphere and the mixture was kept under vacuum at 50 °C for 2 h. The prepolymer was easily dissolved in PDO monomer, and a homogenous system was obtained at low temperature. Under vacuum, the glass tube was sealed and immersed in an oil bath at 110 °C for 48 h. Finally, the glass tube was broken, the contents grinded, and subjected to high vacuum at ambient temperature for 24 h.

### Preparation of random triblock copolymer

Appropriate amounts of PEG and Sn(Oct)<sub>2</sub> were placed into a polymerization tube and kept under a vacuum at 70 °C for 1 h. Then, calculated amounts of  $\epsilon$ -caprolactone and p-dioxanone were added and kept under vacuum at 50 °C for 2 h, until all the volatiles were removed. Then, the tube was sealed under vacuum and placed in a silicon oil bath at 120 °C for 48 h. Subsequently, the tube was broken, and the contents dissolved in ethyl acetate and precipitated by hexane. Finally, the resulting triblock random copolymer was dried under vacuum at 50 °C for 24 h.

### Measurements

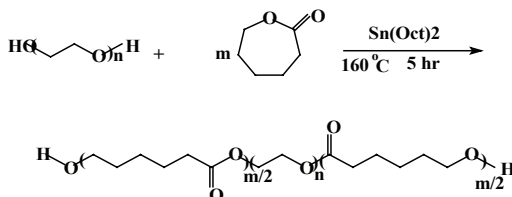
<sup>1</sup>H-NMR spectra of the copolymers were recorded on a Bruker-AC-80 spectrometer at 80 MHz. Chloroform-d<sub>3</sub> and TMS were used as a solvent and an internal standard, respectively. Differential scanning calorimetry (DSC) thermograms were obtained using a Thermal Analysis (TA) DSC-60. Thermogravimetric measurements (TG/DTG) were conducted with a TGA Q50 V6.3 TA instruments thermogravimetric analyser

in platinum pans at a heating rate of 10 °C/min until 0% weight under a steady flow of nitrogen.

**RESULTS AND DISCUSSION**

**Synthesis and characterization of triblock copolymers**

PEG with three molecular weights (3000, 4000, and 15000 Daltons) and CL were used for the synthesis of triblock copolymers in the presence of Sn(Oct)<sub>2</sub> as catalyst:



Sn(Oct)<sub>2</sub> gives a complex with hydroxyl-containing compounds, and this complex initiates the ring-opening polymerization of lactones by a coordination insertion mechanism. In this case, PEG acts as two-functional macro-initiator for the polymerization of CL. The obtained triblock copolymer also has two hydroxyl functional groups for further polymerization with another lactone in the presence of Sn(Oct)<sub>2</sub>. Table 1 gives the characteristics of the obtained triblock copolymers.

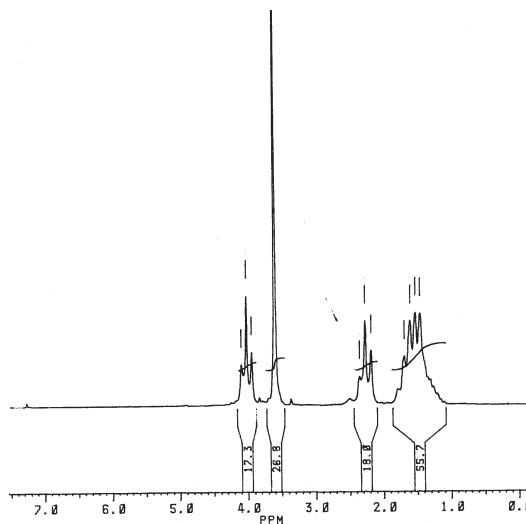
**Table 1.** Characteristics of the obtained copolymers

M <sub>n</sub> ( <sup>1</sup> H-NMR)	Composition <sup>(a)</sup>			Feed ratio(mol%)			M <sub>n</sub> of PEG	Sampl no.
	PEG	ε-CL	PDO	PEG	ε-CL	PDO		
28000	43.6	56.4	0	43	57	0	3000	Jm1
28000	51.7	48.3	0	50	50	0	4000	Jm2
200000	34.6	65.4	0	33	67	0	15000	Jm3
-	0	100	0	0	100	0	-	PCL
-	0	0	100	0	0	100	-	PPDO
-	-	-	-	8.5	8.5	83	4000	Jm4
-	-	-	-	14.2	14.2	71.6	4000	Jm5
-	-	-	-	12.5	16.5	71	3000	Jm6
-	-	-	-	7	12	81	15000	Jm7

(a) Obtained from <sup>1</sup>H-NMR spectrum

PCL is a hydrophobic polymer with long degradation time, but PEG is a hydrophilic and therefore water-soluble polymer. With the introduction of PEG as a block, the hydrophilicity of the copolymer increased with respect to PCL, enhancing the degradability of PCL and lowering its degradation time.

The typical <sup>1</sup>H-NMR spectrum of a triblock copolymer is shown in Fig. 1. In these triblock copolymers, a characteristic <sup>1</sup>H-NMR methylenic moiety in PEG appears at 3.59 δ ppm, caprolactyl methylenic protons appear at 4.01 δ ppm (CH<sub>2</sub>-O) and 2.25 δ ppm (CH<sub>2</sub>-CO), and inner methylenic protons appear at 1.1–1.7 δ ppm. For the calculation of the caprolactone molar percentage in the copolymers, the peak area at



**Fig. 1** <sup>1</sup>H-NMR spectrum of triblock copolymer (Jm1).

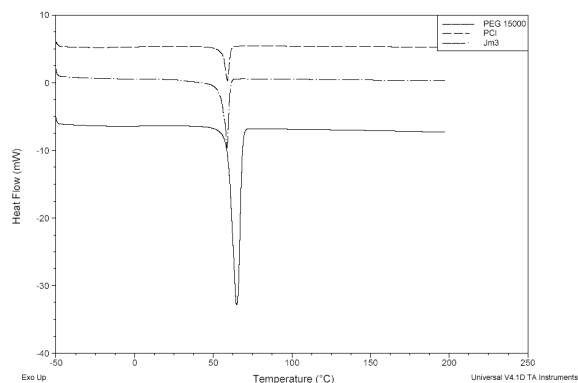
4.01 δ ppm was taken as a reference (Fig. 1). M<sub>n</sub> was estimated from the <sup>1</sup>H-NMR data by considering the relative intensities of the CH<sub>2</sub> oxyethylene and CH<sub>2</sub> moiety of caprolactyl fragments, designated as I<sub>PEG</sub> and I<sub>CL</sub>, respectively, according to the following equations:

$$\begin{aligned} \bar{M}_n(\text{total}) &= \bar{M}_n(\text{PEG}) + \bar{M}_n[\text{P}(\epsilon\text{-CL})] \\ \bar{M}_n[\text{P}(\epsilon\text{-CL})] &= \frac{5I_{\text{CL}}M_w(\epsilon\text{-CL})D_p(\text{PEG})}{I_{\text{PEG}}} \end{aligned}$$

The results are shown in Table 1

Thermal behaviour of the triblock copolymers was investigated by DSC thermograms. Fig. 2 shows DSC thermograms of PEG, PCL, and triblock copolymer (Jm3). This copolymer shows an endotherm at 56.16 °C with ΔH<sub>m</sub> = 59.91 J/g. PEG shows an endotherm at 65.03 °C with a higher enthalpy of melting (ΔH<sub>m</sub>= 191.8 J/g) whereas PCL shows an endotherm at 55.75 °C with a moderate enthalpy of melting (ΔH<sub>m</sub>= 56.05 J/g). Since this typical copolymer has a high mol% of PCL as two end blocks (67 mol%) so that this mol% corresponds to 84 weight percent, the thermal behaviour of the copolymer is similar to that of the PCL homopolymer. In addition, the melting points of the two homopolymers are near to each other and the two endotherms overlap. The existence of a shoulder in the copolymer thermogram is the result of overlapping<sup>8</sup>.

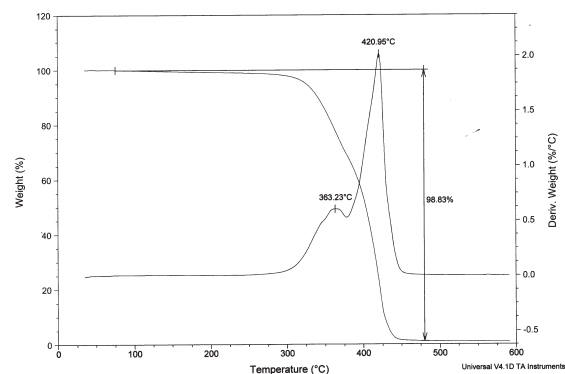
The thermal stability of the copolymers was studied by TGA and DTGA thermograms. A typical TGA thermogram of the triblock copolymer (Jm3) is shown in Fig. 3. The existence of two degradation peaks in the DTGA of the copolymer confirms the



**Fig. 2** DSC thermograms of PEG, PCL, and triblock copolymer (Jm3).

**Table 2.** DSC and TGA data of homo and copolymers

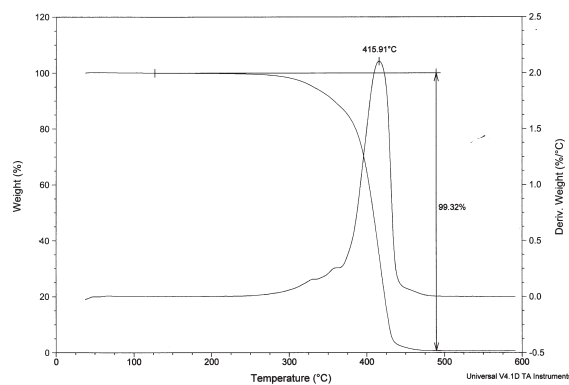
Sample T	m(°C)	$\Delta H_m$ (J/g)	Tdeg(°C)
PEG	65.0	191.8	407.5
PCL	59.0	58.1	415.9
Jm3	58.7	60.0	363.2, 421.0
PPDO	100.8	103.8	296.3
Jm7	100.6	58.8	29601, 331.1, 400.7
Random copolymer	53.1	39.43	16.1, 404.3



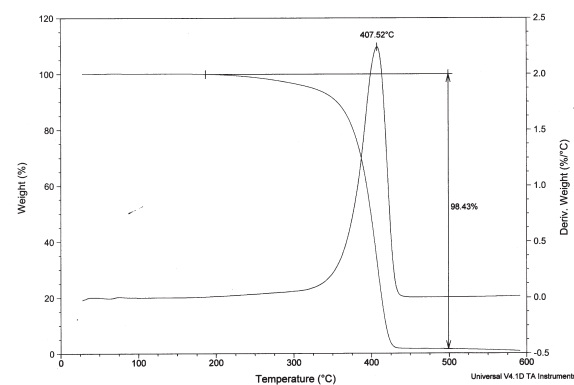
**Fig. 3** TGA thermogram of the triblock copolymer (Jm3).

block structure of the copolymer. These two peaks appear at 363.23 and 420.95 °C.

For comparison, TGA thermograms of PCL and PEG ( $M_n = 15000$ ) are shown in Figs. 4 and 5, respectively. The degradation peak of PEG ( $M_n = 15000$ ) appears at 407.52 °C whereas for the PCL homopolymer this point appears at 415.91 °C. By comparing the mol ratio of the two blocks and from the appearance of two peaks in the case of the copolymer, it is understood that the thermal stability of the PCL block is increased to a small extent. However, the thermal stability of PEG ( $M_n = 15000$ ) block is decreased to a higher extent.



**Fig. 4** TGA thermogram of poly( $\epsilon$ -caprolactone) homopolymer.



**Fig. 5** TGA thermogram of poly(ethylene glycol) ( $M_n = 15000$ ) homopolymer.

### Synthesis and characterization of pentablock copolymers

Using the triblock prepolymer as a two-functional hydroxyl group-containing macro-initiator and  $\text{Sn}(\text{Oct})_2$  as a catalyst, pentablock ABCBA copolymers were prepared in the presence of PDO, where the A block was a PPDO block, and B and C were PCL and PEG blocks, respectively. The polymerization reaction is as follows:

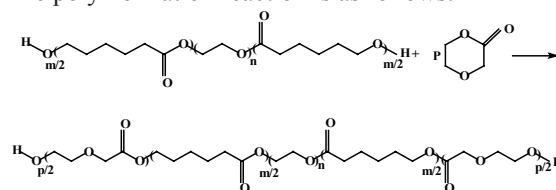
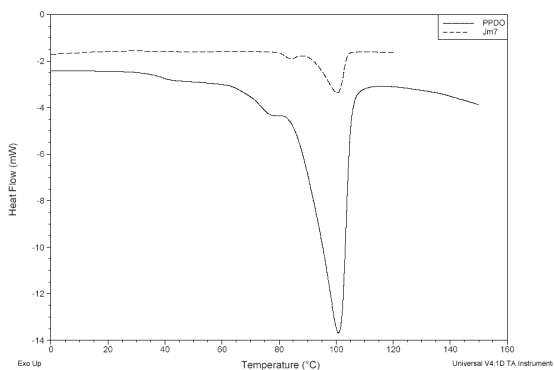
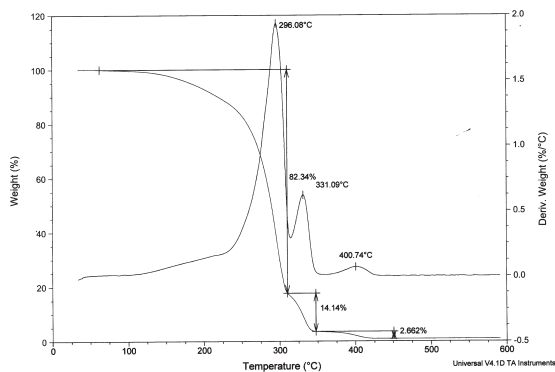


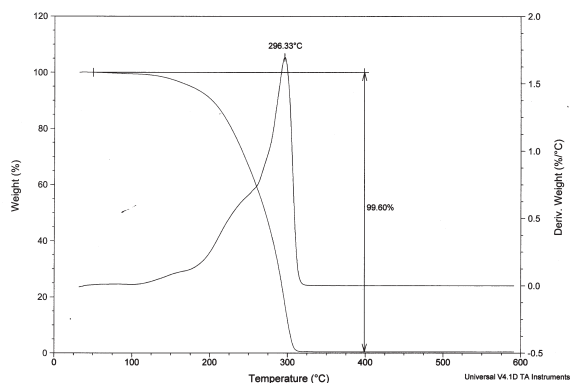
Fig. 6 shows the DSC thermograms of the pentablock copolymer (Jm7) and PPDO. For the pentablock copolymer an endotherm appeared at 100.79 °C with moderate enthalpy of melting ( $\Delta H_m = 58.82$  J/g). Two very small endotherms appeared at lower temperatures relating to other



**Fig. 6** DSC thermograms of PPDO and pentablock copolymer (Jm7).



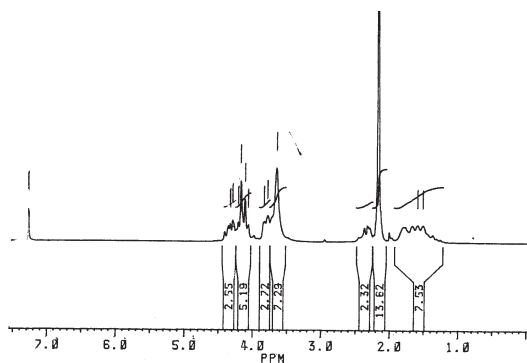
**Fig.7** TGA thermogram of pentablock copolymer (Jm7).



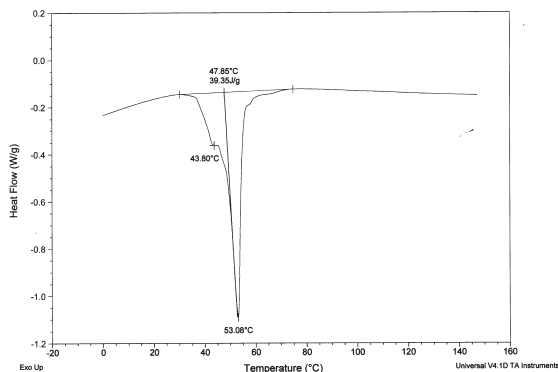
**Fig. 8** TGA thermogram of poly(p-dioxanone) homopolymer.

blocks. Comparison of DSC thermograms of PPDO and copolymer shows that this endotherm relates to a poly(p-dioxanone) block that has high mol% in the block copolymer.

To evaluate the thermal stability and to confirm the block structures TGA, thermograms of pentablock copolymers were recorded. The typical TGA of the



**Fig. 9** <sup>1</sup>H-NMR spectrum of random triblock copolymer.



**Fig. 10** DSC thermogram of random triblock copolymer.

pentablock copolymer is shown in Fig. 7. Three degradation peaks are observed. These three peaks correspond to three main blocks in the copolymer. Also the three weight loss% correspond to the weight% of these blocks in the copolymer. The existence of three peaks confirms the block structure of the copolymer. These three peaks appear at 296.08, 331.09, and 400.74 °C and correspond to thermal degradation of PPDO, PCL, and PEG blocks, respectively.

From comparison of TGA thermograms of PEG (Fig. 5), poly(ε-caprolactone) (Fig. 4) and poly(p-dioxanone) (Fig. 8) the attributed degradation temperatures to three blocks are confirmed. The degradation peak for the PPDO homopolymer appears at 296.33 °C.

### Synthesis and characterization of a random triblock copolymer

To compare the thermal behaviour of block and random copolymers, a random ABA triblock copolymer was synthesized from PEG, ε-caprolactone and p-dioxanone. In this copolymer, the A block was the random copolymer of ε-caprolactone and p-dioxanone, and the B block was the PEG block. The pentablock copolymer poly(p-dioxanone) block

was insoluble in chloroform, preventing a  $^1\text{H-NMR}$  spectrum of from being recorded. But the random triblock copolymer can easily be dissolved in chloroform and its  $^1\text{H-NMR}$  spectrum was recorded. Fig. 9 shows the  $^1\text{H-NMR}$  spectrum of this random triblock copolymer. Because of the presence of some solvents (ethyl acetate and hexane are used for the purification of the copolymer) and the random nature of the two end blocks, the spectrum is noisy. The methylene protons of  $\epsilon$ -caprolactone moiety appeared at 1.3 to 1.7  $\delta$  ppm, 2.25  $\delta$  ppm, and 4.05  $\delta$  ppm. Methylene protons of PEG and three methylene protons of p-dioxanone appeared at 3.6  $\delta$  ppm, 3.77  $\delta$  ppm, 4.16  $\delta$  ppm, and 4.32  $\delta$  ppm, respectively. The DSC thermogram of this copolymer shows only one endotherm, attributed to the PEG block of the copolymer, and the two other end blocks are completely random and amorphous (Fig. 10).

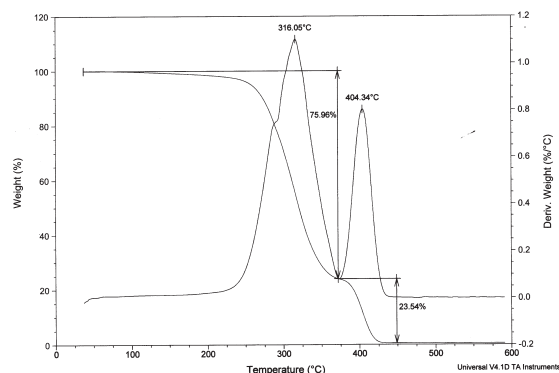


Fig. 11 TGA thermogram of random triblock copolymer.

Fig. 11 shows the TGA thermogram of the random triblock copolymer. Two degradation peaks appeared at 316.05 and 404.34 °C and are attributed to the two random end blocks and the centre PEG block, respectively. The random block degradation peak is greater than that of the poly(p-dioxanone) homopolymer degradation peak, suggesting that random copolymerization increases the thermal stability of the poly(p-dioxanone).

## ACKNOWLEDGEMENTS

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