Enzymatic Synthesis and Characterization of Biodegradable Poly(ω-pentadecalactone-*co*-ε-caprolactone) Copolymers

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ABSTRACT: As an alternative biodegradable aliphatic polyester, poly(ω-pentadecalactone-*co*-ε-caprolactone) copolymer was synthesized via enzymatic ring-opening polymerization. A new biocatalyst, *Candida antarctica* lipase B, immobilized onto rice husk ash was used for catalysis. Reactions were carried out at various temperatures and periods for varied copolymer compositions in order to obtain the highest molecular weight copolymer. The best reaction parameters were found to be 80 °C and 6 hours and molecular weights increased proportionally with the amount of ω-pentadecalactone (ω-PDL). The molecular structure of copolymer with 75% weight ratio of ω-PDL (M_n = 19720 g/mol) was characterized by proton and carbon nuclear magnetic resonance spectroscopies (^{1}H-NMR and ^{13}C-NMR). Thermal properties of the same copolymer and homopolymers were investigated by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Improved thermal features were shown by addition of ω-PDL to the structure and compared with poly(ε-caprolactone) (PCL). Consequently, poly(ω-pentadecalactone-*co*-ε-caprolactone) copolymers were found to be good alternatives to widely used polyester, PCL, with their rapid polymerization tendency, higher molecular weights, and improved thermal features.

KEYWORDS: *Candida antarctica* lipase B, immobilized lipase, rice husk ash, copolymerization, enzymatic ring-opening polymerization, lactones, ε-caprolactone, ω-pentadecalactone

1 INTRODUCTION

There has been increasing attention on the synthesis and application of aliphatic polyesters [1]. These materials are acceptable alternatives for petroleum-based polymers as a result of their convenient physical properties [2]. Moreover, biodegradability and biocompatibility of aliphatic polyesters provide unique advantages over petroleum-based polymers. These features make it possible to safely use them in pharmaceutical and medical applications [1]. Among the aliphatic polyesters, polymers and copolymers of unsubstituted lactones, such as δ-valerolactone (δ-VL), ε-caprolactone (ε-CL), and ω-pentadecalactone (ω-PDL), have received great interest in past years [3]. There exists a large number of publications on enzymatic ring-opening polymerization (eROP) of these lactones. However, there have been only limited studies on eROP of macrolactones, such as 16-membered ω-PDL [1].

Conventionally, macrolactones are converted to aliphatic polyesters by organometallic catalysts such as stannous octoate and zinc lactate [4]. In recent years, enzyme-catalyzed polymerizations have received attention due to mild reaction conditions [5]. In addition, catalysis of ring-opening polymerization by enzymes instead of such organometallic catalysts prevents the final product from having metal impurities that may cause toxic effects for biomedical applications [6–9]. Also, polymerization of high membered (> 7-member) lactones by conventional chemical methods is difficult because of their lower reactivities than medium-size lactones [6, 10]. Lipase is the most preferred enzyme for eROP of macrolactones since it exhibits high activity for macrolactone polymerization, which results in polyesters with higher molecular weights and more rapid polymerization kinetics [5, 6, 9, 11]. Additionally, lipase catalysis may promote copolymerizations and produce well-ordered repeated chain sequences, which are difficult to achieve via conventional chemical methods [12].

In the literature, generally Novozyme 435 (the commercial immobilized form of *Candida antarctica* lipase B) has been preferred for eROP of macrolactones [5, 12, 13]. Also, copolymers of macrolactones and smaller lactones (such as ε-CL) can be produced with high molecular weights via the same route [1].

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When compared to poly(ε-caprolactone) (PCL), poly(ω-pentadecalactone) (PPDL) has a higher melting point (60 °C and 97 °C, respectively), which provides tolerance for use in higher temperatures [5]. Moreover, PPDL is comparable to low-density polyethylene (LDPE) since it has similar thermal and mechanical properties (melting temperature, glass transition temperature, crystallinity, elongation at break) [5, 13, 14]. On the other hand, the biodegradability of PPDL provides an enormous advantage over LDPE [5].

Copolymers of ω-PDL with various monomers have been synthesized to produce biomaterials with improved features. Some such copolyesters are: poly(ω-pentadecalactone-*co*-ε-caprolactone), poly(ω-pentadecalactone-*co*-p-dioxanone),poly(ω-pentadecalactone-*co*-δ-valerolactone), poly(ω-pentadecalactone-*co*-ε-decalactone), and poly(ω-pentadecalactone-*co*-δ-hexalactone) [14]. High crystallinity of PPDL reduces its solubility in most organic solvents. By copolymerization with another lactone it is possible to improve solubility [15].

In the present study, a new biocatalyst, *Candida antarctica* lipase B (CALB), immobilized onto rice husk ash (RHA) via physical adsorption (Im-CALB) was proposed for synthesis of poly(ω-PDL-*co*-ε-CL). The successful performance of this enzyme for PCL synthesis was shown in a previous study [16]. Copolymers of ω-PDL and ε-CL with varied feed ratios were synthesized to show the alteration in properties of polymers (molecular weight and thermal properties) which may be suggested for various biomedical applications. Monomer compositions and total conversions of copolymers synthesized in this work were calculated from proton nuclear magnetic resonance (^{1}H-NMR) spectra. Carbon nuclear magnetic resonance (^{13}C-NMR) was applied for determination of possible dyad units in copolymer. Molecular weights (M_n) and polydispersity indexes (Đ) were obtained from gel permeation chromatography (GPC). Thermal properties were determined by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Consequently, the aim was to synthesize and characterize poly(ω-PDL-*co*-ε-CL) copolymers with a new biocatalyst and compare its performance with the commercial enzyme Novozyme 435.

2 MATERIALS AND METHODS

2.1 Materials

The monomer ω-pentadecalactone (≥ 98%) was purchased from Sigma-Aldrich and used as received. ε-Caprolactone (Alfa Aesar) was dried over molecular sieves before polymerization to avoid moisture. Toluene and deuterated chloroform were obtained from Merck. Chloroform and methanol were purchased from Sigma-Aldrich. Tetrahydrofuran (THF) was used to solubilize polymer samples for GPC analysis and purchased from Carlo Erba as HPLC grade. The free form of *Candida antarctica* lipase B (CALB) was obtained from Sigma-Aldrich and used as immobilized form (Im-CALB) [16]. Also, Novozyme 435 was purchased from Sigma-Aldrich.

2.2 Synthesis of Poly(ω-PDL-*co*-ε-CL) Copolymers

Ring-opening copolymerization of ω-PDL and ε-CL using Im-CALB is the same procedure as in the synthesis of homopolymers of ε-CL as previously described [17]. Polymerization reactions were performed under dry nitrogen in 25-ml three-neck flasks. Reactions proceeded under various conditions (60 °C for17 h, 80 °C for 6 h, and 90 °C for 4 h) in 1 g of toluene with a stirring rate of 120 rpm. One-step copolymerization strategy was applied by reacting ω-PDL and ε-CL at the same time with various feed weight ratios. A calculated amount of Im-CALB, the immobilized form of CALB as powder, and monomers were introduced into the flask with 20% enzyme concentration (weight ratio of enzyme to monomer). Monomer-to-toluene ratio was arranged to be 1:2 (w:w). Reactions were terminated by the addition of excess chloroform and after filtration of enzyme from the polymerization medium, chloroform in the filtrate was evaporated in an oven at 50 °C. Then, the copolymer was precipitated in cold methanol and filtrated for purification. Finally, the product was dried in an oven at 30 °C overnight.

2.3 Instrumental Methods

Molecular weights and polydispersity indexes (Đ) of polymer samples were measured by GPC using an Agilent 1100 model apparatus equipped with a pump, refractive index detector, and Zorbax PSM columns (1000-S, 300-S, 60-S). The calibration curve was generated by polystyrene standards ranging from 580 g/mol to 504500 g/mol. Tetrahydrofuran (THF) was used as the eluent and analyses were carried out at 25 °C with a flow rate of 1 ml/min. Before injection, all samples were filtered via 0.45 μm filter syringe.

^{1}H-NMR analysis was applied on an Agilent VNMRS 500 MHz spectrometer at 25 °C for the determination of poly(ω-PDL-*co*-ε-CL) copolymer compositions and total conversions. ^{1}H-NMR spectra were recorded in deuterated chloroform ($CDCl_3$) with respect to tetramethylsilane (TMS) standard. Total conversion percentages were determined based on

the integral ratios of polymer ($I_{4.06}$) and monomer ($I_{4.16}$) characteristic peaks (Equation 1):

$$Total\,conversion(\%) = \frac{I_{4.06}}{I_{4.06} + I_{4.16}} \times 100 \quad (1)$$

Copolymer compositions were calculated according to Equations 2 and 3, where *m* and *n* are the number of ε-caprolactone and ω-pentadecalactone units, respectively, and $I_{4.06}$, $I_{1.63}$, and $I_{1.28}$ are the related peak integrals. A further description has been given in the results and discussion section.

$$2m + 2n = I_{4.06} \quad (2)$$

$$6m + 24n = I_{1.63} + I_{1.28} \quad (3)$$

^{13}C-NMR spectra were recorded on the same spectrometer at 126 MHz with the same solvent and standard as ^{1}H-NMR. PDL-CL dyad sequences were determined from ^{13}C-NMR spectra.

Thermal properties, glass transition (T_g) and melting temperatures (T_m) of samples were determined by DSC using a PerkinElmer calorimeter. Under inert nitrogen atmosphere at a 20 ml/min flow rate, 5–10 mg samples were analyzed. Sample scans were carried out between –70 and 200 °C at 10 °C/min with heat-cool-heat thermal cycles and T_m was measured at second heating. Crystallinity percentages were calculated by taking the ratio of fusion enthalpy (ΔH_f) of the sample to the fusion enthalpy of 100% crystalline polymer ($\Delta H°_f$) as given in Equation 4 [6]:

$$\chi_c = \frac{\Delta H_f}{\Delta H°_f} \times 100 \quad (4)$$

where $\Delta H°_{f\ PCL}$ = 139.3 J/g [18] and $\Delta H°_{f\ PPDL}$ = 233 J/g [19].

Thermal characterization of the samples was performed by TGA. The samples (5–10 mg) were heated from 25 to 550 °C at a heating rate of 10 °C/min under nitrogen flow. Analyses were performed on a PerkinElmer apparatus.

3 RESULTS AND DISCUSSION

3.1 Synthesis of Poly(ω-PDL-*co*-ε-CL) Copolymers and Their Spectroscopic Characterizations

In a previous study, successful ring-opening polymerization of ε-CL in toluene medium via homemade immobilized lipase, Im-CALB, was shown [20]. PCL with a number average molecular weight (M_n) of 14000 g/mol had been synthesized [20]. In this study, the performance of Im-CALB for copolymerization of ε-CL and ω-PDL was investigated. Copolymerizations were carried out under various reaction conditions to study the effect of temperature and reaction period. Variation in feed ratios of the two monomers were also applied to notice the change in molecular weight and other properties.

Copolymerization results obtained via Im-CALB catalysis are given in Table 1. Molecular weights tended to increase proportionally with the ω-PDL content. This is because lipase exhibits high activity for macrolactone polymerization that gives rise to higher molecular weights [5, 6, 11]. Kobayashi and coworkers reported that the enzymatic polymerization of lactones followed Michaelis-Menten kinetics and V_{max} value (reaction rate) increased with the ring size of lactone [21]. Additionally, under 80 °C and 6 h conditions, polymerization of a monomer mixture with feed ratio of 85% ω-PDL was experienced and 26000 g/mol molecular weight was reached, which further proved this fact.

Highest M_n values (about 20000 g/mol) and conversions (> 94.5%) were reached at 80 °C. The M_n values were decreased above 80 °C, which may result from a loss in some part of enzyme activity. However, Im-CALB showed a satisfying thermal stability that made polymerization possible even at 90 °C. In addition, as the reaction temperature increased, the time needed for polymerization decreased. This mainly resulted from polymerization characteristics of ω-PDL. It is known that ω-pentadecalactone is rapidly polymerized with high monomer conversions at its preferred reaction temperature of 90 °C [12]. ε-Caprolactone (sample PDL-CL-11) could not be polymerized since the reaction conditions (90 °C and 4 h) may not be appropriate for enzymatic activity and/or reactivity of ε-CL.

Since the Đ values given in Table 1 were less than 1.5, poly(ω-PDL-*co*-ε-CL) copolymers and their homopolymers can be said to have a uniform-like structure. These Đ values show the similarity between Im-CALB-catalyzed eROP and living polymerization mechanisms [22]. In some cases, ring-opening polymerization of lactones proceeds with living polymerization mechanism that results in narrow molecular weight distribution [23].

To compare the performance of Im-CALB with a commercial enzyme, Novozyme 435, additional copolymerizations were carried out under best reaction conditions (80 °C and 6 h).

Molecular weights of poly(ω-PDL-*co*-ε-CL) copolymers with 50% and 75% ω-PDL feed ratios were 22000 g/mol and 26000 g/mol, respectively. These results were not very much higher than those synthesized via Im-CALB. Therefore, Im-CALB can be considered as a

Table 1 Copolymerization results obtained via Im-CALB catalysis.

Reaction conditions	Sample name	Feed ratio (PDL : CL) (wt.%)	Composition of PDL (mol %)[a]	Composition of CL (mol %)[a]	Conv. (%)[a]	M_n (g mol^{-1})[b]	Đ[b]
60 °C – 17h	PDL-CL-1	0:100	0	100	90.1	10550	1.48
	PDL-CL-2	25:75	25.9	74.1	91.3	14000	1.43
	PDL-CL-3	50:50	46.7	53.3	92.3	16220	1.51
	PDL-CL-4	75:25	77.8	22.2	93.2	17260	1.46
	PDL-CL-5[c]	100:0	100	0	91.5	–	–
80°C – 6h	PDL-CL-6	0:100	0	100	94.6	9550	1.35
	PDL-CL-7	25:75	22.5	77.5	95.3	14400	1.35
	PDL-CL-8	50:50	37.8	62.2	97.9	20960	1.47
	PDL-CL-9	75:25	70.2	29.8	98.2	19720	1.38
	PDL-CL-10[c]	100:0	100	0	99.2	–	–
90°C – 4h	PDL-CL-11[d]	0:100	–	–	–	–	–
	PDL-CL-12	25:75	48.9	51.1	93.5	4700	1.26
	PDL-CL-13	50:50	68.6	31.4	97.2	7830	1.34
	PDL-CL-14	75:25	74.3	25.7	97.8	13730	1.34
	PDL-CL-15[c]	100:0	100	0	96.2	–	–

[a]Calculated copolymer compositions and conversions are obtained by ^{1}H-NMR. [b]M_n and Đ are measured by GPC. [c]These samples were not able to be measured by GPC, since they were not soluble in eluent solvent THF. [d]This sample could not be polymerized.

new alternative catalyst for synthesis of poly(ω-PDL-*co*-ε-CL) copolymers. It had already been suggested as an alternative to Novozyme 435 for PCL synthesis in previous studies [20].

The GPC traces are given in Figure 1. As seen from the graph, the column retains low molecular weight polymer longer than the high molecular weight polymer. These traces prove that higher molecular weights were reached at 80 °C. The GPC traces of all polymers were monomodal, except the curve for PDL-CL-12 that presents a shoulder at retention time 14 min. This may be a result of transesterification reactions occurring at high temperatures. Bankova and coworkers reported that lipases catalyze transesterification reactions at intrachain positions in addition to chain growth reactions [24]. Moreover, the shoulder at retention time 14 min may have also resulted from the degradation activity of lipase, which shows the biodegradable nature of copolymer sample. It is known from previous studies that CALB is also responsible for degradation of polyesters [17].

Figure 2 presents the ^{1}H-NMR spectrum of the poly(ω-PDL-*co*-ε-CL) copolymer with 70.2% of ω-PDL (PDL-CL-9). Characteristic peaks were assigned to the related protons of ω-PDL and ε-CL homopolymers according to the literature as follows: δ 4.06 (OC***H***$_2$), δ 3.66 (HOC***H***$_2$), δ 2.31 (COC***H***$_2$), 1.63 and 1.28 (all other protons) ppm [2,6,12,19]. Since the structures of ω-PDL and ε-CL are similar to each other, signals overlapped in the spectrum of copolymer coded as PDL-CL-9. Conversion values given in Table 1 were calculated from Equation 1 based on the signal of protons in methylene group bonded to ester group (at 4.06 ppm) and the signal centered at 4.16 ppm, which is specific for ω-PDL and ε-CL monomers. Molar compositions, which were calculated from the simultaneous solution of Equations 2 and 3, are also given in Table 1. In these equations, the coefficients in front of *m* and *n* correspond to the number of protons that give rise to signals at related chemical shift values. As seen from the spectrum, both ε-CL and ω-PDL units have 2 protons responsible for the signal at 4.06. For ε-CL units, the peaks at 1.63 ppm and 1.28 ppm were assigned to 2 and 4 protons, respectively. Similarly, for ω-PDL units, the peaks at 1.63 ppm and 1.28 ppm were assigned to 2 and 22 protons, respectively.

Poly(ω-PDL-*co*-ε-CL) copolymer structure was analyzed by ^{13}C-NMR spectroscopy. Complete ^{13}C-NMR spectra are shown in Figure 3 and peaks were assigned according to the literature as follows: δ 173.94 (O***C***OCH$_2$, *PDL*-PDL), δ 173.86 (O***C***OCH$_2$, *PDL*-CL), δ 173.56 (O***C***OCH$_2$, *CL*-PDL), δ 173.48 (O***C***OCH$_2$, *CL*-CL), δ 64.45 (O***C***H$_2$, *PDL*-CL), δ 64.34 (O***C***H$_2$, *PDL*-PDL), δ 64.09 (O***C***H$_2$, *CL*-CL), δ 63.97 (O***C***H$_2$, *CL*-PDL), δ 34.35 (OCO***C***H$_2$, *PDL*-PDL), δ 34.29 (OCO***C***H$_2$, *PDL*-CL), δ 34.13 (OCO***C***H$_2$, *CL*-PDL), δ 34.11 (OCO***C***H$_2$, *CL*-CL), δ 29.58–δ 29.12, δ 28.60 (***C***H$_2$, PDL), δ 28.3 (OCH$_2$***C***H$_2$, CL), δ 25.88 (***C***H$_2$, PDL), δ 25.48 (OCOCH$_2$***C***H$_2$, CL), δ 24.97 (***C***H$_2$, PDL) and δ 24.55 (OCOCH$_2$CH$_2$***C***H$_2$, CL)

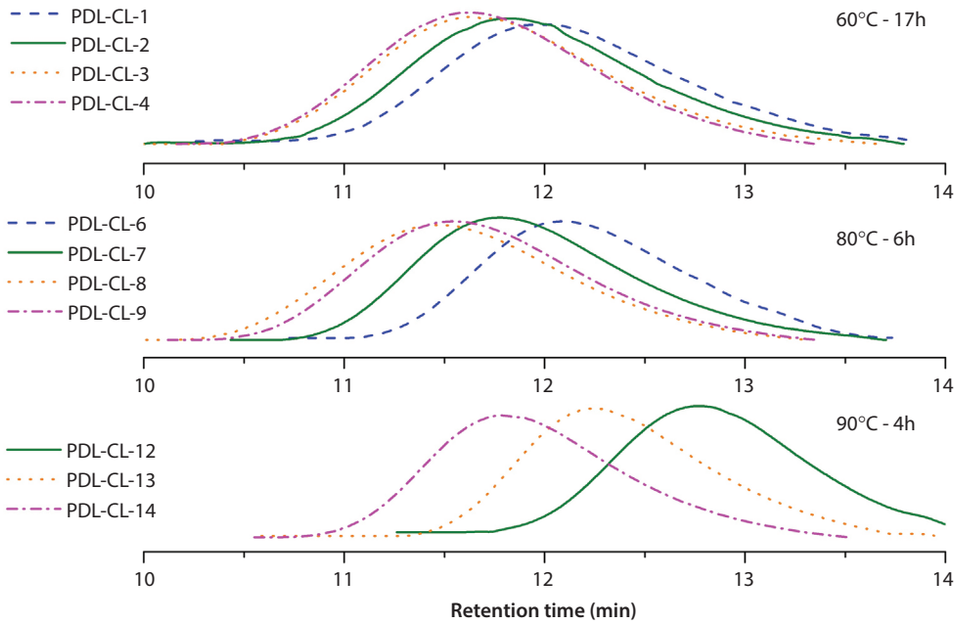

Figure 1 GPC traces of copolymer samples at various reaction conditions.

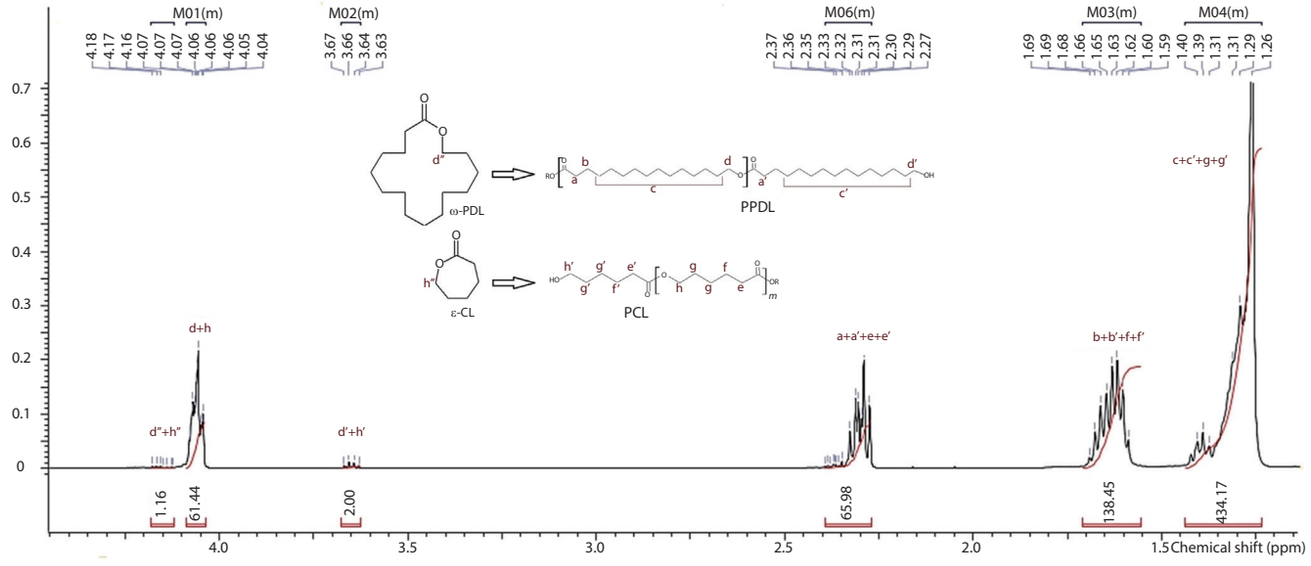

Figure 2 ^{1}H-NMR spectrum of copolymer sample PDL-CL-9.

ppm [12]. Figure 3 also includes the expanded spectral regions (δ 173.25–174.25 ppm and δ 63.80–64.70 ppm) and the four possible dyad arrangements (*PDL*-PDL, *CL*-PDL, *PDL*-CL, *CL*-CL). The signals at expanded region "a" (δ 173.25–174.25 ppm) belonged to carbonyl carbons of ω-pentadecalactone and ε-caprolactone units, whereas peaks at expanded region "b" were assigned to carbon of methylene bonded to the ester group. Possible dyads were assigned to related peaks in these expanded regions [12]. Italics are used to indicate that the analyzed carbon belonged to that unit.

3.2 Thermal Characterization of Poly(ω-PDL-*co*-ε-CL) Copolymers

Characterization of thermal properties of PPDL and PCL homopolymers and the copolymer sample PDL-CL-9 was performed by DSC and TGA.

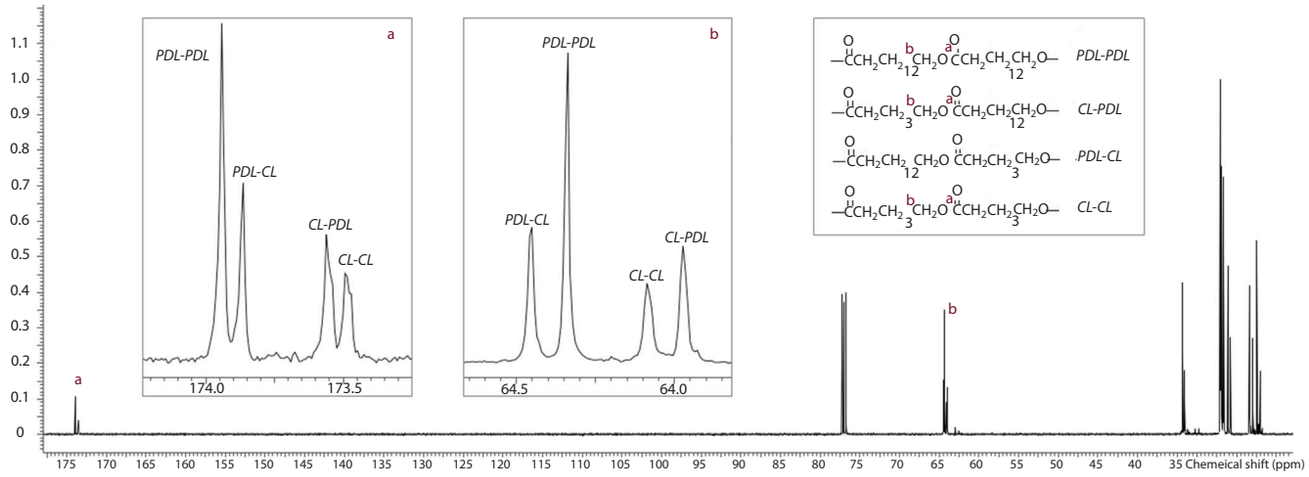

Figure 3 ^{13}C-NMR spectrum of copolymer sample PDL-CL-9.

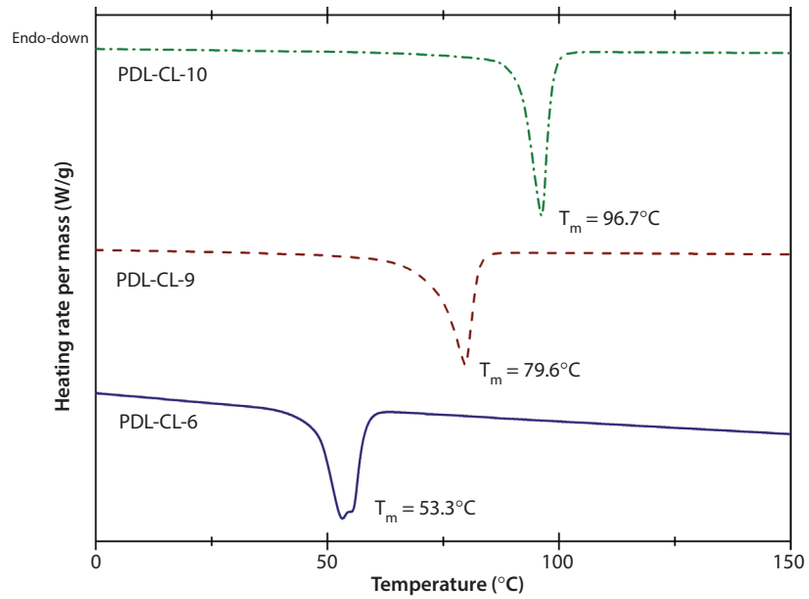

Figure 4 DSC heating curves of homopolymers and copolymer sample PDL-CL-9.

Endo-down DSC heating curves of these samples are given in Figure 4. PPDL homopolymer (PDL-CL-10) exhibited a large melting peak at 96.7 °C, which was close to the literature values with small differences that may be caused from variations in synthesis conditions [6]. The T_m values decreased linearly by increased feed ratios of ε-CL, since PCL has a lower melting temperature which is around 50 °C [1, 25].

Also, melting enthalpies (ΔH_f) showed the same trend that ranged from 116.3 J/g to 83.7 J/g, as given in Table 2. Crystallinity percentages (χ_c) of homopolymers were calculated from Equation 4. PPDL and PCL homopolymers had 49.9% and 60.0% crystallinity, respectively (Table 2).

Since ΔH_f value of copolymer with 70.2% of ω-PDL (PDL-CL-9) was between the melting enthalpy values of homopolymers, its crystallinity was estimated to be in the range of 49.9–60.0%. These results showed the semicrystalline nature of synthesized polymers. As seen from Figure 4, both samples melted over a temperature range instead of showing a sharp melting peak, which was due to the presence of amorphous and crystalline phases together. This fact also proves the semicrystallinity of polymer samples [26]. Glass transition temperature (T_g) of PPDL homopolymer

Table 2 Summary of thermal properties obtained from DSC.

Sample name	T_m (°C)[a]	T_g (°C)[a]	ΔH_f (J/g)[b]	χ_c (%)[c]
PDL-CL-10	96.7	–29.1	116.3	49.9
PDL-CL-9	79.6	–28.7	103.2	–[d]
PDL-CL-6	53.3	-[e]	83.7	60

[a]Measured from DSC. [b]Calculated from the integral area under melting peak. [c]Calculated from Equation 4. [d]Did not calculated since ΔH°f data is not available for that composition of copolymer. [e]It was not able to be measured.

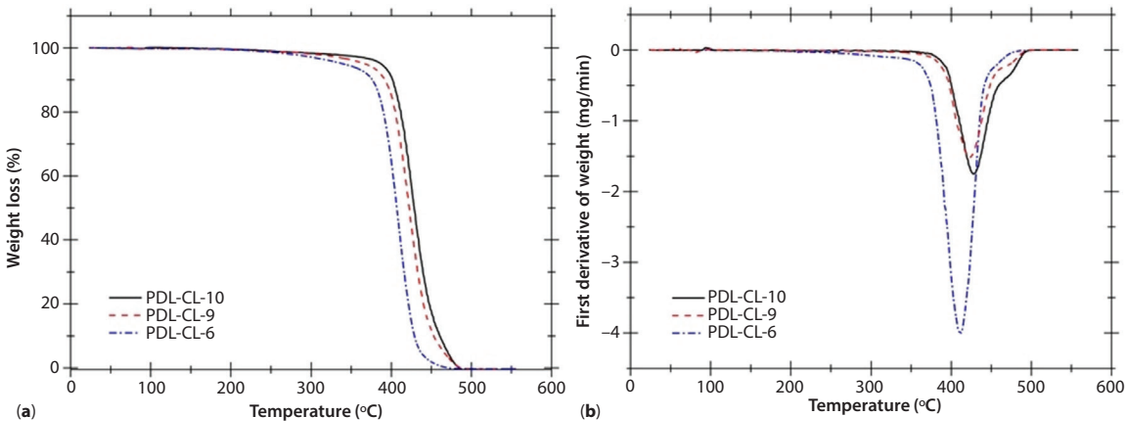

Figure 5 TGA thermograms of homopolymers and copolymer sample PDL-CL-9: (**a**) mass loss and (**b**) first derivative.

was measured as –29.1 °C, which is compatible with the literature [10]. There was no significant change in T_g for PDL-CL-9 sample. On the other hand, it is known from the literature that PCL homopolymer has a very low T_g which is around –60 °C [18]. Higher melting and glass transition temperatures of PPDL and ω-PDL-rich copolymer (PDL-CL-9) provided them with good ductility when compared with PCL.

The TGA thermograms of homopolymers and copolymer sample PDL-CL-9 are given in Figure 5. A single mass loss was observed for both samples; however, the first derivative plots of PPDL homopolymer and copolymer samples revealed two phenomena. One of them resulted from the final decomposition and exhibited a shoulder at about 475 °C. The large part of degradation occurred at 422.5 °C and 428.2 °C for PDL-CL-9 copolymer and PPDL homopolymer, respectively. Degradation temperatures for homopolymer of PPDL were similar to those obtained by Wilberth and coworkers [6]. On the other hand, PCL homopolymer showed a single and lower degradation temperature (411.6 °C). These phenomena proved that, by increasing the amount of ω-PDL in poly(ω-PDL-*co*-ε-CL), copolymers may increase the thermal resistance of the polymer.

4 CONCLUSION

In this work, poly(ω-PDL-*co*-ε-CL) copolymers with various compositions were synthesized by enzymatic ring-opening polymerization. Im-CALB, a new immobilized form of CALB, was used as the biocatalyst. Successful performance of this enzyme was shown by comparing with the commercial lipase Novozyme 435. Dependence of molecular weights of copolymers with reaction temperature and period was investigated. The highest molecular weight copolymers were obtained under 80 °C and 6 h reaction conditions, which ranged from 14400 and 20960 g/mol depending on their monomer compositions. The copolymer synthesized under best reaction conditions with 75% ω-PDL feed weight ratio (PDL-CL-9) was characterized by ^{1}H-NMR and ^{13}C-NMR. Characteristic peaks and possible dyads were assigned according to the literature. Furthermore, thermal properties of homopolymers and PDL-CL-9 copolymer were examined via DSC and TGA. The results showed that increasing the amount of ω-PDL in copolymers may result in more thermally stable polymers. Consequently, with their improved features, enzymatically synthesized poly(ω-PDL-*co*-ε-CL) copolymers may be good alternatives to

PCL homopolymers for use in various applications in the biomedical field. By the addition of ω-PDL to the structure, biodegradable copolymers had comparable thermal properties to LDPE.

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