Journal of Polymer Research (2023) 30:291
https://doi.org/10.1007/s10965-023-03678-7

ORIGINAL PAPER

Microwave assisted ring-opening polymerization of Ɛ-caprolactone using organic acids

Inara Ahmadova[1] · Shamo Tapdiqov[2] · Mehmet S. Eroglu[3,4] · Muge Sennaroglu Bostan[1]

Received: 31 March 2023 / Accepted: 27 June 2023

Abstract

Microwave-assisted ring opening polymerization (ROP) of ε-caprolactone was performed using three different carboxylic acids as initiators. In order to determine the effect of the acidity strength of the initiators on the molecular weight and terminal group functionality, the acids from strongest to weakest, i.e. trifluoro acetic acid, acetic acid, and benzoic acid, were used as initiators. The microwave power was kept at 600 W. The chemical structure and thermal properties of the synthesized low molecular weight PCLs were determined using Fourier Transform Infrared Spectroscopy (FTIR), ^{1}H Nuclear magnetic resonance (^{1}H-NMR) spectroscopy, and differential scanning calorimetry (DSC). The molecular weight of the products was determined and compared using Light Scattering-Gel Permeation Chromatography (LS-GPC) and ^{1}H-NMR spectroscopy. Their spectroscopic analyses showed that microwave-assisted polymerization is a useful technique in synthesizing the low molecular weight PCL without undesirable impurities. Melting points of the synthesized low molecular weight PCLs ranged from 52 °C to 63 °C, as determined by DSC. Their number-average molecular weights (Mn) and polydispersity index (PDI) were between 1.256—1.540 and 1.35—4.90 kDa, respectively. The Mn values obtained from the GPC were consistent with those calculated from ^{1}H-NMR and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) techniques. These findings highlighted the significance of the microwave technique in obtaining low molecular weight PCL for drug delivery formulations.

Keywords Microwave · Ring-opening polymerization · ROP · Acetic acid · Benzoic acid · Trifluoroacetic acid · Poly epsilon-caprolactone · PCL

Introduction

Polycaprolactone (PCL) is a widely used biodegradable polyester in biomedical applications due to its excellent physicochemical properties, good processability, low toxicity, and easy-to-cell internalization [1, 2]. Due to its notable properties, many studies have been conducted on the synthesis of PCL and the preparation of its blend with a broad range of other biodegradable polymers [3]. The molecular weight and degree of crystallinity of PCL greatly influence its physical, thermal, and mechanical properties and play an important role in cell internalization. PCL is a hydrophobic semicrystalline polymer soluble at ambient temperature in organic solvents and easily processed due to its low melting temperature and blending compatibility. These properties have motivated researchers to explore its potential applications as a biodegradable drug carrier [4].

On the other hand, micelles, liposomes, and lipidic nanoparticles are well-known anti-cancer drug carriers used to enhance drug efficacy by targeting cancer cells. While designing a nano-drug carrier system with specific targeting and enhanced cell internalization capability, it is crucial to use low molecular weight hydrophobic polymers. Despite many advantages and superior properties, only a few researchers have prepared nanoparticles from pure PCL

✉ Muge Sennaroglu Bostan
msennaroglu@marmara.edu.tr

1 Engineering Faculty, Department of Chemical Engineering, Marmara University, Aydınevler Maltepe, 34854 Istanbul, Turkey

2 SOCAR Oil and Gas Research and Design Institute, Deparment of Prevention of sand and water appearance, PO Box AZ 1012, Yasamal, Baku, Azerbaijan

3 Technology Faculty, Department of Materials Science and Engineering, Marmara University, Aydınevler Maltepe, 34854 Istanbul, Turkey

4 Chemistry Group Laboratories, TUBITAK-UME, PO Box 54, 41471 Gebze, Kocaeli, Turkey

Published online: 05 July 2023

synthesized by microwave-assisted ROP without any catalyst and the resultant nanoparticles had diameters higher than the desired sizes. On the other hand, addition of a targeting ligand to a drug delivery system provides the nanocarriers with the advantage of binding to target cells, and internalizing and promoting drug release inside the cells [5–7]. Therefore, utilizing low molecular weight biodegradable polymers in the targeted drug carriers is crucial. Considering the low success rates in cancer therapies, designing a small-sized nanocarrier obtained from low molecular weight PCL which is synthesized safely in a non-toxic fashion, is important [8]. ROP of Ɛ-caprolactone (Ɛ-CL) is generally synthesized in bulk or in organic solvents by ionic, organocatalytic, enzymatic, and coordination polymerization mechanisms [2]. The Food and Drug Administration (FDA) has approved PCL and its some copolymers for use in biomedical applications. However, most of the time, metal-based catalysts, especially tin(II) 2-ethyl hexanoate $Sn(Oct)_2$, are used in the ROP mechanism. [9, 10]. Recent studies have explored the solvent-free ROP of ε-caprolactone (ε-CL) using metal-based chlorides (Mg, Sn, Zn, Al, and Sn) as initiators [11]. Funfuenha et al. compared the performance of n-butyltin(IV) chlorides and tin(II) 2-ethylhexanoate (Sn(Oct)2) as initiators, observing that an increased number of chlorine atoms in n-butyltin(IV) chloride led to a decrease in the molecular weight of poly(ε-caprolactone) (PCL) under solvent-free conditions [12]**.** Although FDA has approved some metal-based catalysts, no studies have been reported on their long-term and physiological effects, which may create a different level of risk. The available information on how metal ions affect living organisms allow us to understand the possible risks and harmful effects of metal catalyst-based impurities in biomedical applications. These risks may affect the mammalian cells used in tissue engineering [13]. Therefore, there is a growing interest in using non-toxic or non-metallic catalyst/initiator systems during polymerization reactions of Ɛ-CL [14]. In PCL synthesis and its drug release applications, it is crucial to develop a safer and risk-free ROP method that does not require a catalyst and enables the achievement of low molecular weights [13, 15].

While conventional thermal polymerization methods have found widespread use in polymer synthesis over the past decade, MW-assisted ROP opens a new route providing a faster and more effective polymerization. In addition to polycondensation and free radical polymerization methods, ROP is also possible with microwave synthesis..The kinetics observed under both microwave and thermal conditions demonstrate that the microwave method increases the conversion rate up to three times compared to the conventional heating method [14]. Using microwaves in polymerization as a source of energy also offers several advantages over traditional thermal methods. Microwave energy is highly efficient, leading to faster reaction time and higher yield. Furthermore, it provides a more controlled and uniform heating, which can reduce the formation of by-products [2].

There have been various successful syntheses of polymeric materials using the microwave irradiation technique for a wide range of purposes [16]. Using non-toxic, small organic compounds as an initiator for the ROP reactions might lead to the development of safer, non-toxic and reliable products applicable in the biomedical field, particularly in drug delivery systems. Among the initiators, organic acids are less toxic, readily available, and inexpensive, making them a safer and cost-effective alternative. In addition, their low vapor pressures generate a mild condition for the ROP reactions. Different carboxylic acids, such as lactic, tartaric, hexanoic, propionic, citric, and 6 hydroxy hexanoic acid [17], as well as amino acids like glycine, proline, and serine, have been utilized in studies to effectively open the ring structure of Ɛ-CL in the presence of benzyl alcohol [18]. The pKa value represents the acid dissociation constant and indicates the acidity of a compound in solution. According to the literature, weak organic acids possessing pKa values ranging from 2 to 5 were identified as capable of catalyzing the ROP reaction of Ɛ-CL. This leads to the formation of poly(ε-caprolactone) (PCL) with a comparatively low molecular weight [18–21].

Casas et al. proposed that the initiation and catalyzation of the ROP of Ɛ-CL could occur without using alcohol as an initiator [18]. They indicated that the initiation process commences through either amino or hydroxy group of organic acids. The ROP, initiated by organic acids, is believed to follow a mechanism of monomer activation. This mechanism entails initiation occurring through the reaction of a nucleophile with a proton-activated monomer, leading to the creation of a ring-opened mono ester compound. Thereafter, polymerization advances when the terminal hydroxy group of the growing polyester serves as a nucleophile towards the activated proton monomer. It is worth noting that proton-activation is a technique employed by several enzymes to execute their specific processes [18]. Carboxylic acid-initiated ROP of PCL, with an weight-average molecular weight (Mw) lower than 5500 g/mol, was also investigated by Bixler et al. [22, 23]. In a separate study, succinic acid was used to synthesize PCL having two carboxyl groups at its terminals and a weight-average molecular weight of less than 3000 g/mol. [22, 24]. Song et.al., synthesized PCL with M_w value over 12,000 g/mol with a PDI values less than 1.6, using maleic, succinic and adipic acids. Furthermore, the obtained polymers were used as controlled release systems of ibuprofen [21].Another study utilized salicylic acid as an organo-catalyst and benzyl alcohol as an initiator in bulk at 80 °C to perform the controlled ring-opening polymerization (ROP) of ε-CL. The objective was to obtain a narrowly distributed PCL [25]. Functional groups, such as hydroxyl, carboxyl, and amino, are highly valuable due to their ability

to participate in multiple reactions. They also contribute to the enhancement of the hydrophilicity and degradability of polymers [26]. Additionally, these functional groups provide the polymers with mechanical, thermal, and chemical, properties. PCL with COOH and OH terminal groups are an important class of reactive biodegradable polyesters, as they have the capacity to react selectively with other polymers which enhances the hydrophilicity and biodegradation properties leading to easy endocytosis. Because of these properties, they are preferred to be used in drug carrier formulations. Considering these features, the use of pure PCL, obtained through a microwave-initiated polymerization process without the need for any catalyst, and thus not containing any toxic impurities, gains importance in controlled drug delivery formulations.

For this purpose, we have synthesized low molecular weight PCL through the ROP reaction of Ɛ-CL using weak organic acids such as acetic, benzoic, and trifluoroacetic acids without using any toxic catalysts or solvents under microwave radiation with a maximum output of 600 W. Microwave assisted polymerization is a promising technique for efficient synthesis of low molecular weight PCLs with tuned carboxyl and/or hydroxyl terminal groups, which has the potential to increase the efficiency of targeted drug delivery systems.

Experimental

Materials

ε-caprolacton (ε-CL) (Sigma-Aldrich) was kept over calcium hydride (CaH_2) at room temperature for 24 h and then distilled under reduced pressure in an argon atmosphere. Tin(II) 2-ethylhexanoate (Sigma-Aldrich, 95%) was purified by vacuum distillation. Tetrahydrofuran, Methanol, diethyl ether, benzoic acid, trifluoroacetic acid, and acetic acid were obtained from Sigma Aldrich and used as received. Unless otherwise stated, all the compounds were used without additional purification.

Synthesis of PCL

ε-CL was subjected to a MW-assisted ROP process using three different organic acids as initiator, i.e. acetic acid, trifluoroacetic acid, and benzoic acid, without using any catalysts. The synthesized compounds were named as PCL-AA, PCL-TFA, and PCL-BA, respectively. Impact of the catalyst on the polymerization duration, molecular weight, and molecular structure was examined, employing tin(II) 2-ethylhexanoate as a catalyst in the polymerizations of BA and AA. The control samples were synthesized using tin(II) 2-ethylhexanoate, which were prepared under the same conditions as catalyst-free samples. The only difference was the addition of 6 µL of catalyst. The control samples with added catalyst were named PCL-AA-CAT and PCL-BA-CAT, respectively. Table 1 shows the compositions of the PCL products, the total irradiation time and percent conversions calculated based on gravimetric results. A representative experimental synthesis procedure for PCL-AA is as follows: a mixture of 25 mL (0.225 mol) of ε-CL and 5.13 mL (0.08 mol) of acetic acid was placed in a sealed beaker and irradiated at 600 W microwave power for 30 s, then allowed to cool to room temperature. The same procedure was applied for periodic irradiation times with a total of 9 min until a viscous mass was detected. The resulting polymer was dissolved in 40 mL THF and precipitated using deionized water under magnetic stirring at 2000 rpm for one hour. The precipitated product was filtered and vacuum dried for three days at 40 °C. Each sample underwent different periodic microwave irradiation time until the polymerization was complete (Table 1). The control samples were also prepared using the same procedures, and the amounts of Tin(II) 2-ethylhexanoate catalyst used are shown in Table 1.

Equipments and measurements

The ROP reactions of PCL were performed using a 2,45 GHz microwave oven with a maximum output power of 600 W. ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra of the polymers were recorded on a Varian model NMR (600 MHz) in $CDCl_3$ and used to investigate the

Table 1 Compositions of the PCL samples, total irradiation times, conversions and thermal data

Sample	ε-CL (mol)	AA (mol)	BA (mol)	TFA (mol)	CAT (µL)	Irradiation time (min)	Conversion (wt-%)	Tm (°C)	ΔHm (J/g)	Xc* (%)
PCL-AA	0.225	0.08	—-	—	—-	9	96.95	52.7	99.4	71.5
PCL-BA	0.225	--	0.08	—-	——	9.5	77.85	62.3	106.5	76.6
PCL-TFA	0.225	—	—-	0.12	—	3	97.19	60.6	129.9	93.4
PCL-AA-CAT	0.225	0.08	—	—-	6	4.5	96.52	55.2	120.8	86.9
PCL-BA-CAT	0.225	—	0.08	—-	6	3	99.37	46.7	88.1	63.4

*Crystallization of the samples were calculated using the melting enthalpy of the 100% of crystalline PCL, which was taken as 139 J/g [27]

polymer structures and determine their M_n values. Gel permeation chromatography (GPC) was used to determine the molar mass and molar mass distribution of the polymers. This was achieved using a Perkin-Elmer 200 GPC high-pressure pump, injector, and a series of THF columns consisting of a guard column, Styragel HR2, Styragel HR3, Styragel HR4E, and Styragel HR5E. The analysis was carried out at 25 °C using THF as a mobile phase with a flow rate of 0.7 mL/min. The system was equipped with a Wyatt Optilab differential refractive index detector (RI) set at 654 nm and a Dawn Heleos multi-angle light-scattering (LS) detector. The polymer solutions had concentrations ranging from 5.2 to 6.2 mg/mL, and all the samples were filtered through a 0.45 µm filter before use. DSC was used for monitoring the melting behavior of the samples and the measurements were performed using Perkin Elmer Jade DSC and Pyris software at a heating rate of 10 °C/min under a dynamic argon atmosphere (20 ml min^{-1}). FT-IR spectra of the samples were recorded using Nicolet iS10 FTIR Spectrometer equipped with Smart Orbit high-performance diamond attenuated total reflectance (ATR) accessories. Measurements were performed between 400–4000 cm^{-1} in transmission mode. MALDI-Mass spectra were recorded on a BRUKER Microflex LT instrument equipped with time-off-flight (TOF) analyzer and a nitrogen laser accumulating 50 laser shots in dihydroxybenzoic acid as the MALDI matrix. Ion acceleration and mass range were up to + 20 kV and 500,000 m/z, respectively.

Results and discussion

FTIR analysis

The FTIR spectrum of PCL-AA is presented in Fig. 1, exhibiting the characteristic peaks of PCL. A broad band, observed at 3436.47 cm^{-1}, is due to –OH groups. The peaks at 1723 cm^{-1} is the result of the vibration stretching of C = O symmetric carbonyl groups of PCL [1, 19, 28]. A weak absorption band of C−H deformation vibrations of CH_2 groups was observed at 1463 cm^{-1}, 1375 cm^{-1} and 731.93 cm^{-1}. The peaks at 2924.44 cm^{-1} and 2857.90 cm^{-1} belong to the C-H stretching band of CH_2 groups [19]. All PCL samples showed identical peaks, which are in well agreement with the control samples (PCL-AA-CAT and PCL-BA-CAT)and authoritative PCL polymers. These results demonstrated that the microwave-assisted ROP of Ɛ-CL with AA, BA and TFA occurred successfully. Hydroxyl and carboxyl (also the benzene group of PCL-BA and the CF_3 group of PCL-TFA) groups of all PCLs appeared with a lower transmittance value compared with the peaks of authoritative PCL.

^{1}H-NMR analysis

Figure 2 shows the ^{1}H-NMR spectrum of PCL-AA. The specific peaks of PCL were observed at 4.04 ppm (methylene protons of -O-CH_2- groups), 2.03 ppm (protons of terminal -CH_3 group), 2.28 ppm (methylene protons of

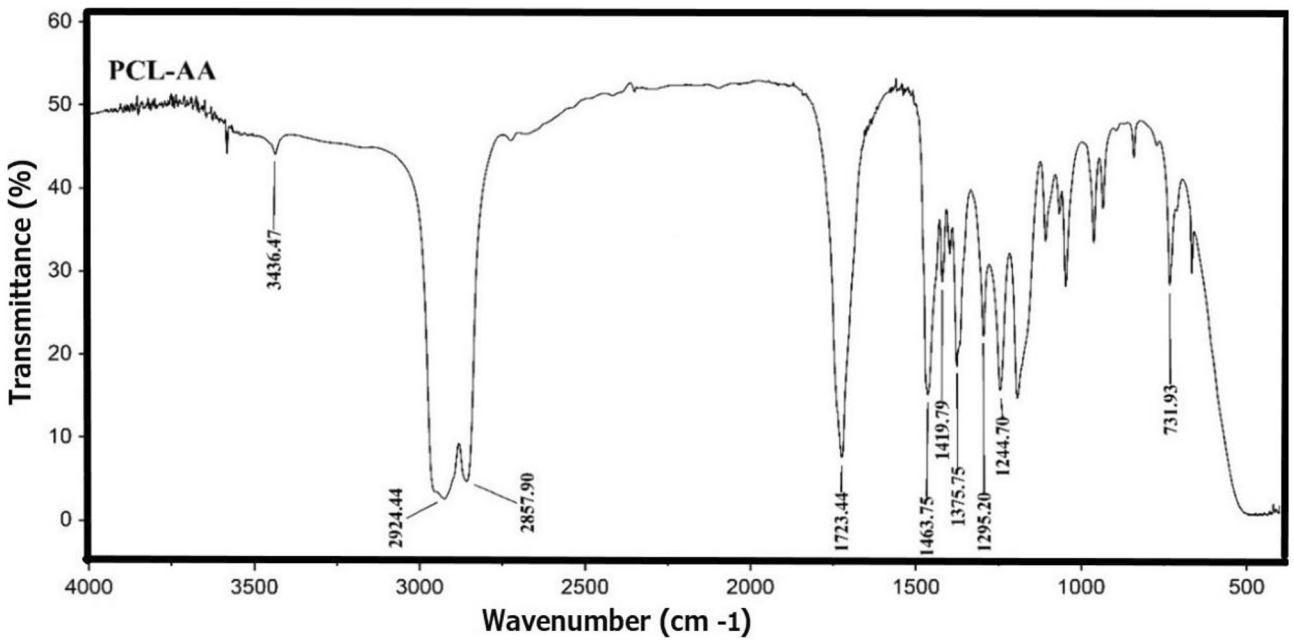

Fig.1 FTIR spectrum of PCL-AA

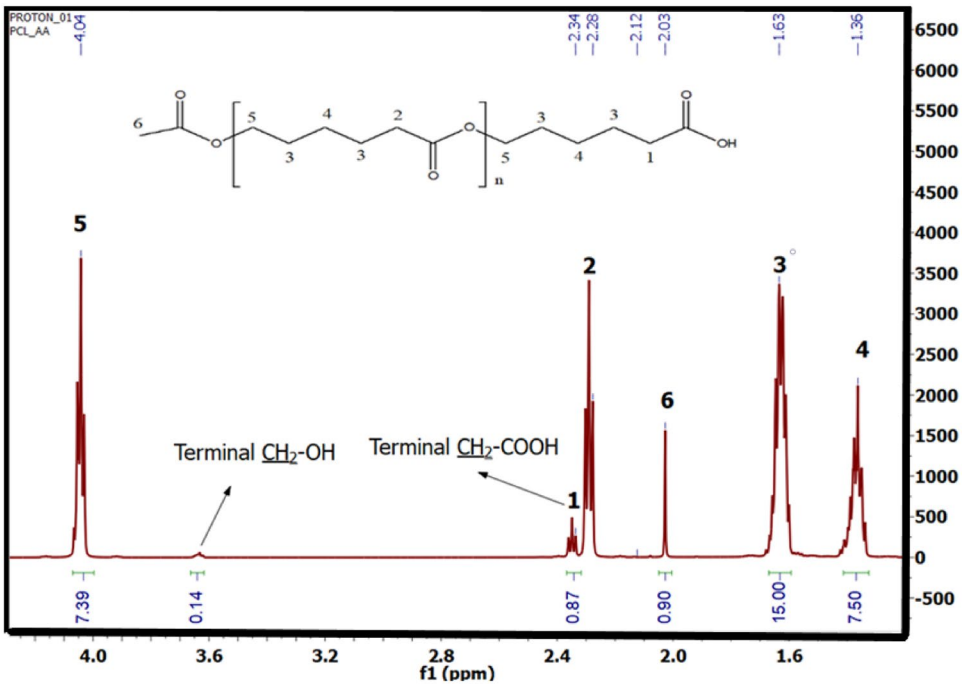

Fig. 2 ^{1}H-NMR spectrum of PCL-AA

-CH_2-C = O-), 2.34 ppm (methylene protons of terminal –CH_2-COOH), 1.63 ppm and 1.36 ppm (H_3 and H_4 protons of methylene groups). Using acetic acid as an initiator resulted in the appearance of two low-intensity proton signals, indicating that the ROP reaction proceeded in two different fashions resulting in the formation of both -CH_2-COOH (major) and -CH_2OH (minor) terminal groups, methylene protons of which were identified to be at 2.34 ppm and 3.63 ppm, respectively. The ration of the COOH/OH terminal groups was determined to be 87/14 from their proton integrations (Fig. 2). The ^{1}H-NMR spectrum of the control sample, PCL-AA-CAT (Fig. 3), synthesized using Tin(II) 2-ethylhexanoate, showed no significant difference compared to PCL-AA.

The synthesis of PCL, initiated by acetic acid, was successful as confirmed by both ^{1}H-NMR and FTIR

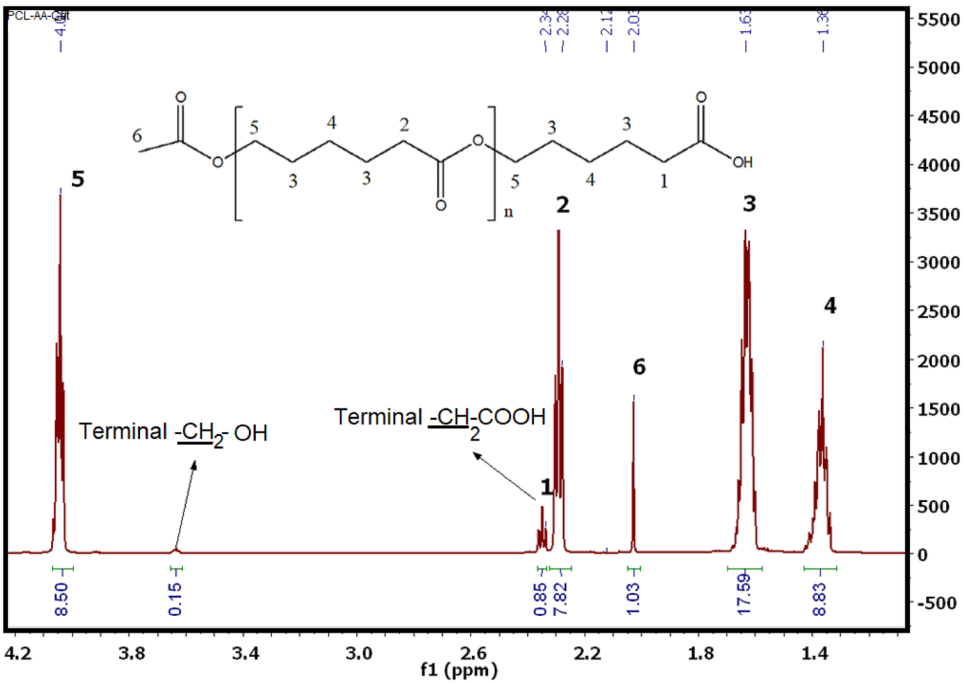

Fig. 3 ^{1}H-NMR spectrum of PCL-AA-CAT sample

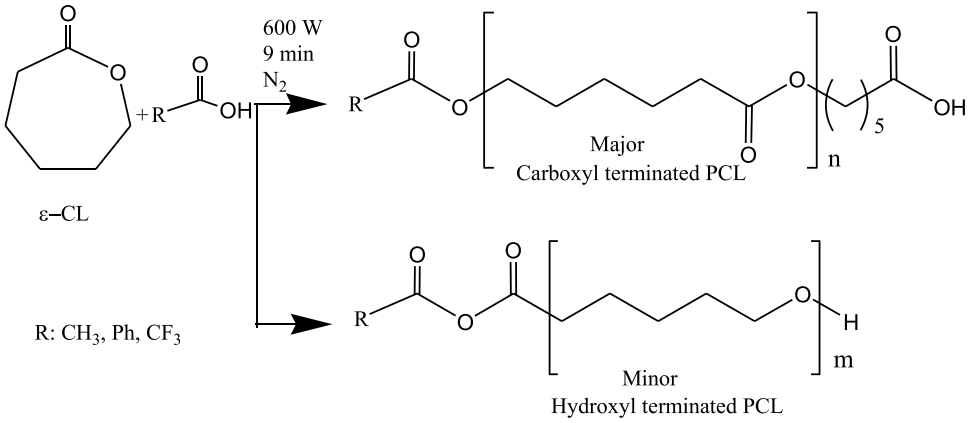

Fig. 4 MW assisted ROP of Ɛ-CL with different carboxylic acid initiator

measurements. The comparison of the ^{1}H-NMR spectra of PCL-AA and PCL-AA-CAT showed that the ROP of Ɛ-CL occurred both with and without the catalyst. Thus, the synthesis without a catalyst can be considered to be innovative. By evaluating the ^{1}H-NMR and FTIR spectra and considering the two different chemical structures of the synthesized PCL using AA as initiator, we propose two different initiation mechanisms (Fig. 4).

Similar results were observed in PCL synthesis using benzoic and trifluoroacetic acids as initiators. These samples were also terminated with OH and COOH groups according to the mechanism given in Fig. 4. The ^{1}H-NMR spectrum of PCL-BA is shown in Fig. 5. The proton signal for the methylene group of CH_2-OH appeared at 3.65 ppm, and the proton signal of the methylene group of CH_2-COOH was observed at 2.4 ppm. Two different terminal groups of PCL obtained from the benzoic acid initiated ROP reaction was observed. Its ^{1}H-NMR spectrum exhibited a doublet at 8.01 ppm and two triplets at 7.54 and 7.43 ppm, which were attributed to the aromatic protons of the phenyl ring. The terminal -CH_2-OH and –CH_2-COOH groups indicated that benzoic acid-initiated ROP of Ɛ-CL was formed. ^{1}H-NMR spectrum of PCL-BA indicated that the peak methyl protons of AA at 2.03 ppm disappeared (Fig. 5), while the phenyl protons of benzoic acid was observed in the range of 7.4–8.0 ppm. Similarly, the proton signal of the methylene group of CH_2-OH and CH_2-COOH appeared at 3.65 ppm and 2.4 ppm, respectively. Their proton integration ratios (-CH_2-COOH/-CH_2-OH) was found to be 36/65 (Fig. 5), which was lower than that of the value for the PCL-AA. It was observed that the reaction with BA initiator resulted in relatively less terminal COOH groups compared to AA. Regarding PCL-BA-CAT (Fig. 6), similar proton signals with similar CH_2-COOH/CH_2-OH methylene terminal groups ratio were observed.

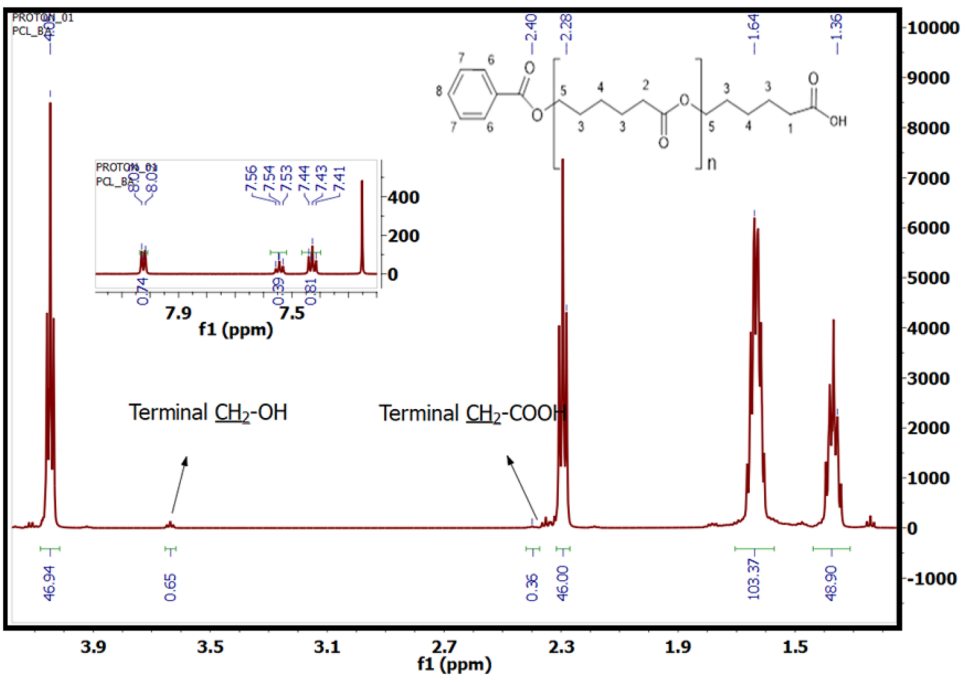

Fig. 5 ^{1}H-NMR spectrum of PCL-BA

Although the ^{1}H-NMR spectrum of PCL-BA-CAT was similar to the NMR spectrum of PCL-BA, the integration ratio of methylene protons of the CH_2-COOH and CH_2-OH groups was different. This ratio was determined to be higher than that of PCL-BA (CH_2-COOH/CH_2-OH is 62/38). This result showed that the use of a catalyst creates relatively more terminal -COOH groups than -OH terminal group.

Yu et al. studied the benzoic acid-initiated microwave assisted ROP of PCL. They did not observe the methylene proton signals of the terminal –CH_2-COOH groups in the ^{1}H-NMR spectrum. They also did not observe the phenyl group in their ^{1}H-NMR and FTIR spectra. They used UV spectroscopy to identify the terminal groups as well [22]. On the other hand, Liu & Liu investigated the production of PCL using natural amino acids as initiators and analyzed the incorporation of amino groups into the PCL chain using ^{1}H-NMR technique. Additionally, amino acid incorporation was also confirmed through carboxyl group titration. Polymers initiated by L-alanine and L-phenylalanine amino acids clearly showed the formation of the -NHCO- group, indicating the incorporation of amino groups into the PCL chain, and terminal CH_2OH groups were observed from the spectra. The phenyl moiety belonging to phenylalanine was also observed at 7.18 ppm through ^{1}H-NMR analysis, providing a clear structural explanation similar to our results [29]. Oledzka et al. investigated the polymerization of Ɛ-CL using α-amino acids as initiators. Natural L-arginine and L-citrulline were used as α-amino acids, and the structure was verified using FTIR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and MALDI-TOF MS analysis. Incorporation of initiators into the PCL chain was found to be similar to Liu and Liu's study, and both studies could easily detect the amino acid functionalized PCL through ^{1}H-NMR analysis [30].

Characteristic peaks of PCL were observed in ^{1}H-NMR spectrum of the PCL-TFA as well (Fig. 7). Moreover, the peak integration ratio of CH_2-COOH and CH_2-OH terminal methylene protons was found to be different than the others (Tables 1 and 2).

Analysis of ^{1}H-NMR and FTIR spectra indicated that acetic, benzoic, and trifluoroacetic acids successfully resulted in ROP for Ɛ-CL under microwave irradiation in a short time to yield PCL with hydroxyl and carboxylic acid terminal groups. A quantitative ^{1}H-NMR analysis of the terminal groups showed that the highest COOH/OH ratio was obtained with AA initiated ROP, and the catalyst did not affect the ratio. In BA-initiated polymerization, this ratio was found to be lower than that of the AA-initiated polymerization. Regarding the polymerization initiated with TFA, equal amount of COOH and OH terminal groups were obtained. High monomer conversion was observed within 9.5 min without use of any catalysis (Table 1). Although all the PCL products were terminated with the hydroxyl and carboxylic

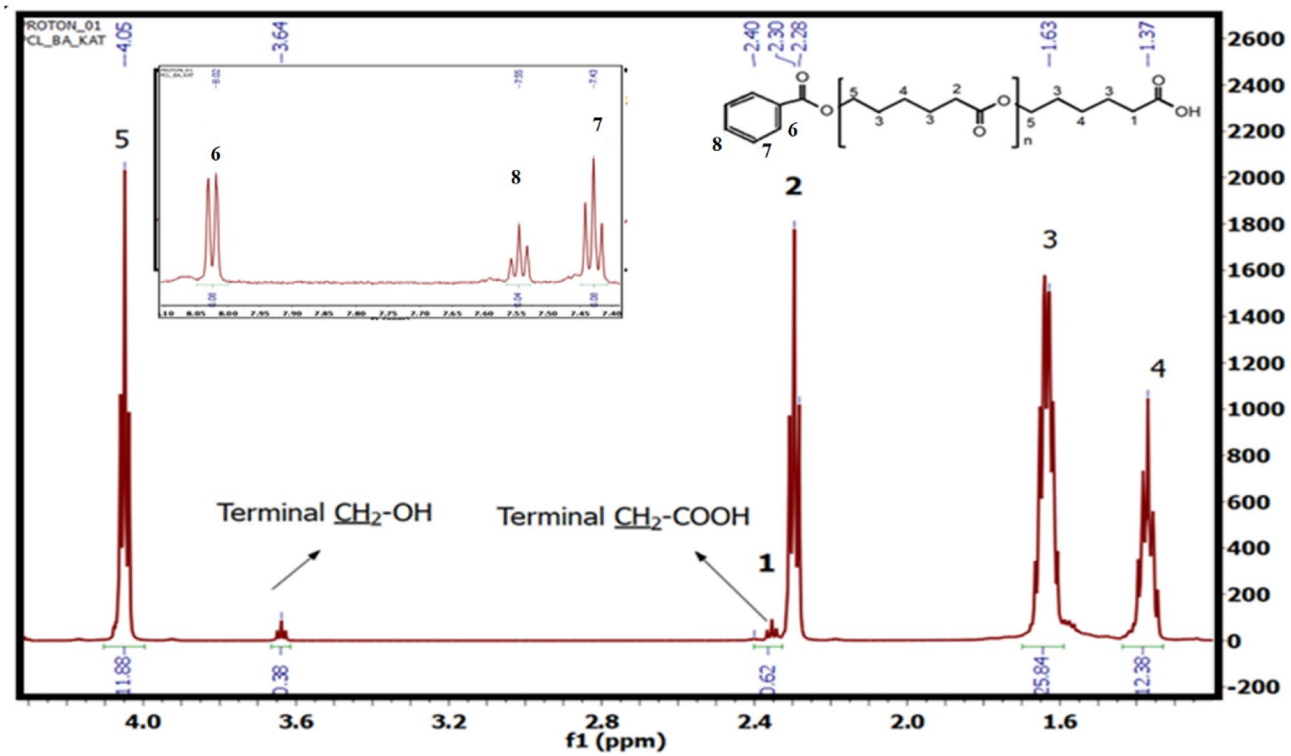

Fig. 6 ^{1}H-NMR spectrum of PCL-BA-CAT

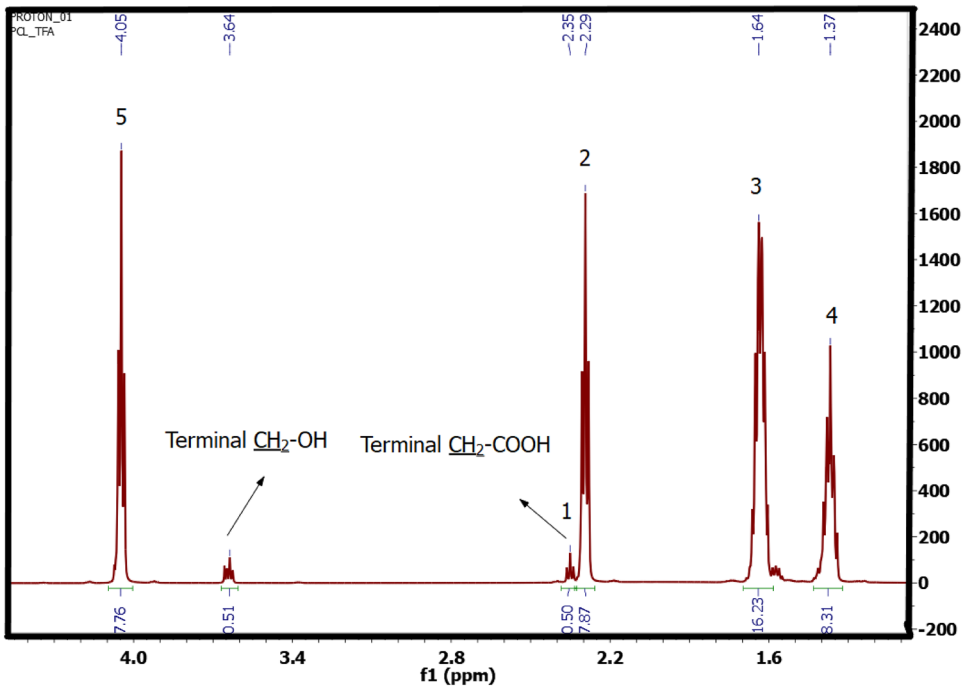

Fig. 7 ^{1}H-NMR spectrum of PCL-TFA

acid groups, the ratios of carboxylic acid to hydroxyl groups varied depending on the type of organic acid initiator. These differences were attributed to the chemical structure and the reactivity of the used organic acid initiators and their pKa values. There might be some advantages of the dependence on the type of the initiator for the terminal group ratio of the low molecular weight PCL considering its use in some possible modification reactions, such that the tunable terminal group ratio can be achieved by using different carboxylic acid initiators.

GPC analysis

The molecular weight and molecular weight distribution of the samples, obtained with and without the use of tin(II) 2-ethylhexanoate catalyst, were calculated using an online GPC-LS system. The results of the number average molecular weight (Mn), weight average molecular weight (Mw), and polydispersity index (Mw/Mn) of the PCL samples are given in Table 2. Figure 8 illustrates the GPC-LS results of the PCL samples. For clearity, their only refractive index curves are given. THF was utilized as a mobile phase, and the differential refractive index detector was used to determine the specific refractive index increment (dn/dc) of the polymers as 0.07 ml/g. Additionally, the Mn values, calculated from the GPC results, were compared to those determined through ^{1}H-NMR analysis (Table 2).

The GPC results indicated that PCL-AA, PCL-BA and PCL-TFA had Mn values of 1355 g/mol, 4900 g/mol and 1507 g/mol, respectively. The control samples PCL-AA-CAT and PCL-BA-CAT had average number molecular weights of 1590 and 3970, respectively. The lowest number average molecular weight was obtained with the acetic acid-initiated PCL sample (PLC-AA), which was slightly lower than that of the control sample obtained by a microwave-assisted ROP, using a catalyst (PCL-AA-CAT). Conversely, the benzoic acid-initiated PCL sample (PCL-BA) had a relatively higher number average molecular weight than that of the catalyst added PCL-BA-CAT sample. The polydispersity indexes of the samples were between 1.26

Table 2 Molecular weight of the PCL samples initiated by different organic acids determined by ^{1}H-NMR and GPC-LS

Sample	Mn (g/mol) (^{1}H-NMR)	Mn (g/mol) (GPC-LS)	Mw (g/mol) (GPC-LS)	PDI (Mw/Mn)	Number of monomer unit	Terminal COOH/OH
PCL-AA	914	1355	1830	1.351	8	0.86/0.14
PCL-AA-CAT	1085	1590	2000	1.26	9	0.85/0.15
PCL-BA	5365	4900	6192	1.256	46	0.36/0.65
PCL-BA-CAT	1489	3970	5,298	1.330	12	0.62/0.38
PCL-TFA	1025	1507	2300	1.544	8	0.50/0.50

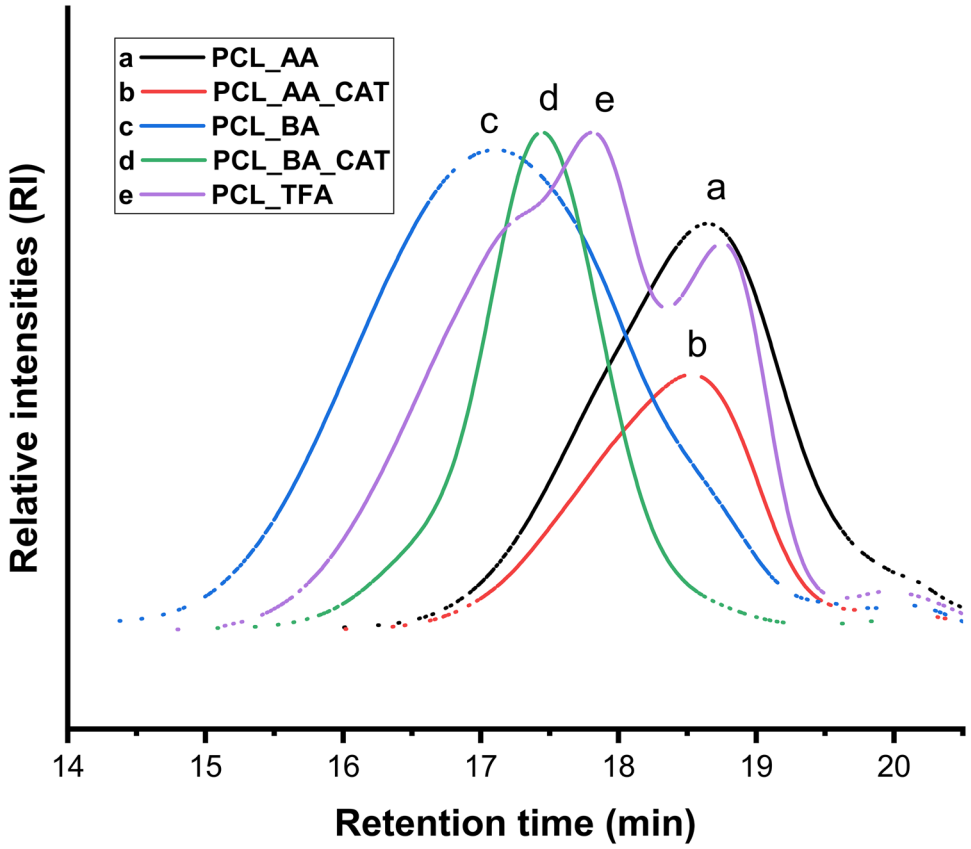

Fig. 8 GPC-Refractive index chromatograms of the PCL products

and 1.54, indicating that all the samples had moderate polydispersity. Moreover, all the samples had a unimodal distribution, observed with the GPC chromatograms. The lowest dispersity was obtained with PCL-BA among the catalyst-free samples. The number average molecular weights obtained from GPC differed from that of calculated by ^{1}H-NMR. MacLain and Drysdale previously proposed a conversion factor of 0.45 to adjust the molecular weight values obtained from the GPC to the actual molecular weight of PCL, which was achieved utilizing a polystyrene standard calibration as a reference and then the relative values were determined [31, 32]. In a separate study, the Mn values, obtained from GPC, were found to be higher than the results obtained from the end-group analysis [31, 33]. However, our LS-GPC results provided a more precise and absolute method for determining the molecular weight of PCL, without requiring a conversion factor and enabled us to determine the absolute Mn values. As the yields were clear enough, they did not require any further normalization, which are the results of more precise and accurate measurements compared to the previous studies. Nevertheless, differences between the results obtained from GPC and ^{1}H-NMR still exist. These differences are considered to be reasonable due to the variations in the methods utilized for each analysis. It is essential to consider carefully the analytical techniques employed and their inherent limitations to obtain valid and accurate molecular weight values for a specific polymer system.

MALDI-TOF analysis of the PCL samples initiated by acetic acid and trifluoroacetic acid were recorded for supporting the ^{1}H-NMR and GPC-LS results (Fig. 9). The main peaks observed in Fig. 9A (m/z 995.3, 1109.1, 1223.4, 1336.7, and 1451.7) were attributed to the acetic acid initiated PCL chains with the degree of polymerization of mainly 8, 9, 10, 11 and 12, respectively. In Fig. 9B, the series of main m/z peaks between 1069.5 and 1983.3 correspond to the degree of polymerization between 8.0 and 16.0 (molecular weight values of TFA and ε-CL are 149 g/mol and 114 g/mol, respectively). The degree of polymerization of PCL-TFA was higher than that of PCL-AA. These values coincide with the molecular weight values obtained in GPC-LS and ^{1}H-NMR analysis.

Differential scanning calorimeter (DSC)

The DSC curves of microwave-irradiated PCL, synthesized in the presence and absence of catalyst, are shown in Fig. 10 and their melting temperature (T_m), melting enthalpy (ΔH), and calculated crystallinity (Xc) values [34] are given in Table 2. The PCL synthesized by thermal methods had a small melting T_m between 59–64 °C, and it is known that there is a decreasing crystallinity trend with decreasing

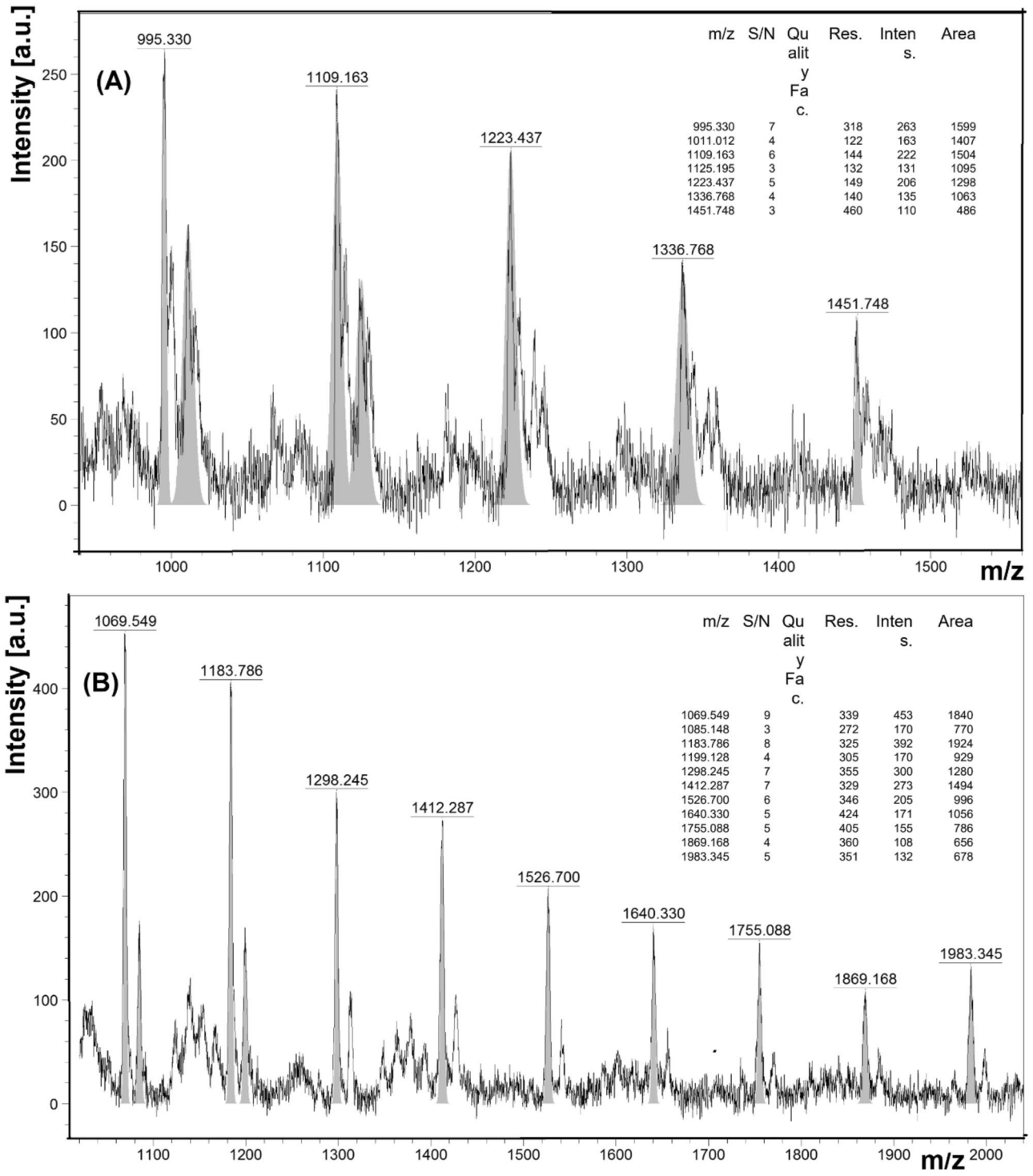

Fig. 9 MALDI-TOF spectra of PCL products. **A** PCL-AA. **B** PCL-TFA

molecular weight [1, 35, 36]. The DSC thermograms of the synthesized organic acid-initiated samples showed a sharp melting point (T_m) between 52 and 63 °C. Similar results were observed when the T_m values were compared with PCL synthesized applying conventional heating processes. For example, the PCL-AA sample had a melting point of 52.7 °C, which is lower than the melting temperature of thermally obtained PCLs available in the literature [1]. Melting temperatures of the PCL-BA and PCL-TFA products were 62.3 °C and 60.5 °C, respectively, where these

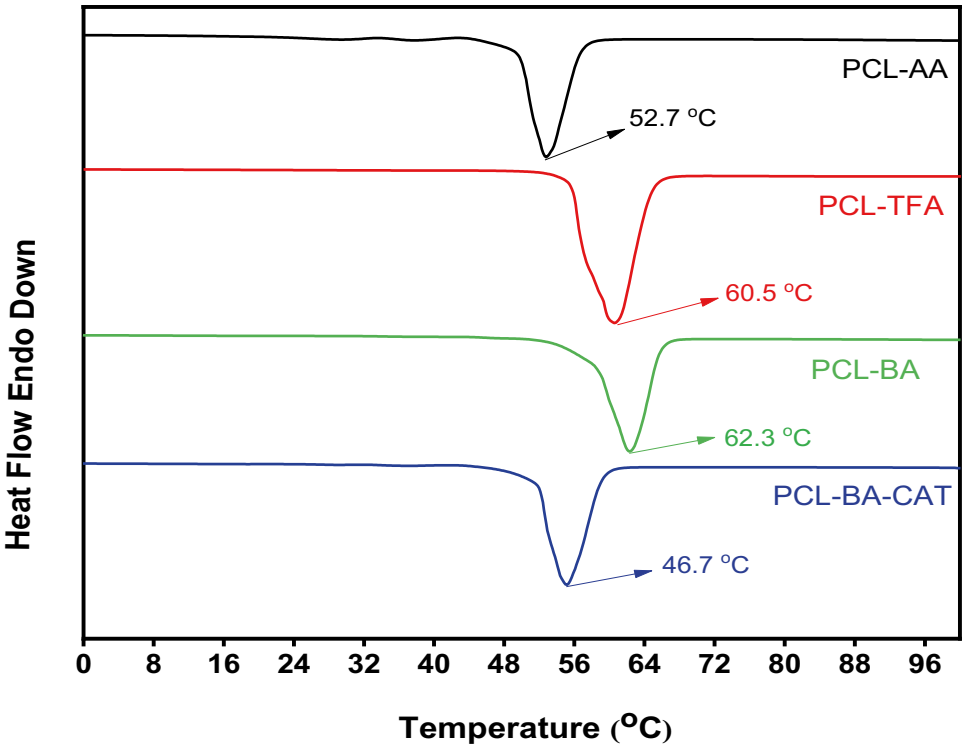

Fig. 10 DSC thermogram of PCL-AA, PCL-TFA, PCL-BA and PLC-BA-CAT

T_m values fall within the range of the thermally synthesized PCL. Yu et. al. studied the microwave-assisted ROP of Ɛ-CL, initiated by benzoic acid at different monomer/initiator ratios, and reported that the obtained PCL had a Mw of 44,800 with a melting point of 65.9 °C [22, 36]. This T_m value is slightly higher than that of thermally produced PCLs [22]. The difference between T_m values was attributed to the higher Mn of PCL. Dzienia et al. reported that the melting point of PCL polymers shifted to higher temperatures with 10 K increase in Mn values compared to the polymers with Mn values lower than 20,000 g/mol. They also pointed out that the melting temperature of PCL does not change only for the polymers with Mn > 20,000 g/mol. It is also clear from the DSC thermograms that different organic acid initiators yielded varying molecular weights and T_m values. Notably, the T_m value of the PCL product initiated with acetic acid (PCL-AA) is the lowest compared to the other samples. The Mn value of PCL-AA obtained from ^{1}H-NMR and GPC is likewise the lowest. The melting point of PCL samples could also be influenced by various factors such as the dispersity index, morphology, size, and degree of crystalinity of the polymers [37, 38]. The observed changes in the melting points of our PCL samples are consistent with previous findings in the literature [37–40]. As a result, DSC values do not reveal a significant difference between the organic acid initiated low molecular weight polymers and there is also not a significant difference between the microwave irradiated samples and thermally synthesized available PCL samples [40]. The overall DSC results revealed that high-quality PCL could also be prepared by microwave irradiation and ROP mechanism within minutes without any impurities like any catalyst or solvent. Instead of the traditional thermal processes, requiring more than ten hours, short times will be enough to obtain pure PCL products with low molecular weights, which is essential for controlled drug delivery applications.

Conclusion

In this study, we present a straightforward and effective approach for the synthesis of low-molecular weight PCL without any toxic impurities, which is safer for use in the human body. Our method involved a one-step ROP of Ɛ-CL using AA, BA, or TFA as initiators, and not requiring any solvent and catalyst. This approach allows for easy and high-yield production of PCLs with molecular weights suitable for biomedical applications. The development and use of biocompatible, non-toxic initiators are critical for their use in biomedical applications, as high purity and absence of any toxic compounds are required. Our results showed that each carboxylic acid initiator leads to a different reaction efficiency, resulting in PCLs with different proportions of -OH and -COOH terminal groups. It is worth noting that the use of different carboxylic acids as initiators allowed fine-tuning of the terminal groups, and thus their reactivity. This enabled controlled polymerization conditions to produce PCLs with tailored functionalities for

specific biomedical applications. Low molecular weight PCL products with different functionalities are crucial for drug delivery and medical applications, as degradation times of PCL and nanoparticle sizes largely depend on the molecular weights. The safety and purity of these products are of outmost importance for their use in the human body. We anticipate that our obtained PCLs can have practical applications as biomaterials, with the potential use in the development of new biomedical technologies. We hope that our results are of the interest in the development of new biomaterials for biomedical technologies.

Funding No funding was received to assist with the preparation of this manuscript.

Data availability The date that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Tian H, Wu F, Chen P, Peng X (2020) Fang H (2020) Microwave-assisted in situ polymerization of polycaprolactone/boron nitride composites with enhanced thermal conductivity and mechanical properties. Polym Int 69(7):635–643. https://doi.org/10.1002/pi.6000
2. Yang G, Ma R, Zhang S, Liu Z, Pei D, Jin H et al (2022) Microwave-assisted in situ ring-opening polymerization of epsilon-caprolactone in the presence of modified halloysite nanotubes loaded with stannous chloride. RSC Adv 12(3):1628–1637. https://doi.org/10.1039/d1ra07469e
3. Ünal S, Doğan O, Aktaş Y (2022) Paclitaxel-Loased Polycaprolactone nanoparticles for lung tumors; Formulation, Comprehensive in vitro characterization and release kinetic studies. J Fac Pharm Ankara 46:1009–1029. https://doi.org/10.33483/jfpau.1161238
4. Jenkins M, Harrison K (2006) The effect of molecular weight on the crystallization kinetics of polycaprolactone. Polym Adv Technol 17(6):474–478. https://doi.org/10.1002/pat.733
5. Sun IC, Eun DK, Na JH, Lee S, Kim IJ, Youn IC et al (2009) Heparin-coated gold nanoparticles for liver-specific CT imaging. Cent Eur Hist 15(48):13341–13347. https://doi.org/10.1002/chem.200902344
6. Camacho KM, Menegatti S, Mitragotri S (2016) Low-molecular-weight polymer–drug conjugates for synergistic anticancer activity of camptothecin and doxorubicin combinations. Nanomedicine (Lond) 11(9):1139–1151. https://doi.org/10.2217/nnm.16.33
7. Stylianopoulos T (2013) EPR-effect: utilizing size-dependent nanoparticle delivery to solid tumors. Ther Deliv 4(4):421–423. https://doi.org/10.4155/tde.13.8
8. Witt S, Scheper T, Walter JG (2019) Production of polycaprolactone nanoparticles with hydrodynamic diameters below 100 nm. Eng Life Sci 19(10):658–665. https://doi.org/10.4155/tde.13.8
9. Storey RF, Sherman JW (2002) Kinetics and mechanism of the stannous octoate-catalyzed bulk polymerization of ε-caprolactone. Macromolecules 35(5):1504–1512. https://doi.org/10.1021/ma010986c
10. Liao L, Liu L, Zhang C, He F, Zhuo R, Wan K (2002) Microwave-assisted ring-opening polymerization of ϵ-caprolactone. J Polym Sci Part A: Polym Chem 40(11):1749–1755. https://doi.org/10.1002/pola.10256
11. Limwanich W, Rakbamrung N, Meepowpan P, Funfuenha W, Kongsuk J, Punyodom W (2023) Solvent-free ring-opening polymerization of ε-caprolactone initiated by Mg (II), Sn (II), Zn (II), Al (III), and Sn (IV) derivatives: a comparative study. Reac Kinet Mech Cat 136(1):381–395. https://doi.org/10.1007/s11144-023-02354-7
12. Funfuenha W, Punyodom W, Meepowpan P, Limwanich W (2023) Microwave-assisted solvent-free ring-opening polymerization of ε-caprolactone initiated by n-butyltin (IV) chlorides. Polym Bull 1–16. https://doi.org/10.1007/s00289-023-04720-w
13. Hege CS, Schiller SM (2014) Non-toxic catalysts for ring-opening polymerizations of biodegradable polymers at room temperature for biohybrid materials. Green Chem 16(3):1410–1416. https://doi.org/10.1039/C3GC42044B
14. Tan Y, Cai S, Liao L, Wang Q, Liu L (2009) Microwave-assisted ring-opening polymerization of ε-caprolactone in presence of hydrogen phosphonates. Polym J 41(10):849–854. https://doi.org/10.1295/polymj.PJ2009079
15. Zhang C, Liao L, Gong SS (2007) Recent developments in microwave-assisted polymerization with a focus on ring-opening polymerization. Green Chem 9(4):303–314. https://doi.org/10.1039/B608891K
16. Babaladimath G, Chapi S (2018) Microwave-assisted synthesis, characterization of electrical conducting and electrochemical xanthan gum-graft-polyaniline. J Mater Sci: Mater Electron 29:11159–11166. https://doi.org/10.1007/s10854-018-9201-2
17. Persson PV, Schröder J, Wickholm K, Hedenström E, Iversen T (2004) Selective organocatalytic ring-opening polymerization: a versatile route to carbohydrate-functionalized poly (ε-caprolactones). Macromolecules 37(16):5889–5893. https://doi.org/10.1021/ma049562j
18. Casas J, Persson PV, Iversen T, Córdova A (2004) Direct Organocatalytic Ring-Opening Polymerizations of Lactones. Adv Synth Catal 346(9–10):1087–1089. https://doi.org/10.1002/adsc.200404082
19. Abdelrazek E, Hezma A, El-Khodary A, Elzayat A (2016) Spectroscopic studies and thermal properties of PCL/PMMA biopolymer blend. Egypt j basic appl sci 3(1):10–15. https://doi.org/10.1016/j.ejbas.2015.06.001
20. Labet M, Thielemans W (2009) Synthesis of polycaprolactone: a review. Chem Soc Rev 38(12):3484–3504. https://doi.org/10.1039/B820162P
21. Song Y, Liu L, Weng X, Zhuo R (2003) Acid-initiated polymerization of ε-caprolactone under microwave irradiation and its application in the preparation of drug controlled release system. J Biomater Sci Polym Ed 14(3):241–253. https://doi.org/10.1163/156856203763572699
22. Yu Z, Liu L, Zhuo R (2003) Microwave-improved polymerization of ϵ-caprolactone initiated by carboxylic acids. J Polym Sci Part A: Polym Chem 41(1):13–21. https://doi.org/10.1002/pola.10546
23. Bixler K, Calhoun G, Scholsky K, Stackman R (1990) Polymerization of epsilon-caprolactone in the presence of carboxylic acids. Polym Prepr 31(2):494–495
24. Oledzka E, Narine SS (2011) Organic acids catalyzed polymerization of ε-caprolactone: Synthesis and characterization. J Appl Polym Sci 119(4):1873–1882. https://doi.org/10.1002/app.32897
25. Xu J, Song J, Pispas S, Zhang G (2014) Controlled/living ring-opening polymerization of ε-caprolactone with salicylic acid as

the organocatalyst. J Polym Sci Part A: Polym Chem 52(8):1185–1192. https://doi.org/10.1002/pola.27104
26. Chen T, Cai T, Jin Q, Ji J (2015) Design and fabrication of functional polycaprolactone. e-Polymers 15(1):3–13. https://doi.org/10.1515/epoly-2014-0158
27. Amestoy H, Diego P, Meaurio E, Muñoz J, Sarasua J-R (2021) Crystallization behavior and mechanical properties of poly (ε-caprolactone) reinforced with barium sulfate submicron particles. Materials 14(9):2368. https://doi.org/10.3390/ma14092368
28. Huang A, Jiang Y, Napiwocki B, Mi H, Peng X, Turng L-S (2017) Fabrication of poly (ε-caprolactone) tissue engineering scaffolds with fibrillated and interconnected pores utilizing microcellular injection molding and polymer leaching. RSC Adv 7(69):43432–442. https://doi.org/10.1039/C7RA06987A
29. Liu J, Liu L (2004) Ring-opening polymerization of ε-caprolactone initiated by natural amino acids. Macromolecules 37(8):2674–2676. https://doi.org/10.1021/ma0348066
30. Oledzka E, Sokolowski K, Sobczak M, Kolodziejski W (2011) α-Amino acids as initiators of ε-caprolactone and L. L-lactide polymerization Polym Int 60(5):787–793. https://doi.org/10.1002/pi.3016
31. Báez JE, Martínez-Richa A, Marcos-Fernandez A (2005) One-step route to α-hydroxyl-ω-(carboxylic acid) polylactones using catalysis by decamolybdate anion. Macromolecules 38(5):1599–1608. https://doi.org/10.1021/ma0491098
32. Kricheldorf HR, Eggerstedt S (1998) Macrocycles 2. Living macrocyclic polymerization of ε-caprolactone with 2, 2-dibutyl-2-stanna-1, 3-dioxepane as initiator. Macromol Chem Phys 199(2):283–90. First published: 16 December 1998
33. Huang C-H, Wang F-C, Ko B-T, Yu T-L, Lin C-C (2001) Ring-opening polymerization of ε-caprolactone and L-lactide using aluminum thiolates as initiator. Macromolecules 34(3):356–361. https://doi.org/10.1021/ma0014719
34. Chapi S (2021) Influence of Co2+ on the structure, conductivity, and electrochemical stability of poly (ethylene oxide)-based solid polymer electrolytes: energy storage devices. J Electron Mater 50(3):1558–1571. https://doi.org/10.1007/s11664-020-08706-6
35. Hayashi T (1994) Biodegradable polymers for biomedical uses. Prog Polym Sci 19(4):663–702. https://doi.org/10.1016/0079-6700(94)90030-2
36. Yu Z, Liu L (2004) Effect of microwave energy on chain propagation of poly (ε-caprolactone) in benzoic acid-initiated ring opening polymerization of ε-caprolactone. Eur Polym J 40(9):2213–2220. https://doi.org/10.1016/j.eurpolymj.2004.05.007
37. Dzienia A, Maksym P, Tarnacka M, Grudzka-Flak I, Golba S, Zięba A et al (2017) High pressure water-initiated ring opening polymerization for the synthesis of well-defined α-hydroxy-ω-(carboxylic acid)polycaprolactones. Green Chem 19(15):3618–3627. https://doi.org/10.1016/j.eurpolymj.2004.05.007
38. Chen H-L, Li L-J, Ou-Yang W-C, Hwang JC, Wong W-Y (1997) Spherulitic crystallization behavior of poly (ε-caprolactone) with a wide range of molecular weight. Macromolecules 30(6):1718–1722. https://doi.org/10.1021/ma960673v
39. Tuba F, Olah L, Nagy P (2014) Towards the understanding of the molecular weight dependence of essential work of fracture in semi-crystalline polymers: A study on poly (ε-caprolactone). Express Polym Lett 8(11). https://doi.org/10.3144/expresspolymlett.2014.88
40. Barbier-Baudry D, Brachais CH, Cretu A, Loupy A, Stuerga D (2002) An Easy Way Toward ε-Caprolactone Macromonomers by Microwave Irradiation Using Early Lanthanide Halides as Catalysts. Macromol Rapid Commun 23(3):200–204