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PRELIMINARY STUDY OF 4-ARMS POLY(CAPROLACTONE) STAR-SHAPED POLYMER: SYNTHESIS AND CHARACTERIZATION

Siti Hajar Ahmad Shariff, Mohamad Wafiuddin Ismail*
Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia, 25200, Kuantan, Pahang, Malaysia

**Corresponding author: wafisnj@iium.edu.my*

Abstract

Star-shaped polymers have vast potential in bioapplication due to their architecture. In this study, the suitability of ring opening polymerization (ROP) technique to synthesis star-shaped poly(caprolactone) and the thermal properties of the synthesized star-shaped polymers were demonstrated. The 4 -arm star-shaped of poly(caprolactone) (4s PCL) with -OH terminal and average molecular weight (M_n) of 5000, 10000, and 15000 g/mol were synthesized via ROP of ε-caprolactone (ε-CL) using a symmetric pentaerythritol (PET) as the core. Different molecular weights were obtained by using different ratios of ε-CL and PET in the presence of catalyst, stannous octoate ($Sn(Oct)_2$). The FTIR spectra showed the presence of bands of methylene group of polymer repeating chain which confirm ROP of the ε-caprolactone. The average molecular weight (M_n) determined from proton nuclear magnetic resonance (^1H NMR) analysis showed that all 4s PCL have approximately the same molecular weight as the theoretical values. All polymers obtained had high yield with >85%. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) analysis showed that there were no significance different in the thermal properties of the synthesized polymers. A single step degradation for all 4s PCL was observed and the crystallization melting point of the polymers was within the range of melting point of PCL.

Keywords: Star-shaped PCL, ROP, ε-caprolactone, bioapplication

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Introduction

In recent years, star-shaped polymers have been given extensive attention in bioapplications (Chong, Zainol, Ng, & Ooi, 2019; Duro-Castano, Movellan, & Vicent, 2015; Kostka et al., 2020; Kostková et al., 2017; Lotocki & Kakkar, 2020). Star-shaped polymers were identified as a potential candidate for drug delivery system due to their capabilities to encapsulate molecules and enhance drug entrapment efficiency, where the system is dependent on parameters such as molecular weight, arm length, preparation method, and drug dosage (Yang, Oo, Deen, Li, & Loh, 2017). It has been found that star polymers showed superior physicochemical properties compared to the linear polymers with the same molecular weight such as encapsulation capabilities due to their three-dimensional (3D) globular structures, viscosity, and flexibility (Sulistio, Gurr, Blencowe, & Qiao, 2012). In addition, the degree of dynamic entanglement of star-shaped polymers are notably lower compared to their linear analogs with the increasing number of arms (Wu, Wang, & Li, 2015). The branched structures also enhance the solubility and processability of star-shaped polymers, and lower the crystallization of the polymers due to lower molecular packing in the star topology compared to the long chain of a linear structure (Michalski, Brzezinski, Lapienis, & Biela, 2019). Furthermore, compared to their linear counterparts, they possess higher functional end groups that increase the probability of attachment with other polymers (Tinajero-Díaz et al., 2014). Star-shaped poly(caprolactone) has been given attention in the drug delivery system owing to their biocompatibility, biodegradability, adaptability and nontoxicity (L. Wang, Cai, & Dong, 2008).

Poly(caprolactone), PCL is a family of the biodegradable polyesters alongside poly(lactic-co-glycolic acid) (PLGA) and poly(l-lactic acid) (PLLA). It is a Food and Drug Administration (FDA) approved hydrophobic, aliphatic semi-crystalline polymer with non-toxic and biocompatible properties (Lee & Chang, 2013). PCL has the potential to be widely used in bioapplications such as tissue scaffolds and drug delivery systems due to its low melting point, good solubility, and excellent blend-compatibility. Besides, PCL has low rate of degradation (2-3 years) compared to its polyesters family, hence making it suitable to be used as drug-delivery devices that remain actives for over one year, and in slow-degrade suture materials (Dwivedi et al., 2020; Woodruff & Hutmacher, 2010). For example, PCL has been used as a 3D porous scaffold for sustain release of melatonin which increased the healing effect of the engineered cartilage regeneration. Melatonin loaded with bovine serum albumin nanoparticles (MNP) embedded into the PCL scaffolds revealed amorphization of melatonin from the X-ray diffraction and Raman analysis which is desirable in drug delivery applications (Manjunath Kamath et al., 2020). In another study, a wound dressing is designed based on PCL nanofiber coated with gamma oryzanol and chitosan for delivery of drug mupirocin. The results showed the wound area and total bacteria count ($P < 0.05$) in a mouse model is greatly reduced when treated using PCL loaded with mupirocin (Hajilou, Farahpour, & Hamishehkar, 2020). PCL has also been used for dual drug delivery applications. In the study, PCL is used as the core layer for the robust tripolymeric, triaxial electrospun fibrous scaffolds for regenerative engineering and drug delivery. The addition of the PCL as the core is found to contribute to a higher tensile modulus. The systems minimized the shrinkage of fibers normally found with conventional electrospun systems which are ideal for the support of mesenchymal stem cell growth. These fibers are found to be biomechanically competent, biocompatible, and capable of dual drug release (Nagiah et al., 2020). Apart from that, PCL is also incorporated into poly(ethylene-co-vinyl acetate) (EVA) film as drug carrier for iprodione. The use of iprodione loaded poly(ethylene glycol)-poly(ε-caprolactone) (IPP) micelles enabled the films with antifungal and controlled release ability for pre-harvest treatment of grapes where it improved antifungal ability and temperature-sensitive drug release behavior, and enhanced the quality of grapes (Xiao et al., 2020).

There are several polymerization techniques reported for the synthesis of star-shaped polymers such as atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain-transfer (RAFT), nitroxide-mediated free-radical polymerization (NMRP), and ring opening polymerization (ROP). However, the widely used method of synthesis of PCL is ring-opening polymerization (ROP) of ε-caprolactone (Chen et al., 2005; Maglio et al., 2004; Ren et al., 2011). Stannous octoate is the most commonly used organometallic catalyst, alongside hydroxy-containing compounds are used as initiators. This widely accepted 'coordination-insertion' catalytic method is claimed to produce high yield, controlled molecular weight and narrow-distributed polyesters (Cui, Ma, Tang, & Luo, 2004). Apart from that, ROP technique is a robust and simple method because it is immune to radical scavengers such as oxygen, and more stable as compared to other techniques (Ren et al., 2016). Previously, ROP technique has been adopted in a study by de Freitas et al. (2013) in a controlled one pot synthesis of polystyrene-block-polycaprolactone (PS-b-PCL) copolymers. In the study, a low dispersity index ($M_w / M_n = 1.19\text{-}1.40$) and narrow molecular weight distribution of synthesized polymers is obtained by using catalyst stannous octoate (Sn(Oct2)) for the ROP of ε-caprolactone (de Freitas et al., 2013). In another study by Shadi et al. (2014), a 4-arm star-shaped PCL has been synthesized using the same method mentioned before to prepare electrospun nanofibers of star-shaped PCL with polyaniline blend. In the study, the ROP of ε-CL has given the yield of 96% of PCL (Shadi, Karimi, Ramazani, & Entezami, 2014). Despite numerous studies available on the synthesis of star-shaped PCL via ROP, however, as to our knowledge, there are lacking in the numbers of studies on the synthesis and thermal properties of the star-shaped PCL with molecular weight of 5000, 10000, and 15000 g/mol with the same architecture which is 4-arm.

Hence, this work serves as a preliminary study to synthesize 4-arms star-shaped PCL (4s PCL) with molecular weights of 5000, 10000, and 15000 g/mol using ROP. The confirmation of their chemical structures will be observed using Fourier-transform infrared (FTIR) and proton nuclear magnetic resonance (^{1}H NMR) analysis. While, the thermal analysis of the polymers will be studied using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

Methods

Materials

Pentaerythritol (PET, purity 99%), ε-caprolactone (ε-CL, purity 97%), and stannous octoate ($Sn(Oct)_2$, purity 92.5-100%) were purchased from Sigma-Aldrich (Darmstadt, Germany).

Synthesis of 4-arm star-shaped PCL (4s PCL)

A certain amount of PET, $Sn(Oct)_2$ (0.1 wt.% of ε-CL) and ε-CL were put in a three-neck round-bottom flask according to the molar-feed-ratio of monomer and initiator for 4s PCL(s) as listed in Table 1. The reactions were refluxed under nitrogen atmosphere for 24 hours with stirring in an oil bath at 110 °C. The products were cooled at room temperature and were dissolved in diethyl ether to be precipitated. The star-shaped hydroxyl-terminal 4s PCL(s) were obtained after the products were dried at room temperature for 48 hours (Nabid et al., 2011). Figure 1 represents the schematic route of the reaction.

Table 1. Composition of monomer and initiator for 4s PCL

Product	Initiator	Monomer	Molecular weight (g/mol)
4s PCL-5k	0.001 mol, 0.136 g	0.044 mol, 5.02 g	5100
4s PCL-10k		0.088 mol, 10.03 g	10100
4s PCL-15k		0.132 mol, 15.05 g	15100

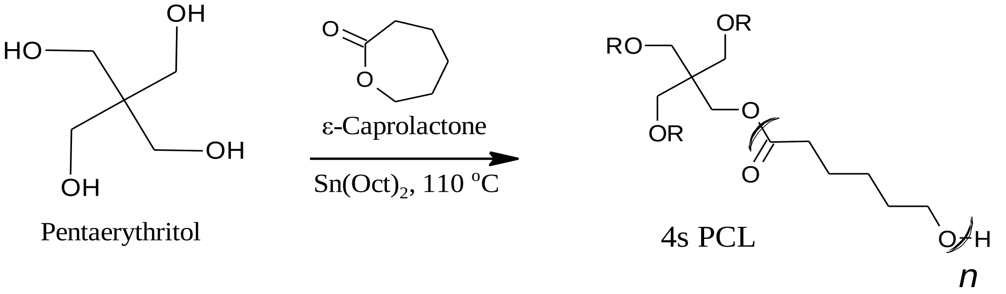

Figure 1. Schematic route of preparation of 4s PCL

Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR spectra for the synthesized polymers were recorded using a Perkin Elmer Fourier transform infrared spectroscopy-attenuated total reflectance (FTIR-ATR) in the region of 4000-400 cm^{-1}.

Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra (^1H) of the synthesized polymers were reported using a Bruker Ultra Shield Plus NMR spectrometer at 500 MHz. The polymers were dissolved in deuterated chloroform and tetramethylsilane was used as the internal reference.

Thermogravimetric Analysis (TGA)

The TGA/DTG analysis of the synthesized polymers was done using Mettler Toledo Thermogravimetric Analyzer with the temperature in the range of 30 °C to 600 °C, under nitrogen atmosphere at flow rate of 50 mL/min and heating rate of 10 °C.

Differential Scanning Calorimetry (DSC) analysis

The DSC analysis was carried out using a NETZSCH Differential Scanning Calorimeter 214 Polyma under nitrogen atmosphere with flow rate of (10 mL/min) and a heating rate of 10 °C/min over the range of 0 °C to 100 °C. The crystalline melting temperature of the polymers were recorded.

Determination of Average Molecular Weight (M_n) of PCL

The M_n of the polymers was determined using ^1H NMR analysis. The ^1H NMR analysis was used to determine the degree of polymerization of, DP. The M_n are determined using equation (1) based from Izunobi & Higginbotham (2011).

$$M_n = (DP \times (\text{no. of arms}) \times M_w CL) + \text{Core} \quad (1)$$

Where M_n = Average molecular weight of PCL
DP = degree of polymerization of PCL arms
M_w CL= molecular weight of ε-caprolactone

Results and Discussion

Synthesis of 4-arm star-shaped PCL

The star-shaped 4s PCL homopolymers were synthesized via ROP of ε-CL in bulk at 110 °C. The hydroxyl-terminal 4s PCL were produced using a symmetrical PET as the initiator with four hydroxyl end groups. Three 4s PCL with different molecular weights were obtained by changing the ratio of monomer to initiator. The temperature of 110 °C was selected as it was the best temperature for ROP of ε-CL using $Sn(Oct)_2$ as the catalyst as reported in previous studies (Bhaw-Luximon, Jhurry, Motala-Timol, & Lochee, 2005; Ismail et al., 2019; Zhu et al., 2020). This is because a higher temperature will promote the intermolecular and intramolecular esterification that widens the polydispersity of the synthesized star-shaped PCL (Labet & Thielemans, 2009). After being cooled at room temperature and precipitated in cold diethyl ether, off-white solid was formed. The yield obtained for all of the synthesized 4s PCL were ≥ 85% which indicate the efficiency of bulk polymerization of 4s PCL(s) using ROP technique and $Sn(Oct)_2$ as a catalyst which has been reported previously (Labet & Thielemans, 2009; Stassin & Jérôme, 2003).

The IR spectrum of the 4s PCL(s) shown in Figure 2 indicates the occurrence of ROP of cyclic ε-CL by the presence of polymer backbone of PCL. The C-H band of methylene group of the PCL repeating chain appeared at around 2980 cm^{-1} and 2850 cm^{-1}. Apart from that, the presence of the ester group (C=O stretching) around 1705 cm^{-1} and the C-O stretch bands of the polymer backbone around 1195 cm^{-1} indicates the successful ROP of ε-CL. While, the low intensity of the bands around 3500 and 3400 cm^{-1} were attributed to the hydroxyl group, which is due to the low content of hydroxyl group per PCL chain (Ismail et al., 2019; Nabid et al., 2011).

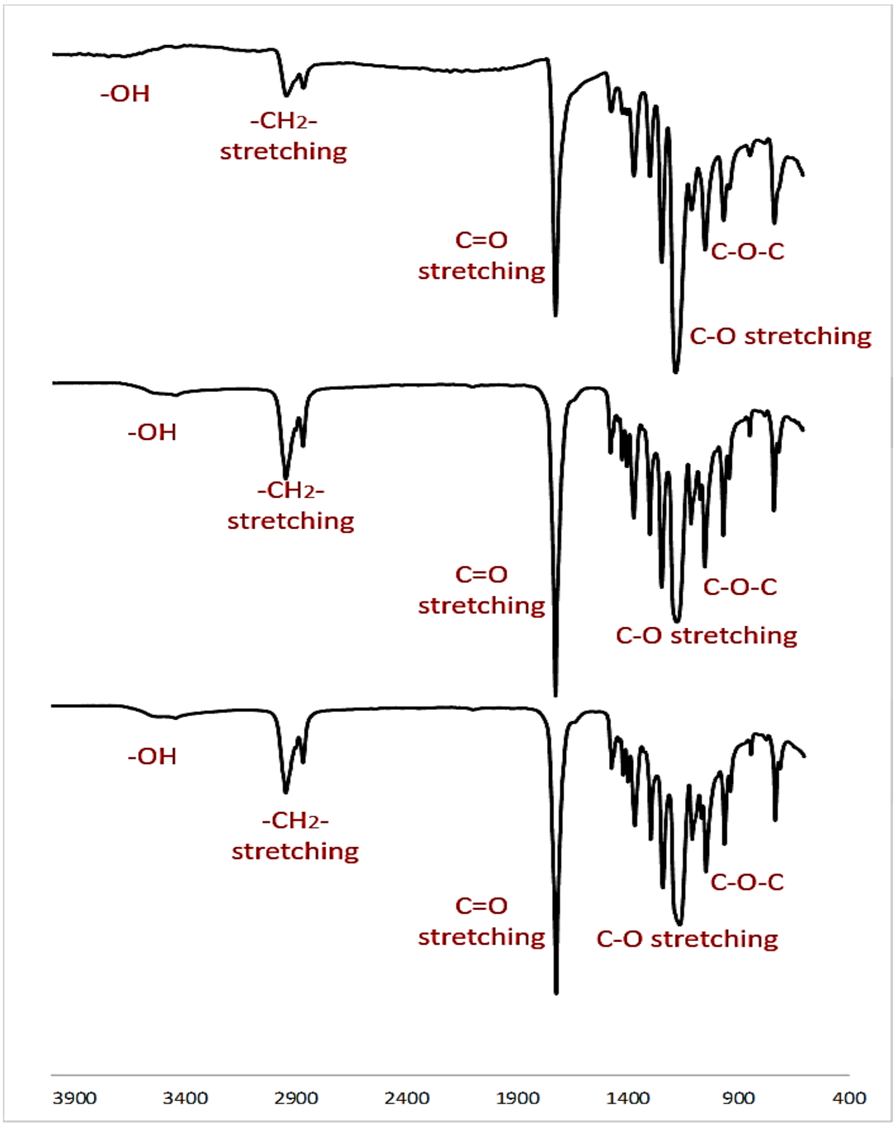

Figure 2. FTIR spectra for 4s PCL (a) 15k, (b) 10k and (c) 5k

Next, ^{1}H NMR was performed to analyze the molecular structure of the 4s PCL(s) and their molecular weight. Figure 3 shows the ^{1}H NMR spectra of the 4s PCL(s). The presence of six signals in the spectra indicated the successful polymerization of ε-caprolactone. The signal of the methylene (a) protons of the pentaerythritol initiator was detected around 4.10 ppm. The major resonance peaks (b-e) detected around 1.30 ppm to 4.00 ppm (δ 1.3 and δ 1.6, δ 2.2, δ 4.0, (m, $-CH_2-$), (t, $-CH_2-$), (t, $-CH_2-O-$)), were denoted to the PCL backbone which indicated the successful occurrence of ROP of ε-CL. While the terminal methylene (f) proton peak was observed around 3.60 ppm (t, $-CH_2-OH$) indicating the hydroxyl-terminal of the PCL chains (Gjerde, Zhu, Nyström, & Knudsen, 2018; Zhang et al., 2014). Since all core arms had the same terminal active hydroxyl group that can initiate the ROP of the cyclic ε-caprolactone, it is assumed that the polymerization reaction towards each arm of the core is to be the same and only one resonance peak are to be observed for all pentaerythritol protons (Letchford, Zastre, Liggins, & Burt, 2004; Shadi et al., 2014). Therefore, it can be concluded that each arm of pentaerythritol undergoes ROP of ε-CL and formed homopolymer 4s PCL based on the correlation between past study (Chen et al., 2005; Ismail et al., 2019; Nabid et al., 2011) and data obtained from ^{1}H NMR analysis.

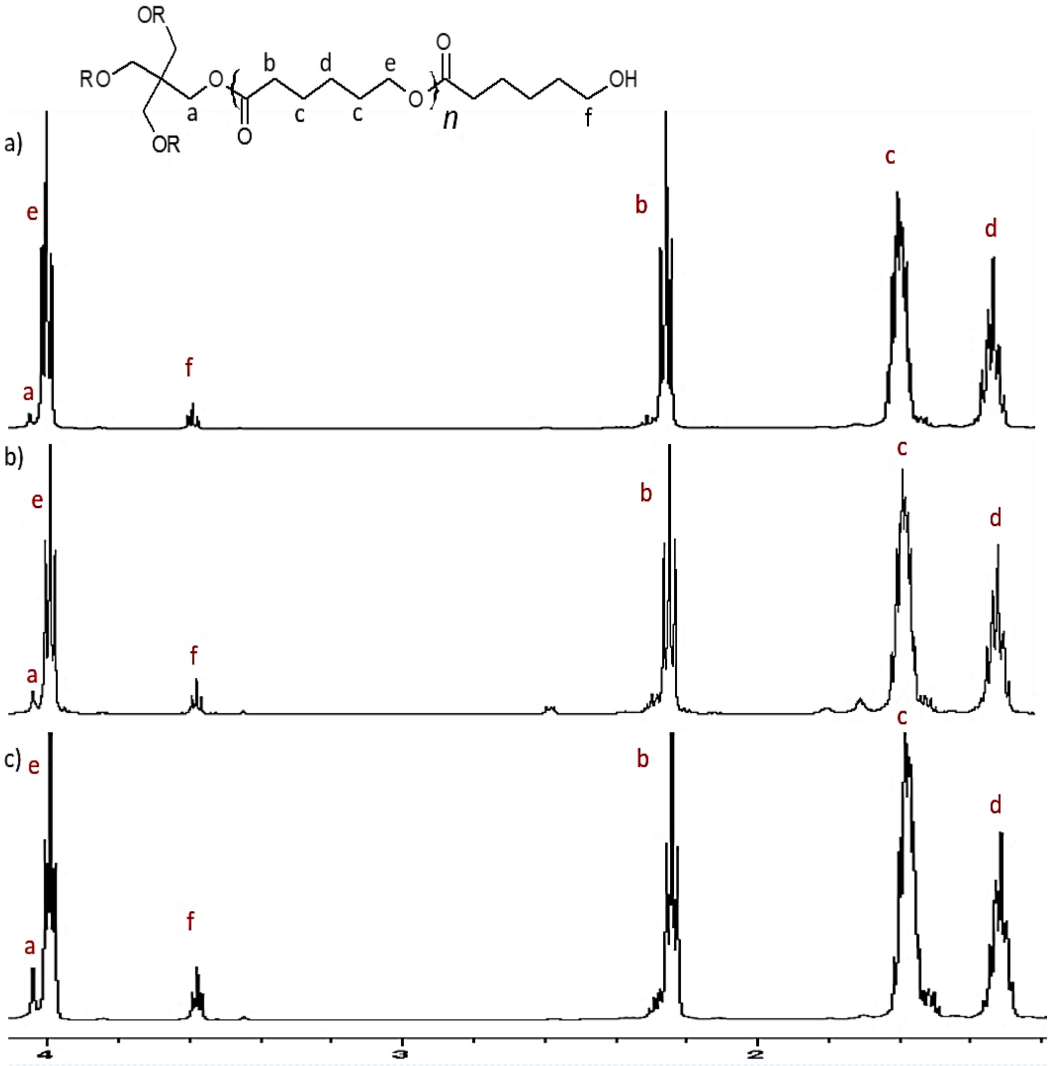

Figure 3. NMR spectra for sample 4s PCL (a) 15k, (b) 10k, and (c) 5k

The DP for the PCL repeating chains was calculated from the ratio of integration between the methylene protons in the repeating units (b) and proton in the terminal unit (f) based on the ^{1}H NMR spectrum (Bhayo, Abdul-Karim, Musharraf, & Malik, 2018). The M_n of 4s PCL(s) determined by ^{1}H NMR spectrum were listed in Table 2. Based on the calculation, the M_n obtained from the synthesized polymers were approximately close to the theoretical weight. The results confirmed that ratio between monomer and initiator can be used to synthesize star-shaped polymers of targeted weight, and different ratios of monomer to initiator will give different molecular weights.

Table 2. Molecular weight analysis of 4s PCL(s)

Product	**M_n,theoretical (g/mol)**	**DP star**	**M_n,NMR (g/mol)**	**% Yield**
4s PCL-5k	5100	44	5300	93.4
4s PCL-10k	10100	84	9800	85.0
4s PCL-15k	15100	128	14800	99.2

TGA/DTG and DSC analysis

TGA/DTG analysis and DSC analysis were used to examine the thermal properties of the synthesized 4-arm star-shaped polymers. TGA is a method for evaluating the heat stability of a substance and its fraction by observing the change of weight when a sample is subjected to heat at a constant rate (Rajisha, Deepa, Pothan, & Thomas, 2011). Table 2 shows the TGA analysis of the synthesized polymers. All 4s PCL(s) showed high thermal stability based on initial major thermal degradation temperature ($T_{d\text{-initial}}$) occurring at the range between 300-351°C. All thermograms showed a single step degradation (Figure 4). However, the temperature for the major thermal degradation decrease with the increase of molecular weight of PCL. The increase of molecular weight of each PCL arm that is attached to the PET initiator decrease the stability and degradation temperature of the branched polymer (Oledzka et al., 2012). This is because thermal stability of polymers is highly dependent on their chemical structure and molecular weight. Double bonds or oxygen-containing structures such as C-O in the polymer chains make them less resistant to high temperatures (Król-Morkisz & Pielichowska, 2019). As such, the higher the molecular weight, the higher the number of double bonds and oxygen-containing structures in the 4s PCL(s) as the polymer chain is made up of ester linkage.

Table 3. TGA results for synthesized PCL polymers

Product	**$T_{d\text{-initial}}$ (°C)**	**$T_{d\text{-max}}$ (°C)**
4s PCL-5k	350.8	599.4
4s PCL-10k	343.6	382.2
4s PCL-15k	307.3	350.3

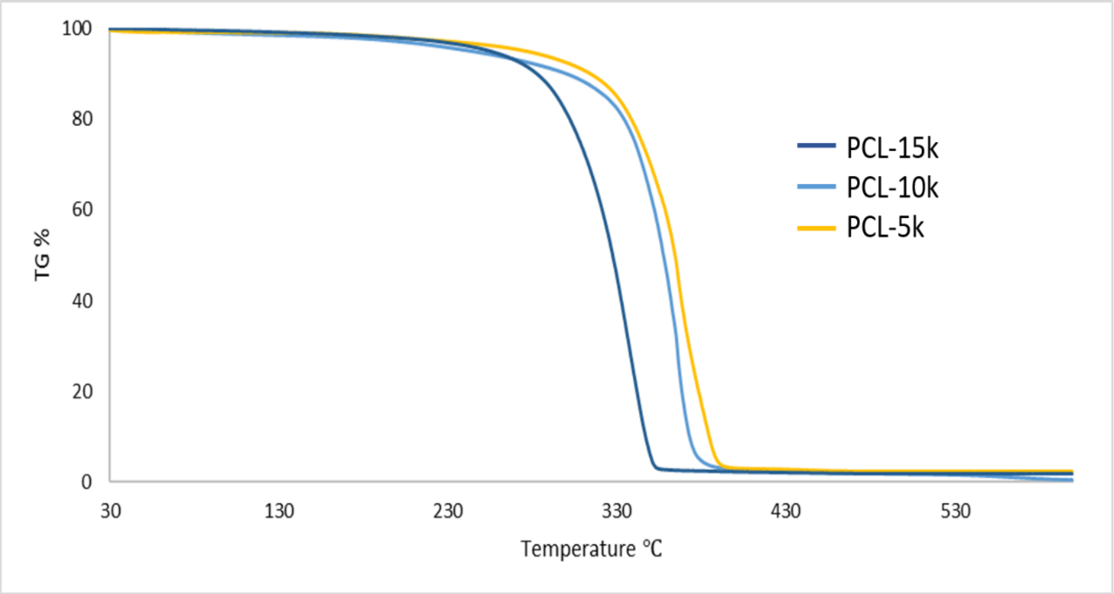

Figure 4. TGA curves of all synthesized polymers

The derivative thermogravimetric (DTG) curves (Figure 5) confirmed the single-stage degradation of the synthesized 4s PCL(s) at approximately 339, 368, and 372 °C respectively (Shadi et al., 2014).

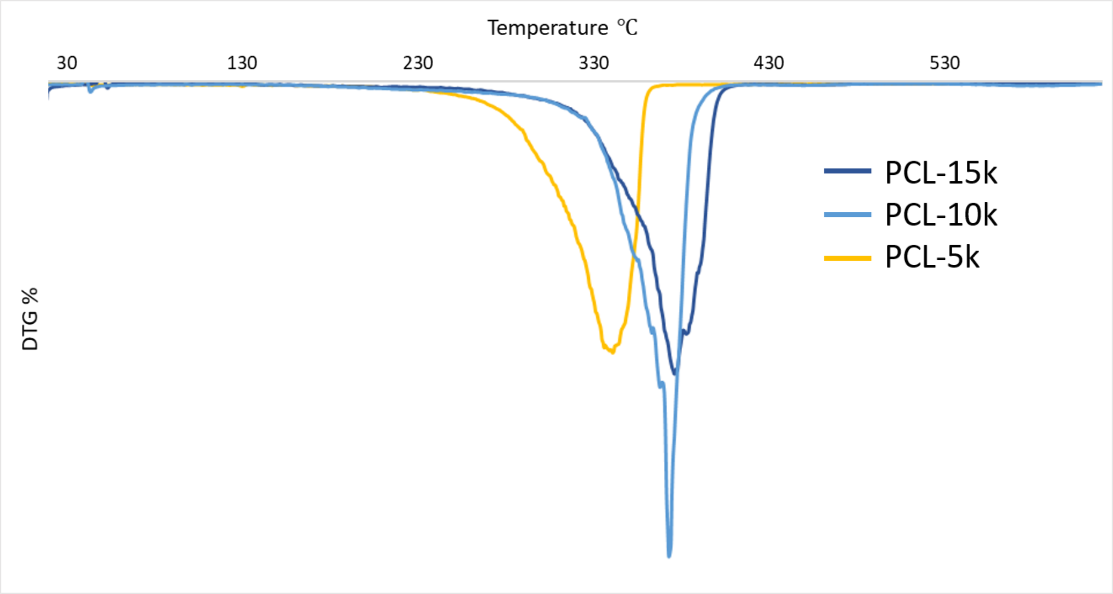

Figure 5. DTG curves of all synthesized polymers

DSC thermal analysis provided details on how the star-shaped polymers in bulk are self-organized and crystallized (Ismail et al., 2019). It measures the temperature and heat produced as a function of time and temperature during phase transition and provides detailed information about physical or chemical changes either endothermic or exothermic (Kong & Hay, 2002). Heat is released or taken in during the phase transitions to maintain the sample at the same temperature and DSC measures this as a function of time and temperature. The DSC thermogram with monomodal exotherm is shown in Figure 6. Based on Table 4, the polymers have crystalline melting point within the melting range of PCL which is around 60 °C (Kelly, Harrison, Leeke, & Jenkins, 2013). The melting point of the synthesized 4s PCL(s) increase with the increase in M_n. This is because the crystalline melting point is affected by the length of arm as mentioned previously (J.-L. Wang & Dong, 2006). The melting point of a crystal is influenced by the strength of hydrogen bond of the molecules, the effects from molecular shape, size, and symmetry towards the crystals packing, and other forces such as charge transfer and dipole-dipole interactions in the solid phase (Katritzky et al., 2001). Therefore, increasing molecular weight (chain length) will restrict the free molecular motion by crystallization and increase the molecular packing in the crystals, making them difficult to rearrange to form lamellae region (Hatakeyama, Yamashita, & Hatakeyama, 2019; Ismail et al., 2019). As such, they required absorption of higher energy for the melting process to occur (Szymańska & Winnicka, 2015). This phenomena is similar to the previous study by done by Sánchez-Soto et al. (2004) and Wang et al. (2008). Apart from that, the crystallinity of the synthesized 4s PCL(s) can be observed from the broadness of the DSC peaks in Figure 6. The broader the peak, the lower the crystallinity of the polymer due to the size distributions of the crystallites (Shawe, Riesen, Widmann, & Schubnell, 2000). From the thermograms, it can be seen that 4s PCL-5k possessed the broadest peak, indicating the lowest crystallinity, followed by PCL-15k and PCL-10k.

Table 4. Crystalline melting temperature for synthesized PCL polymers

Product	**T_m (℃)**
4s PCL-5k	49.4
4s PCL-10k	56.7
4s PCL-15k	57.1

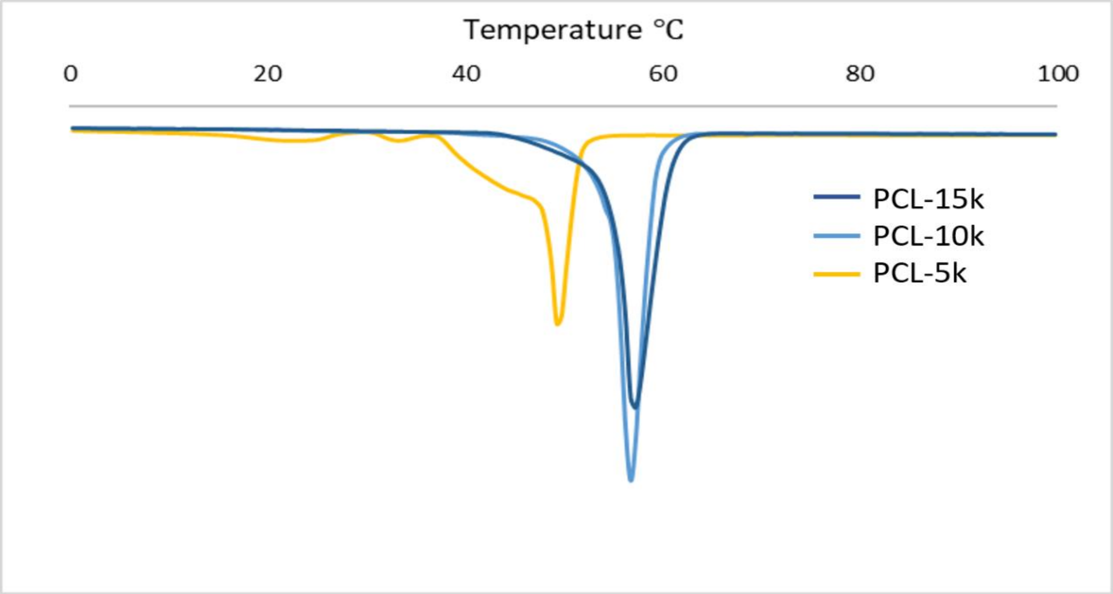

Figure 6. DSC curves of all synthesized polymers

Conclusions

In conclusion, ROP was a suitable technique to synthesis star-shaped polymers. The 4s PCL with M_n of 5000, 10000, and 15000 g/mol were successfully synthesized using ROP technique by varying the ratio of initiator and monomer. ROP technique gave high yield for the synthesis of the 4s PCL with more than 85% yield. The structure and M_n of the 4s PCL(s) were proven using FTIR and ^{1}H NMR analysis. TGA and DSC analysis demonstrated the thermal properties of all 4s PCL(s). Based on the analysis, there are no major difference in the thermal properties of the polymers with different molecular weights. Hence, it can be concluded that molecular weight was not a major influence on the thermal properties of the star-shaped polymers when the number of arms remained constant. However, the trend that was observed for the thermal properties was the temperature for thermal decomposition decrease when molecular weight increase, while the melting temperature increase when molecular weight increase.

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