Microwave-Assisted Synthesis of Poly(ε-caprolactone)-*block*-poly(ethylene glycol) and Poly(lactide)-*block*-poly(ethylene glycol)

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Summary: This study reported the preparation and characterization of PCL-b-mPEG (poly(ε-caprolactone)-block-poly(ethylene glycol)) and PLL-b-mPEG (poly(L-lactide)-block-poly(ethylene glycol)) diblock copolymers by microwave heating and comparison of resulted products the ones with prepared by conventional heating. Diblock copolymers were synthesized successfully by the microwave-assisted ROP in the presence of stannous octoate ($SnOct_2$) as catalyst under nitrogen atmosphere in different monomer ratios. Structural and functional characterization of copolymers were performed by FTIR, ^{1}H-NMR and DSC. Molecular weight values were determined by GPC and also calculated from ^{1}H-NMR. According to the results, microwave irradiation allowed to obtain polymers with very narrow size distribution in very short reaction time. Similar polymers prepared by conventional heating were also synthesized for comparison. Molecular weight and conversion of polymers were increased by irradiation time. This change was continued until a certain time point after which no more increase was observed. It was concluded that microwave irradiation is a succesful method to obtain these diblock copolymers in very short reaction time and with a similar conversion obtained by conventional method.

Keywords: diblock copolymers; microwave heating; PCL-b-mPEG; PLL-b-mPEG; ring-opening polymerization

Introduction

Nowadays, the use of microwave irradiation as a heating source for polymerization reactions is a rapidly growing branch in polymer science. Over the last decade, microwave heating has been widely applied in polymer synthesis, such as polycondensation, free and controlled radical polymerization, and ring opening polymerization (ROP) in significantly less time [1]. Over the past decade, the use of biodegradable polymers for the administration of pharmaceuticals and biomedical devices has increased dramatically. The most important biomedical applications of biodegradable polymers are in the areas of controlled drug delivery systems, in the form of implants and devices for bone and dental repairs. Poly(ε-caprolactone) (PCL), an aliphatic polyester, is one of the most important biodegradable polymer in medicine. To overcome the problems associated with PCL in drug delivery applications, copolymers with polyethyleneglycol (PEG) showing superior properties of nontoxicity, flexibility, hydrophilicity, and biocompatibility have been prepared [2]. The another group of widely investigated and advanced polymers in regard to available toxicological and clinical data are the aliphatic polyesters based on lactic and glycolic acids. Homo- and copolymers of these aliphatic polyesters are synthesized by ring opening polymerization in high temperatures and long reaction time. Block copolymers of these units with PEG has been applied for different applications especially

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as miscelles, particles for drug delivery systems [2–3].

In this study, diblock copolymers of PCL-b-mPEG and PLL-b-mPEG were prepared under microwave irradiation in shorter reaction time than conventional method. The effect of microwave irradiaton on the characteristics of resulted product was investigated and compared with the ones prepared by conventional heating. Advantage of microwave heating for the preparation of corresponding copolymers was discussed.

Experimental Part

PCL-mPEG diblock copolymers were synthesized with ε-caprolactone (ε-CL, Aldrich, USA) and methoxy PEG (mPEG, Mn: 2,000; Sigma-Aldrich, Germany and 5,000; Fluka, Germany) using stannous octoate ($SnOct_2$, Sigma, USA) as catalyst under nitrogen atmosphere at 100 °C by microwave irradiaton for a period of time (5-60 min) with different mole and catalyst ratios. After the irradiation was completed, polymerized products were dissolved in chloroform and precipitated from diethyl ether to remove unreacted monomer and oligomers. This procedure was repeated three times. Similar procedure was applied also for L-lactide/mPEG (Lactide; Aldrich, USA) diblock copolymers but at 120 °C and the product was dissolved in dichloromethane. The precipitate was collected and dried at room temperature. All polymerizations were carried out in a Milestone S.r.l MicroSYNTH microwave synthesis unit with a maximum operating power of 800 W. The temperature of the reaction system was detected by a built-in infrared sensor. Diblock copolymers were also synthesized by conventional heating (in oil bath) at 100 °C and 120 °C (for PCL-b-mPEG and PLL-b-mPEG, respectively) for 24h. Structural and functional group analysis were performed by FTIR (Shimadzu-IRPRESTIGE-21) and ^{1}H-NMR (BRUKER). The number average- and weight average molecular weight and polydispersity index (PDI) values of the copolymers were determined by gel permeation chromatography (GPC) by using polysyrene as standard. Conversions were estimated by weighing out of the products. The differential scanning calorimetry (DSC) measurement was performed on DSC-50 instrument in aluminum pans under nitrogen at a heating rate of 10 °C/min.

Results and Discussion

FTIR Results

PCL-mPEG; as mentioned earlier, PEGs with different molecular weight (2000 and 5000) were used in polymer synthesis. Figure 1 shows FTIR spectra of PCL-mPEG2000s in different caprolactone and mPEG ratios (10:1, 4:1, 1:1) synthesized in the presence of 1.5 mol% $SnOct_2$ by microwave heating. FTIR spectrum of a copolymer (4:1) prepared by conventional heating was also placed in this Figure. For comparison, spectrum of mPEG was also included. According to the spectra, the frequency value for caprolactone (carbonyl group) was seen at 1720 cm^{-1}. For PEG blocks, the peaks at 1100 cm^{-1} for C-O vibration and 3000 cm^{-1} for methylene groups were significant. Note that, as increase in caprolactone ratio in feed, the intensity of corresponding peaks was also increased. As we compare the peaks for the copolymer (4:1) synthesized by microwave and conventional heating, no significant difference was observed approving the advantage of microwave heating over conventional one in terms of very short reaction time. Similar results were also obtained for PCL-mPEG5000 (10:1, 4:1, 1:1) synthesized in the presence of 1.5 mol % $SnOct_2$ for 30 min by microwave heating and for conventional one. The advantage of microwave heating was also confirmed for PCL-mPEG5000.

PLL-mPEG; according to FTIR spectra, peaks were very similar to the ones obtained for PCL-mPEGs. Carbonyl group and PEG blocks appeared at similar regions with caprolactone based polymers as seen

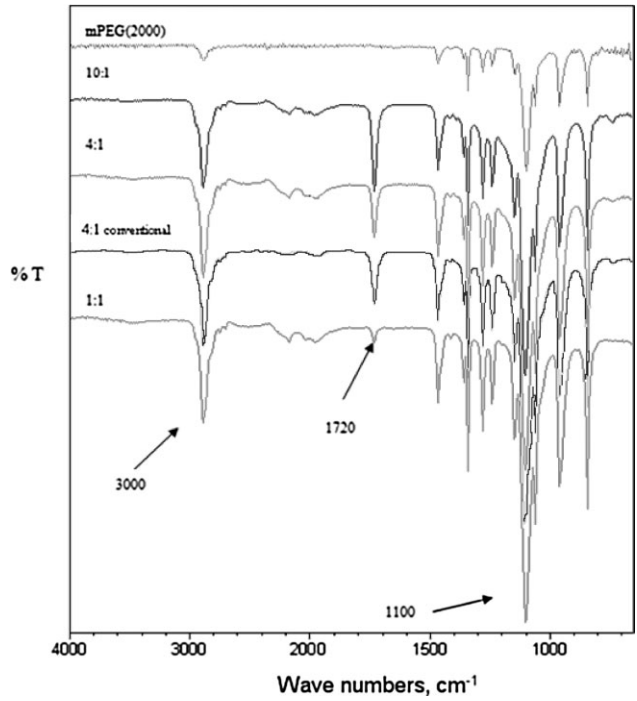

Figure 1.
FTIR spectra of PCL-b-mPEG2000 (1.5 mol% catalyst).

in spectra. Increased lactide units in feed (37,5:1, 10:1, 4:1, 1:1) caused increased intensity of corresponding peaks. Comparison of the peaks for the copolymer (4:1) synthesized by microwave and conventional heating caused no significant difference. This result confirmed the efficiency of microwave irradiation for this synthesis.

1H-NMR Results

Figure 2 represents ^{1}H-NMR spectra of diblock copolymers of caprolactone and mPEG2000 in 4:1 ratio synthesized by microwave irradiation and conventional heating. Each peaks were represented by letters. The most distiguished peaks are methoxy protons in PEG (indicated as ''a'') and metylene groups attached to carbonyl of caprolactone (indicated as ''d''). This observation agrees with what has been reported in the literature [4]. According to the spectra, copolymer obtained successfully. As compared to the conventional one, microwave synthesis seems very effective. Note that the change in ratio of PEG and caprolactone reflected to the all spectra which can be accepted as a proof of copolymer formation but these spectra were not included here. ^{1}H-NMR spectra of PLL-mPEG2000 in different ratios (10:1, 4:1, 1:1) were also investigated. The most distinguished peaks are as follows: (5 ppm) $-$CH and $-CH_3$ protons of lactide (1.5 ppm) and methoxy protons of PEG (3.1 ppm). Liao et al. prepared polymers containing PEG with different molecular weights and obtained similar peaks [5].

Molecular Weight Analysis

This was performed by GPC using chloroform as mobile phase and polystyrene as standard. ^{1}H-NMR spectra were also used to calculate molecular weight of polymers. To do this, for PCL-mPEG, methylene protons of caprolactone (d, $-COCH_2$) and methoxy protons of PEG (a, $-OCH_3$) were evaluated whereas methyl protons of lactide ($-CHCH_3$) and methoxy protons of

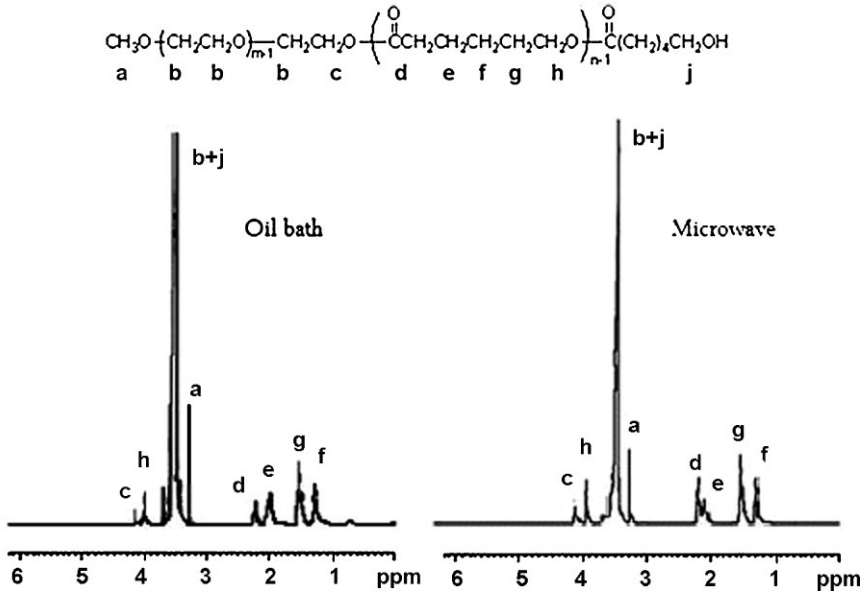

Figure 2.
^{1}H-NMR spectra of PCL-b-mPEG2000 (1.5 mol % catalyst, 30 min reaction time, 4:1) synthesized by microwave and conventional heating.

PEG ($-OCH_3$) were used for PLL-mPEG. Table 1 gives all molecular weight, conversion and PDI data. As seen here, PDI values are close to 1 which means very low size distribution was achieved. This result confirmed one of the advantages of microwave synthesis which is a technique allowing products very low by-products [6]. It is not surprising that the GPC results were obtained higher than theoretical values as this is not an absolute technique. Besides, molecular weight values determined by GPC and NMR can not be expected as exact values. According to the unimodal GPC traces, both block segments were succesfully introduced into the polymer chains and no peaks of homopolymers were found which is a demonstration of diblock formation [5]. According to the Table 1, molecular weight of the polymers prepared by conventional heating is very close to the one prepared with microwave requiring much less reaction time. Converisons of the polymers are not less than in the conventional analogs. Because of the applied purification procedure, a certain quantity

Table 1.
PCL-mPEG and PLL-mPEG diblock copolymers synthesized by microwave and conventional heating.

Polymer	Ratio (mole)	Conversion(%)	Mn[a]	Mw[a]	$Mn_{theoretical}$[b]	Mn_{NMR}[c]	PDI
PCLmPEG2000	1:1	69.87	5000	5800	2067	2100	1.16
PCLmPEG2000	4:1	80.18	5700	6500	2268	2400	1.14
PCLmPEG2000	10:1	65.58	6500	7400	2670	2300	1.14
PCLmPEG2000*	4:1	74.96	5600	6700	2268	2200	1.19
PCLmPEG5000	4:1	83.94	13000	14500	5268	5300	1.12
PCLmPEG5000*	4:1	75.64	–	–	5268	5200	–
PLLmPEG2000	1:1	71.09	4300	5000	2073	2100	1.16
PLLmPEG2000	4:1	65.71	5800	6700	2292	2100	1.15
PLLmPEG2000	10:1	60	6700	8000	2730	2500	1.19
PLLmPEG5000	4:1	74.29	10700	11800	5292	5100	1.10

[a]: Obtained by GPC,[b]: Calculated by feed ratio,[c]: Calculated by ^{1}H-NMR spectra,*: Conventional heating.

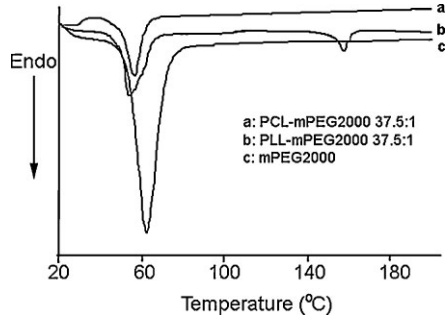

Figure 3.
The DSC plots of mPEG2000, PCL-b-mPEG2000 (37.5:1) and PLL-b-mPEG2000 (37.5:1).

of product was lost causing less conversion for all polymers.

Figure 3 shows DSC curves of mPEG-2000, PCL-b-mPEG2000 (37.5:1) and PLL-b-mPEG2000 (37.5:1). Crystalline melting temperature of PEG was obtained as 62°C and it showed a shift towards smaller values after copolymerization with both lactide and caprolactone units.

Effect of Time and Catalyst Ratio on Microwave Synthesis of Diblock Copolymers

Effect of time and catalyst ratio on microwave synthesis of PCL-mPEG was investigated for diblock copolymers in 37.5:1 ratio.

The effect of irradiation time on diblock copolymer formation was evaluated at different time intervals (5, 20, 30, 45, 60 min) at 120 °C with the PCL/PEG feed ratio of 37,5:1 (Figure 4). Average of

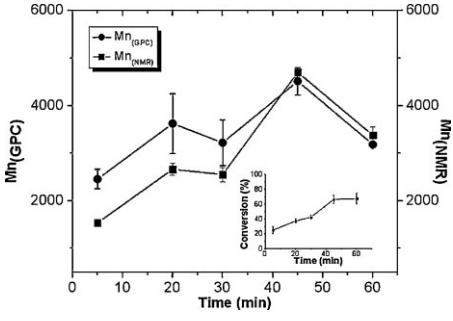

Figure 4.
Effect of time on conversion and molecular weight of microwave-synthesized PCL-mPEG2000 (37.5:1).

different sets of experiments were plotted. When the polymerization mixtures were irradiated for 5 min, PCL-mPEG2000 diblock copolymers with a $M_{n,GPC}$ of 2500 g/mol, $M_{n,NMR}$ of 1500 g/mol and conversion of 25% was obtained. When the irradiation time was increased from 5 to 20 and 30 min, the $M_{n,GPC}$ and $M_{n,NMR}$ of the resulting diblock copolymer increased from 2500 to 3600 and 3300 g/mol, and 1500 to 2700 and 2600 g/mol, and the conversion increased from 25% to 38% and 43%, respectively. When the irradiation time was extended to 45 min, the $M_{n,GPC}$ and $M_{n,NMR}$ of the resulting diblock copolymer achieved to 4700 and 4500g/mol, respectively, with a conversion of 67%. At the irradiation time of 60 min, the $M_{n,GPC}$ and $M_{n,NMR}$ of the resulting diblock copolymer decreased to 3200 and 3400 g/mol with a conversion of about 68%. These results indicated that the polymerization was completed within 45 min. Similar result was reported in Liao et al.'s study that prolonged microwave irradiation probably caused random thermal degradation of the polymer segments. At initial stages of the reactions, only ring-opening polymerization and chain propagation take place. But, thermal degradation occurs with prolong microwave irradiation [5]. Jun Yin et al reported that molecular weight and conversion of poly(ethylether ketone) were increased when compared to the conventional method [7]. Zhang et al reported that reaction taking 10 hours to complete was achieved in only 3 min and 92% conversion for PLL-PEG-PLL synthesis. Demoncau et al. prepared polymers of methyl methacrylate at 120 °C by microwave heating and reported that the required reaction time for polymer formation as 3 times less than the conventional one [8].

For the investigation of catalyst ratio effect, diblock copolymers were synthesized in similar conditions by changing catalyst quantity as 0.64, 1.28, 1.92 ve 6.4 (mol%). Up to a certain ratio (6.4 mol%), molecular weight and also conversion were increased. Similar catalyst effect were reported for the synthesis of poly(lactide)

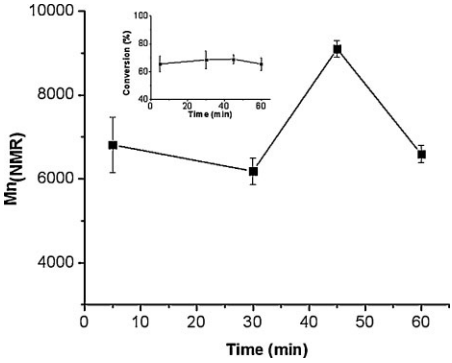

Figure 5.
Effect of time on conversion and molecular weight of microwave-synthesized PLL-mPEG2000 (37.5:1).

by conventional way [9]. Similar studies were also performed for PLL-mPEG2000 (37.5:1). The effect of irradiation time on diblock copolymer formation was evaluated at different time intervals (5, 30, 45, 60 min) at 100°C with the PLL/PEG feed ratio of 37,5:1 (Figure 5). When irradiated for 5 min, PLL-mPEG2000 diblock copolymers were already in $M_{n,NMR}$ of 6800 g/mol, and conversion of 65%. This shows some of the product was obtained in 5 minutes. When the irradiation time increased from 5 to 30 min, the $M_{n,NMR}$ of diblock copolymer showed a small decrease from 6800 to 6200 g/mol, and the conversion decreased from 66% to 69%. However, we can not conclude that the reaction completed at this point and went to degradation. Because, at the end of the 45 min molecular weight was achieved to 9100 g/mol again, with a conversion of 69%. At the irradiation time of 60 min, the $M_{n,NMR}$ of the resulting diblock copolymer was 6600 g/mol with a conversion of about 66%. Here, it may be conluded that the most of the reaction was completed within 45 minutes. Effect of catalyst ratio was investigated by changing quantity as 0.05, 0.1, 1.5, 10 (mol%). 1,5 mol% catalyst ratio is the highest quantity to obtain product in good molecular weight and conversion characteristics. Molecular weight of diblock copolymers was increased up to 5900 and conversion were in the range of 76 and 62%. This result is similar to the one obtanied for PCL-mPEG2000 diblock copolymers. In both polymer systems we can say that it is possible to obtain copolymer even in initial stages of reaction but in smaller molecular weight. Therefore, prolong microwave irradiation allow us to obtain higher molecular weight and conversion.

Figure 6 represents the comparison of conversion for all polymers (PCL-b-mPEG, PLL-b-mPEG) prepared by conventional method (for 1 day) and microwave irradia-

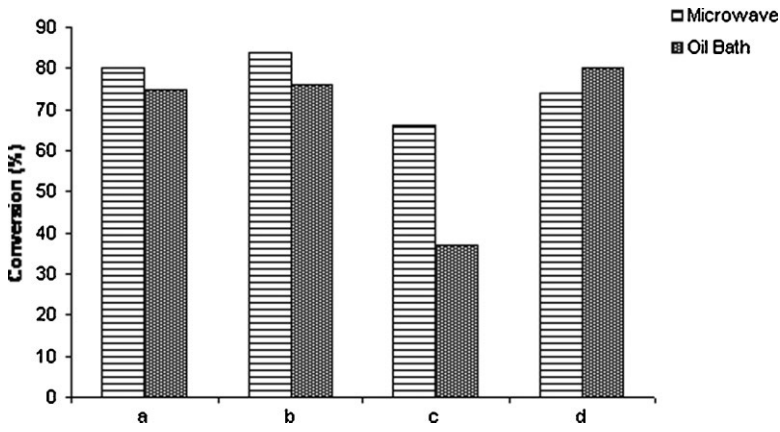

Figure 6.
Comparison of conversion for polymers synthesized by microwave (45 min) and conventional heating (1 day) (a) PCL-mPEG(2000), (b) PCL-mPEG(5000), (c) PLL-mPEG(2000), (d) PLL-mPEG(5000).

tion (for 45 min). Compared with the polymerization conducted in an oil bath, the polymerization under microwave irradiation produced higher conversion as also reported in Liao et al.'s study [5]. To achieve similar conversion performed by microwave irradiation, it is required to apply at least 1 day-heating in conventional method.

Conclusion

This study reported the preparation and characterization of PCL-b-mPEG and PLL-b-mPEG diblock copolymers by microwave heating and comparison of resulted products prepared by conventional heating. Effect of irradiation time on molecular weight and conversion of polymers were investigated. Up to a certain time, molecular weight an conversion increased depending on ongoing polymer formation for PCL-b-mPEG. However, prolonged microwave irradiation did not make anymore difference on the product. Therefore, microwave heating is an advantageous technique to obtain these diblock copolymers in much less reaction time with similar conversion and molecular weight with very low PDI.

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