Fast and Efficient Synthesis of High Molecular Weight Poly(epsilon-caprolactone) Diols by Microwave-Assisted Polymer Synthesis

Gustavo A. Gotelli,[1] Pablo Bonelli,[2] Gustavo A. Abraham,[2,3] Alejandro Sosnik[1,2]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmacy and Biochemistry,*
University of Buenos Aires, The Group of Biomaterials and Nanotechnology for Improved
Medicines (BIONIMED), Buenos Aires CP1113, Argentina
[2]*National Science Research Council (CONICET), Argentina*
[3]*Materials Science and Technology Research Institute (INTEMA), CONICET and National University of Mar del Plata (UNMdP), Mar del Plata, Argentina*

Received 26 July 2010; accepted 25 October 2010
DOI 10.1002/app.33664

ABSTRACT: Because of advantageous features such as shorter reaction times, greater yields, limited generation of by-products and relatively easy and straightforward scale-up, microwave-assisted synthesis has become a very appealing tool in organic synthesis. Conversely, its implementation in the context of the synthesis of biomaterials for biopharmaceutical applications has been more limited. The present work reports on the fast and efficient microwave-assisted synthesis of poly(ethylene glycol) (PEG)-initiated poly(ε-caprolactone) diols (PCL) by the ring-opening polymerization (ROP) of ε-caprolactone using stannous octanoate as catalyst. Since the PEG content in the synthesized copolymers was extremely low (0.2–1.9%), products were highly hydrophobic and displayed the intrinsic thermal properties of pure PCL. As opposed to the more time-consuming conventional thermally-driven synthesis that usually demands 2–3 h, the microwave technique resulted in intermediate to high molecular weight PEG-PCL derivatives within 10–15 min. The influence of different parameters affecting the synthetic process, namely monomer-to-initiator ratio, reaction time, catalyst concentration and the presence, type, and concentration of solvent were thoroughly investigated. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 121: 1321–1329, 2011

Key words: biomaterials; high molecular weight poly(ε-caprolactone) diol; ring opening polymerization (ROP); microwave-assisted polymer synthesis (MAPS)

INTRODUCTION

Features such as molecular weight and molecular weight distribution govern the performance of polymer-based drug delivery systems both *in vitro* and *in vivo*. Paradoxically, the industrial production of synthetic polymeric biomaterials is usually characterized by limited reproducibility.[1] In this context, to assure reproducible, scalable and cost-viable synthetic procedures, novel synthetic approaches are demanded. For example, the bacterial production of poly(hydroxyalkanoate)s in large scale has been extensively investigated.[2] An additional (and not negligible) issue pertains to the impact that the emission of gases (e.g., CO_2) and heat associated with these syntheses may have on the environment. Thus, sustainable chemistry has emerged as a new philosophy in synthetic chemistry that aims to minimize (i) the use of nonrenewable resources and solvents, (ii) the generation of toxic secondary products, (iii) the energy consumption, and (iv) the emission of gases.[3,4]

In the 1990s, the microwave radiation technology came out as a new and powerful synthetic tool in organic chemistry. Its most appealing features are (i) shorter reaction times, (ii) greater conversion percentages and reaction yields, (iii) limited formation of by-products, and, due to radiation homogenously distributed, (iv) the relatively easy scale-up without detrimental effects.[5] In addition, when one of the reagents is liquid and can perform also as solvent, reactions can be conducted under solvent-free conditions.

The microwave-assisted synthesis of biomaterials for pharmaceutical and biomedical applications has been much more sparse.[6] Having expressed this, the solid expertise gained in the organic synthesis field motivated applied chemists to explore the potential of microwaves in the synthesis of ceramics[7] and polymers.[4,8]

Poly(ε-caprolactone) (PCL) is a highly hydrophobic and semicrystalline polyester that, owing to its

---

Correspondence to: A. Sosnik (alesosnik@gmail.com).
Contract grant sponsor: University of Buenos Aires; contract grant numbers: UBACyT-B424, UBACyT-B041.
Contract grant sponsor: CONICET; contract grant number: PIP 522-2008.

Journal of Applied Polymer Science, Vol. 121, 1321–1329 (2011)

proven biocompatibility and biodegradability, has found extensive applications in the biomedical field.[9,10] PCL implants display high permeability to both hydrophilic and hydrophobic drugs, becoming a very versatile platform for the design of drug delivery systems.[11–13] Because of a higher hydrophobicity and more limited water permeability than other polyesters (e.g., poly(lactic acid), PLA) PCL withstands better the hydrolytic biological environment[14,15] and sustains the release of the loaded drugs over more prolonged times.[16] Moreover, PCL displays relatively low glass transition and melting temperatures of −60°C and 60°C, respectively.[17] These thermal properties were exploited to produce drug-loaded implants employing relatively simple processes [18,19]. For example, our group has reported on the production of PCL (14 kDa) implants by a melt-molding/compression technique for the sustained release of gabapentin [20,21] and topotecan.[22] Also, the development of a growth hormone-loaded injectable implant has been addressed.[23]

Previous works have described the synthesis of PCL by microwave-assisted ring opening polymerization (ROP) of ε-caprolactone (CL) using diverse initiators and catalysts.[24–26] Since CL is liquid and displays a tan δ value of ∼ 0.35,[27] most of the reactions were conducted under bulk conditions; tan δ values between 0.1 and 0.5 indicate a moderate ability to absorb the microwaves, this phenomenon leading to effective dielectric heating.[4] In general, the molecular weights obtained were relatively low or, conversely, the times employed for the reaction were comparable with those used under conventional thermally driven methods. For example, Barbier-Baudry and coworkers produced PCL with molecular weights between 2.9 and 14.1 kDa employing irradiation times between 2 and 90 min, the optimal irradiation time being ∼ 45 min.[24] Poydispersity indexes ranged between 1.3 and 2.2. In a more efficient synthetic setup, Liao et al. described the production of PCL homopolymers with molecular weights as high as 124 kDa and PDI values in the 1.2–1.8 range.[23]

Aiming to investigate the versatility of this technology to develop block copolymers that display tunable hydrophilic-lipophilic balance (HLB), the present work reports on the microwave-assisted synthesis of poly(ethylene glycol) (PEG)-initiated synthesis of intermediate to high molecular weight poly(ε-caprolactone) diols (PCL-PEG-PCL) under bulk or solvent conditions. PEG is a hydrophilic poly (ether) commonly copolymerized with very hydrophobic biomaterials to increase their hydrophlicity and degradability in the physiological environment; the HLB can be tailored by adjusting the molar ratio between both components. For example, we recently reported on the microwave-assisted synthesis of relatively hydrophilic PCL-PEG-PCL amphiphiles employing PEG initiators of molecular weights between 6 and 20 kDa.[28] Then, the molecular implications governing the encapsulation of the antituberculosis drug rifampicin within flower-like polymeric micelles were investigated.

The goal of this study was to gain further insight into the key parameters that govern the polymerization process. In this context, the synthesis of highly hydrophobic PCL diols employing a low-molecular weight bifunctional initiator, namely PEG with a molecular weight of 400 Da, was investigated. Since the final products contained extremely low PEG contents (0.2–1.9%), they were expected to display the properties of pure PCL diols and not of the more hydrophilic PCL-PEG amphiphiles.[27] A simple method was used to establish the areas in the oven cavity with the maximum irradiation and the optimal dimensions of the reaction vessel; multimode domestic ovens display a less homogeneous distribution of the microwaves than professional equipment. The influence of monomer-to-initiator ratio, reaction time and the presence, type and concentration of solvent were evaluated.

MATERIALS AND METHODS

Materials

ε-caprolactone (CL, Aldrich) and stannous (II) 2-hexylhexanoate (SnOct, catalyst, Sigma) were used as received. Poly(ethylene glycol) of average molecular weight 400 Da (PEG400, Aldrich) was dried with molecular sieves 3A (Sigma) at least 24 h before use. Analytical-grade *N,N*-dimethylformamide (DMF, Sintorgan, Argentina) and dimethylsulfoxide (DMSO, Sintorgan, Argentina) were dried with molecular sieves. Other solvents were of analytical grade and were used as received.

Microwave apparatus

The apparatus used for the polymerization was a household microwave oven (Whirlpool^{TM}, radiation frequency 2.45 GHz, potency 800W) with 5 power levels. Conventional multimode ovens graduate the irradiation power by means of "on/off" cycles of the magnetron (pulsed irradiation).[4] Basically, the potency is maintained constant at 800W though the duration of the "on" and "off" periods in the cycle is modified according to the power level employed. The energy distribution in different positions inside conventional ovens is often not homogeneous. To determine the energy pattern distribution (EPD), a filter paper was embedded in $CoCl_2$ solution, dried and then irradiated in longitudinal and crosswise positions under different oven powers.[29]

Microwave-assisted polymerization

Different PCL-PEG400-PCL triblocks displaying a general molecular structure HO-(CH_2-CH_2-CH_2-CH_2-CH_2-CO-O)$_n$-(CH_2-CH_2-O)$_{36}$-(CO-CH_2-CH_2-CH_2-CH_2-CH_2-O)$_n$-H were synthesized by the ring-opening polymerization (ROP) of CL, catalyzed by SnOct. This catalyst has been approved by the US FDA for use in biomedical devices and as stabilizer in food industry.[30] The reaction mixture (5–10 g) containing monomer, initiator, catalyst and solvent (when needed) was poured into a glass vial (10 mL, 20 mm diameter, 50 mm height) and irradiated under power 1 during 10 min; power 1 combines “on” and “off” cycles of 6 and 24 s, respectively. One reaction was conducted under power 2 (12 and 18 s for “on” and “off”). Different monomer-to-initiator molar feeding ratios (*M/I*) were used to produce copolymers of different molecular weight (Table I). Catalyst concentrations were usually 3.5% (weight percentage to CL). However, to investigate the effect of the concentration on the polymerization process, a series of copolymers employing SnOct in the 0.8–5.3% range was synthesized. Reactions were conducted in open vials and the weight loss monitored. Due to the fast polymerization rate, a fast and pronounced viscosity increase was observed. Aiming to maintain the viscosity relatively low and favor the total conversion of the monomer, reactions were also conducted in solution (1–40 wt % DMF or 5 wt % DMSO) and the results were compared to those obtained in bulk. Under these conditions, evaporation was also negligible (<1%). To conduct reactions under pressure, a hermetic reaction vessel (1.25 cm internal diameter, 3.85 cm height, ~ 4.7 cm^3 volume) made of poly(vinyl chloride) (PVC) was used; PVC is transparent to microwave radiation. To isolate the product, the crude material was dissolved in acetone at 60°C, precipitated in distilled water, washed several times with distilled water, and dried at room temperature. All the products were white to yellowish powders.

Characterization

NMR spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on Bruker 300 MHz NMR spectrometer from deuterated chloroform ($CDCl_3$, Aldrich) solutions, at room temperature. PCL/PEG molar ratios and number molecular weight, M_n (^{1}H NMR), were calculated by taking the ratio between the integration area of the peaks of PEG (4H, multiplet, 3.65 ppm) and PCL (2H, triplet, 2.30 ppm) (see below). Monomer conversion percentages (% Conversion) were estimated according to % Conversion = M_n (Theor.)/M_n (^{1}H NMR) × 100, where M_n (Theor.) and M_n (^{1}H NMR) are the molecular weights calculated from the *M/I* molar feeding ratio (theoretical) and the average number-molecular weight determined by ^{1}H NMR, respectively.

Molecular weight analysis

Number- and weight-average molecular weights (M_n and M_w) and molecular weight distributions (polydispersity, PDI = M_w/M_n) were determined by gel permeation chromatography (GPC) using a Knaüer GPC instrument (Berlin, Germany) provided with a refractive index detector. A set of 50 Å, 100 Å, and M2 (Phenomenex Inc, Torrance, CA, USA) and 10^4 Å (Waters, Inc, Milford, MA) columns ultrastiragel column, conditioned at 25°C was used to elute samples at 1 mL/min HPLC-grade tetrahydrofuran (THF) flow rate. Polystyrene standards (Polymer Laboratories, Shropshire, UK) were used for calibration. Samples were filtered by 0.22 μm Teflon filters before the analysis.

FT-IR spectroscopy

Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer. The samples were prepared by solvent casting from chloroform solutions on NaCl windows.

Thermal analysis

Differential scanning calorimetry (DSC) was performed in a Mettler TA-400 differential scanning calorimeter. The samples were sealed in 40-μL Al-crucible pans. All runs were conducted from 25° to 100°C at 10°C/min under nitrogen atmosphere. The melting temperature (T_m) and degree of crystallinity were determined considering that the enthalpy of melting (ΔH_m) of 100% crystalline PCL is 139.5 J/g.[31]

RESULTS AND DISCUSSION

To produce highly hydrophobic block copolymers that display thermal properties similar to those of pure PCL, a low molecular weight initiator, namely PEG 400 Da, was used. The goal of the preliminary experiments was to establish the EPD inside the oven cavity. Conventional fixed-frequency microwave heating often leads to uneven heating.[28] The different color patterns revealed in the $CoCl_2$-soaked paper indicated the zones of maximum irradiation and consequently greatest temperature[28]; $CoCl_2$ is pink and blue when wet and dry, respectively. A high-intensity central band (38 mm wide) and two

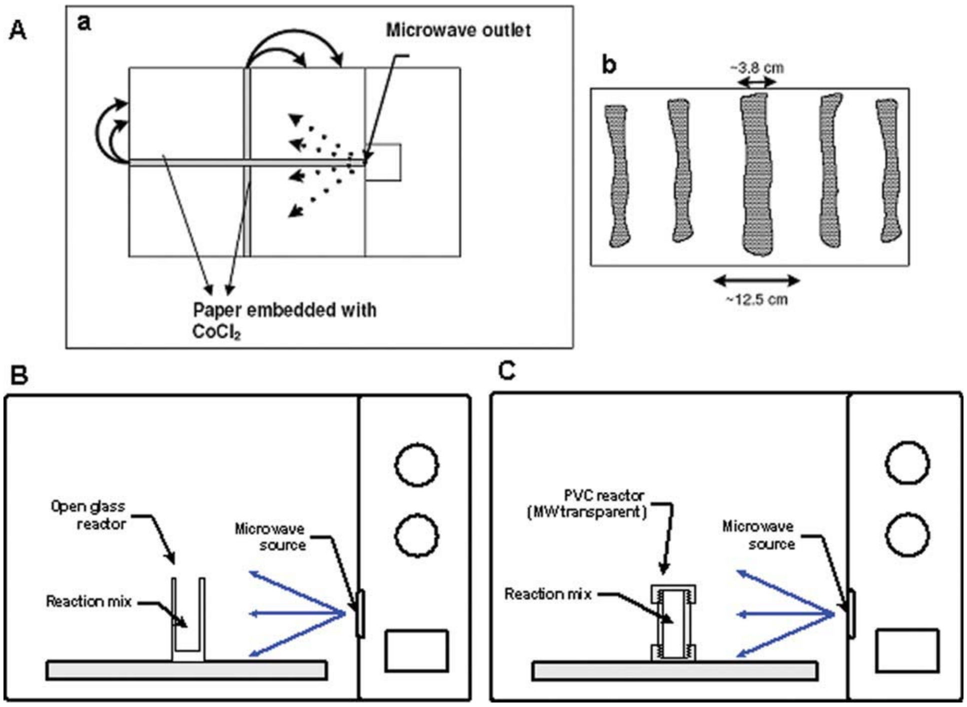
TABLE I
Synthesis Conditions, Theoretical, and Experimental Molecular Weight Values of the Different PCL Diols Synthesized Under Bulk and Solvent Conditions

Polymer	M/I[a]	Solvent	Solvent content (wt%)	Irradiation time (min)	Theoretical[b] M_n (kDa)	M_n[c] (kDa)	M_n[d] (kDa)	M_w[d] (kDa)	PDI[d] (M_w/M_n)
P1	193	–	–	10	22.4	23.9	20.1	31.7	1.6
P2	315			10	36.4	39.0	31.1	47.3	1.5
P3*	328			4	37.8	49.4	19.0	27.7	1.5
P4	628			10	72.1	68.0	33.3	51.4	1.5
P5	1140			10	130.5	89.8	36.9	60.3	1.6
P6	1139			14	130.4	118.8	40.4	64.2	1.6
P7	1137			30	130.2	130.6	16.4	30.1	1.8
P8	1138			60	130.3	120.8	18.0	34.5	1.9
P9	1228			14	140.6	40.3	2.8	6.6	2.5
P10	1228			14	140.6	121.5	29.0	44.3	1.5
P11	1226			14	140.4	129.1	29.1	48.3	1.7
P12	1178			14	134.9	64.2	2.9	7.3	2.4
P13	191	DMSO	5	10	21.5	18.5	8.8	15.4	1.8
P14	160	DMF	1	10	18.7	19.3	16.0	26.0	1.6
P15	185		5	10	21.5	18.5	18.5	29.5	1.6
P16	177		10	10	20.7	18.8	16.5	29.9	1.8
P17	200		20	10	23.2	22.6	15.1	23.6	1.6
P18	195		30	10	22.7	23.2	12.2	19.8	1.6
P19	176		40	10	20.5	9.2	6.7	8.7	1.3
P20	426		30	10	49.0	24.7	13.1	18.7	1.4
P21	940		30	10	107.6	86.0	15.8	25.2	1.6
P22	968		30	20	110.9	91.0	22.4	39.1	1.7
P23	1670		30	10	191.0	114.0	23.0	33.3	1.4
P24**	1775		30	10	202.9	225.0	31.5	44.0	1.4

* Power level was 2 (out of 5 levels).
** Reaction conducted in a closed PVC vessel.
[a] *M/I*: feeding monomer-to-initiator molar ratio.
[b] Molecular weight determined according to the molar feeding ratio *M/I*.
[c] Number-molecular weight as determined by ^{1}H NMR.
[d] Molecular weight and PDI as determined by GPC.

side bands of weaker intensity were observed [Scheme 1(A)]. Not surprisingly, the distance between the bands (6 cm) was similar to one half of the wavelength (12.5 cm for 2.45 GHz). This EPD was repeated in both the longitudinal and the crosswise direction. On the basis of this, the optimal dimensions and position of the reaction vessel inside the cavity were adjusted to enable the homogeneous irradiation of the whole sample. This is a central issue that was not addressed by other research groups employing domestic equipment for polymer synthesis. In general, it is assumed that the maximum heating performance takes place in the center of the cavity, though this would need to be established prior to any synthesis. In addition, the irradiation potency is often calculated by taking the ratio between the power level and the maximum potency of the oven; e.g., when a power level of 5 (out of 10) in an oven of maximum potency 800 W is used, an "average irradiation potency" of 400 W is informed. However, multimode ovens usually irradiate at a constant potency and the power is graduated by changing the duration of alternating "on" and "off" times and not by controlling the irradiation potency.[4] This calculation methodology is unreliable and misleading. Thus, this procedure should be conducted in every new domestic oven employed for synthesis. This phenomenon also stresses the fact that the reaction conditions could be nonreproducible when different ovens are used.

The experimental conditions (*M/I*, reaction time, type of solvent and concentration) used in this work and the molecular properties of the synthesized PCL diols are summarized in Table I. By increasing the *M/I* feeding ratio, increasingly longer terminal PCL blocks were produced. The synthesis of block copolymers by using an active-hydrogen compound as initiator in the ring-opening polymerization of CL has been widely investigated. Following the conventional synthetic route, triblock copolymers consisting of PCL-PEG-PCL with different hydrophilic-to-hydrophobic ratio were successfully synthesized[32,33]; some of these macrodiols were used as precursors in polyurethane formulations. In a previous study, Abraham et al. investigated the final composition of reaction mixtures of low molecular weight diethyleneglycol-initiated (DEG) PCL[34] and triethyleneglycol-initiated (TEG) PCL[35] by means of ^{1}H NMR. Findings



Scheme 1 (A) Determination of the EPD in the oven cavity by means of the $CoCl_2$-soaked paper. (a) Upper view of the setup employed to evaluate the irradiation pattern inside the oven cavity. (b) Irradiation pattern in the microwave oven employed during the study. The shade areas represent areas of maximum temperature ($CoCl_2$ turns from pink to blue). (B) Reaction setup in an open glass vial. (C) Reaction setup in a closed PVC reactor. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

indicated the presence of very low concentrations of free DEG,[33] though no free TEG.[34] Accordingly, we envisioned high conversion extents that would result in the formation of HO-PCL-PEG-PCL-OH disubstituted species. In addition, the presence of a PEG central segment enabled the calculation of the M_n by ^{1}H NMR (Fig. 1). It is important to remark that for especially high *M/I* ratios, the integration of the relevant peaks in ^{1}H NMR spectra could result in significant deviations. Hence, NMR was used as a complementary technique for molecular weight analysis and not as the ultimate one.

First, reactions were conducted under bulk conditions in an open vessel setup [Scheme 1(B)]. FT-IR spectroscopy revealed the presence of the characteristic bands of the polyester (e.g., carbonyl vibration band at 1724 cm^{-1}). The thermal behavior was investigated by DSC. All the products exhibited the characteristic semicrystalline nature of PCL.[19] T_m values were in the 53–64°C range and the degree of crystallinity between 14 and 48% (data not shown); the higher the molecular weight, the lower the degree of crystallinity obtained. When copolymers of intermediate molecular weight (up to 36 kDa, $M/I <$ 315) were prepared in bulk, very high monomer conversions ($\sim$ 100%) were obtained (Table I, P1-P4). For example, P1 and P2 presented M_n (^{1}H NMR) of 23.9 and 39.0 kDa, respectively, while the theoretical values were 22.4 and 36.4 kDa. The absence of the characteristic peak of free CL in ^{1}H NMR spectra at 4.25 ppm (Fig. 1) was also confirmed.[36] GPC analysis revealed the presence of unimodal molecular weight distributions and, often, relatively low PDI values (<1.6) (Fig. 2). Also, M_n values measured by GPC were in full agreement with ^{1}H NMR data. These results indicated that a 10 min irradiation was enough to complete the polymerization. When *M/I* ratios greater than $\sim$ 315 were intended irradiating

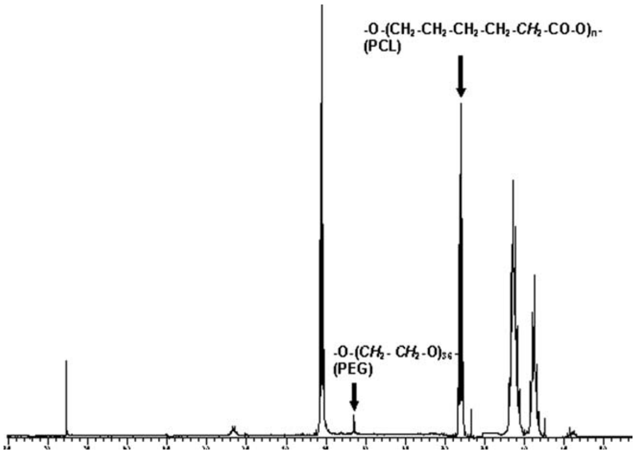


Figure 1 ^{1}H NMR spectrum of PCL diol (sample P4). The signals employed for the calculation of M_n are indicated.

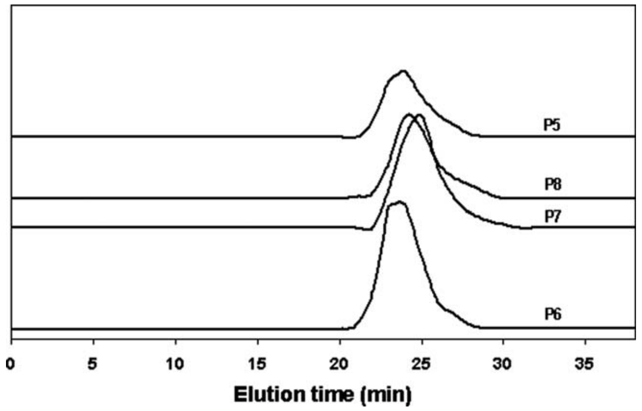


Figure 2 GPC chromatograms of copolymers P5-P8. Products showed unimodal molecular weight profiles and relatively low PDI values usually < 1.9.

over 10 min, M_n (^{1}H NMR) (and conversions) gradually decreased with respect to the theoretical values. For example, P5 showed a % conversion of approximately 69%. GPC-measured molecular weights were even smaller, at least when a 10 min irradiation was used (e.g., P5); the higher the *M/I* was, the greater the gap between NMR and GPC data. To further investigate the effect of the irradiation time on the polymerization, four reaction mixtures of similar composition ($M/I = 1137$–1140) were irradiated over 10–60 min (P5-P8). A slightly longer irradiation time of 14 min led to a clear increase of the monomer conversion from 69% (P5) to 91% (P6). On the other hand, molecular weights (GPC) remained smaller than the theoretical ones. Then, irradiation times longer than 14 min lead to a further decrease of the chromatographic molecular weight (Fig. 3); e.g., M_w values of P6 and P8 were 64.2 and 34.5 kDa, respectively. These findings were in full agreement with previous reports [35,37] and would suggest that a thermal degradation process takes place upon microwave overexposure. It is worth stressing that all the samples were analyzed by GPC, showing always unimodal patterns. Also, elution peaks belonging to low molecular weight fractions were not observed. It should be remarked though, that no additional evidence of this degradation process is available. On the other hand, an identical reaction mixture irradiated over more than 14 min rendered lower molecular weight copolymers. Thus, it seems reasonable to assume that at certain time point (when almost all the monomer has been consumed), the probability of generating new ester bonds decreases pronouncedly, while the chance of chain scission concomitantly increases.

Sample weights were monitored over time to establish any potential monomer evaporation. Results indicated that no monomer was lost (<1 wt %); the boiling point (BP) of CL is 253°C, far above the reaction temperature (150–160°C). These observations suggested that the deleterious effect on the molecular weight could not be attributed to monomer evaporation. On the other hand, the decrease of the M_n (^{1}H NMR) with respect to the theoretical value indicates that the monomer conversion is incomplete. Since CL residues are totally eliminated during the purification process, they are not observed in ^{1}H NMR (Fig. 1) and GPC (Fig. 2) analyses of the purified copolymers. Conversely, nonreacted CL was apparent in the chromatograms of high molecular weight crude products. Moderate to noticeable deviations of GPC data from average molecular weights calculated by ^{1}H NMR for high molecular weight polymers synthesized by ROP have been previously described for PLA-PEG-PLA[38] and PCL-PEG-PCL triblocks[27] and poly(trimethylene) carbonate (PTMC)[39] and PTMC-PEG-PTMC copolymers.[40] Zhang et al. suggested that a lower conversion extent for LA/PEG *M/I* ratios greater than 200 and a sharp M_n (GPC) decrease would stem from more limited reaction rates[37] (see below). In this work, the fast and sharp viscosity increase observed after 10–20 s irradiation together with the decreasing CL concentration could explain the pronounced decline of the reaction rate, especially for high *M/I* ratios.[37] In a more recent work, the decrease of M_n (GPC) with respect to theoretical and ^{1}H NMR values together with a high % conversion was attributed to monomer homopolymerization, this phenomenon being more pronounced for growing *M/I* ratios.[38] Storey and Taylor suggested that in the absence of initiator (e.g., ethylene diol), the SnOct-catalyzed homopolymerization of CL could be initiated by water traces that are introduced with the catalyst.[41] In this context, it is expected that the sharp increase of the *M/I* feeding ratio could favor this secondary polymerization pathway over the primary

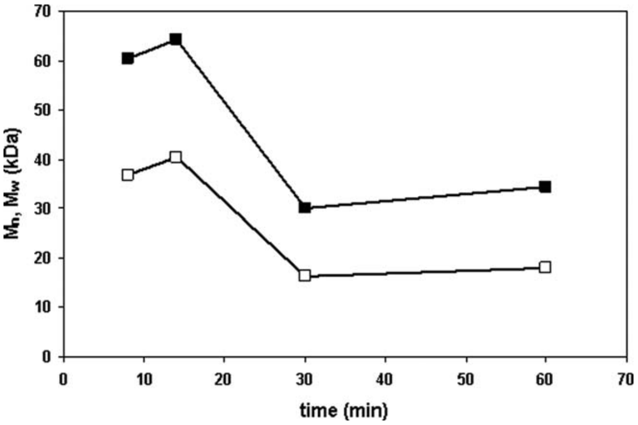


Figure 3 M_n (☐) and M_w (■) as a function of MW irradiation time for copolymers with initial *M/I* molar ratio of ~ 1140 (samples P5–P8).

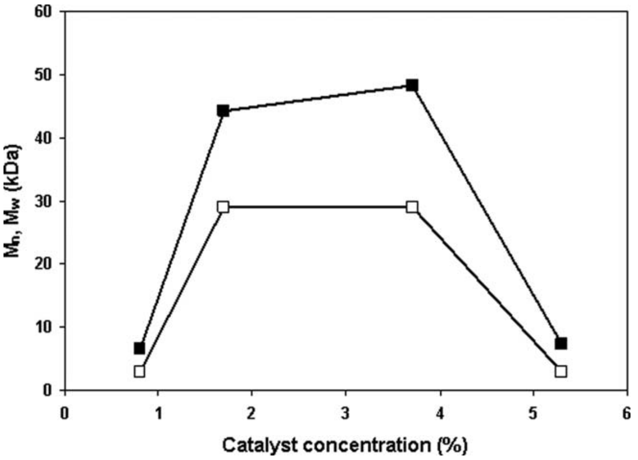


Figure 4 M_n (☐) and M_w (■) as a function of the catalyst concentration for copolymers with initial *M/I* molar ratio of 1178–1228 (samples P9–P12).

one. In other words, high conversions associated with a drop in the chromatographic molecular weight could be only explained by a homopolymerization route. Having expressed this, in the case of copolymers displaying also a decrease of the M_n (^{1}H NMR) (and the calculated % conversion), a combined detrimental effect of viscosity growth (and slower polymerization rate) and homopolymerization seem to undermine the attainment of higher molecular weights.

To evaluate the combined effect of radiation power and exposure time on the ROP, two copolymers of similar *M/I* ratio were synthesized under different conditions; P2 (*M/I* = 315) and P3 (*M/I* = 328) were exposed to power levels of 1 and 2 for 10 and 4 min, respectively. M_n and M_w (GPC) values were substantially higher for P2. These results strongly suggest that, once the minimum irradiation power is achieved, the reaction time is a more crucial parameter. As previously reported, excessive power usually leads to polymer thermal degradation and a reduction of the final molecular weight.[37,38]

Another key parameter is the catalyst concentration. P9-P12, four PCL diols with similar theoretical molecular weight (135–140 kDa), were synthesized in the presence of increasing catalyst concentrations. The increase of the catalyst concentration from 0.8% to 1.2% led to a clear increase of M_n and M_w (GPC) from 2.8 to 29.1 kDa and from 6.6 to 44.3 kDa, respectively, (Fig. 4). A higher conversion extent was also found (29–86%). This molecular weight growth was accompanied by a sharp decrease of the PDI. A further increase to 3.7% led to an additional growth in M_w, while M_n remained almost unchanged. In addition, the conversion grew to 92%. Then, 5.3% catalyst resulted in a sharp decrease of the molecular weight (P12). ^{1}H-NMR also evidenced a clear decrease of the monomer conversion for 0.8 and 5.3% SnOct. These findings indicated that the optimal catalyst concentration for the synthesis of these copolymers would range between 2 and 3% and that is higher than the reported by other authors.[23] It should be mentioned though that these reactions were conducted under different conditions.[23] Molecular weights determined by ^{1}H NMR for P10 and P11 showed relatively high conversion extents, indicating that for the production of PCL-PEG-PCL diblocks and triblocks, higher catalyst concentrations might be required.[11,42]

Regardless of the synthetic approach employed, the reproducible synthesis of large polymer amounts represents a challenging goal. To assure the maintenance of low viscosity and, thus, enable greater conversion extents, we were interested in exploring the effect of solvent type and concentration on the polymerization progress. It is worth stressing that, to the best of our knowledge, this study is the first investigating the microwave-assisted ROP of CL under solvent conditions.

The ability of a molecule to translate electromagnetic energy into heat at a given frequency and temperature is determined by the loss tangent (tan δ).[4] The higher the tan δ, the more efficient the radiation absorption and the faster the heating are. Thus, solvents with tan δ > 0.5, 0.1–0.5, and < 0.5 are considered as high-, medium-, and low-absorbing compounds. To study the effect of this parameter on the synthetic performance, two solvents displaying relatively high boiling point (BP), though sufficiently different tan δ were primarily considered: (i) DMSO (tan δ = 0.825, BP = 189°C) and (ii) DMF (tan δ = 0.165, BP = 153°C). Thermally driven ROP reactions usually take place at temperatures above 120–150°C.[11,23,41] Because of the higher capacity of DMSO to absorb microwaves, faster reaction rates and higher polymerization efficiencies than those attained with DMF were expected. P13 and P15, two PCL copolymers with *M/I* of 191 and 185, respectively, and exposed to 10 min irradiation were synthesized with the addition of 5% solvent (DMSO and DMF, respectively). Results indicated that the polymerization performance in DMF (P15) was similar to that observed under bulk conditions (see P1), M_n and M_w (GPC) values being 18.5 and 29.1 kDa. A similar behavior was observed with 10% DMF (P16). In contrast, 5% DMSO (P13) led to lower molecular weights; e.g., M_n and M_w (GPC) of 8.8 and 15.4 kDa, respectively. DMSO is relatively stable under thermal treatment, though it decomposes into dimethylsulfide, dimethyldisulfide, bismethylthiomethane, water, and formaldehyde upon prolonged heating.[43] In contrast, DMSO decomposes very rapidly under the extremely energetic microwave conditions.[42] This behavior is intimately associated with its high absorbing properties. In this context, DMSO overheating could probably explain the smaller molecular weights obtained. Even though DMF was also reported to react in the presence of Pd catalysts under microwave irradiation,[44] the milder conditions of the present study did not lead to any apparent decomposition. To gain further insight into the effect of the solvent, in advance, reactions were conducted with increasing DMF concentrations. The synthesis of copolymers displaying moderate molecular weight (~ 20 kDa) in up to 30 wt % DMF were also efficient; note the relatively good agreement between the theoretical and the experimental molecular weights of polymers P17 and P18 (Table I). Contrary to this, when DMF concentrations greater than 30% were intended, a pronounced deleterious effect was apparent. For example, a polymer with theoretical M_n of 20.5 kDa (P19) showed experimental M_n values of 9.2 and 6.7 kDa by ^{1}H NMR and GPC, respectively, (Table I). These findings not only indicated a smaller degree of polymerization, as expressed by the lower molecular weight, but also a dramatically smaller monomer conversion. A similar trend was found with increasing M/I ratios, even when 30% DMF was used; e.g., reaction mixtures with theoretical molecular weights of 49.0 ($M/I = 426$; P20), 107.6 ($M/I = 940$; P21) and 191.0 kDa ($M/I = 1670$; P23) led to M_n (^{1}H NMR) values of 24.7, 86.0, and 114.0 kDa, respectively. In addition, GPC showed even smaller molecular weights, consistent with a homopolymerization pathway (see below). This behavior was similar to the one shown for copolymers with relatively high M/I and synthesized in bulk (see above). The performance of the polymerization was slightly improved with longer reaction times. For example, P21 ($M/I = 940$, $M_n = 107.6$ kDa) and P22 ($M/I = 968$, $M_n = 110.9$ kDa) were irradiated over 10 and 20 min, respectively. The generated copolymers displayed ^{1}H NMR values of 86.0 and 91.0 kDa, conversion extents being ~ 80%. In addition, a moderate increase of the chromatographic molecular weight for a longer irradiation was observed. It is worth mentioning that reactions were conducted in open vials to minimize the pressure rise. This procedure was supported by the fact that reaction times were relatively short and that the temperature of the reaction mixture usually rose up to 130–150°C, a temperature range slightly below the BP of DMF. It is worth stressing that also under solvent conditions, negligible weight losses (<1%) were recorded. In any event, it has been clearly shown that the synthesis of copolymers displaying moderate molecular weights can be conducted even with DMF contents as high as 30%. A slight molecular weight decrease between P1 (bulk) and P18 (30% DMF), two copolymers with almost identical M/I, could be attributed to the introduction of additional water amounts present in this hygroscopic solvent, this water favoring the secondary polymerization pathway (homopolymerization).

Previous investigations showed that reactions conducted in closed reaction vessels could be faster and more efficient.[4] If the reaction is conducted under atmospheric pressure in an open vessel, the heating process is conditioned by the solvent boiling point and the rate enhancement is more limited; the superheating effect is up to 40°C.[4] In an attempt to conduct the ROP under pressure and evaluate the enhancement of the reaction efficiency, open glass vials were replaced by a sealed PVC reactor [Scheme 1(C)]. In general, polymers are transparent to MW-radiation.[45] Results indicated that the lower viscosity generated in presence of 30% DMF enabled the complete monomer conversion (P24). On the other hand, it is worth mentioning that GPC data deviated remarkably from NMR, M_n and M_w (GPC) values being 31.5 and 44.0 kDa, respectively. These findings support that homopolymerization is the preferred polymerization pathway when very high M/I molar ratios are reacted. When a higher dilution (>40%) was explored in a closed reactor setup, the polymerization efficiency decreased even further (not shown). In this framework, longer irradiation times could lead to a recovery of the polymerization extent and to higher chromatographic molecular weights. These aspects need to be further investigated and the conditions for the synthesis of high molecular weight PEG-PCL copolymers under solvent conditions conveniently fine tuned. In any case, the range of molecular weights attained in this work (M_w up to 64.0 kDa) would enable the fast and efficient production of derivatives with a broad range of molecular weights, HLB values and physicochemical and mechanical properties. These biomaterials could fit a variety biomedical applications, from those requiring relatively low mechanical properties (e.g., micro and nanoparticles [27,46] for drug delivery), to mechanically challenged systems such as nanofibers[47] and to tissue engineering scaffolds.[48]

Finally, scale up is an intrinsic challenge of MAPS. In the present work, the polymerization of five identical reaction mixtures (in the same irradiation session) was intended. However, no polymerization took place. In this context, we are assessing additional modifications that could be performed to the oven to improve the ability to synthesize greater batches.

CONCLUSIONS

The PEG-initiated ring-opening polymerization of CL under microwave irradiation was successfully carried out under bulk and solvent conditions. Polymers with molecular weights (as determined by

GPC) as high as 64.0 kDa were obtained. This synthetic approach could be also exploited to synthesize PCL derivatives displaying different molecular architectures; e.g., mono-, bi-, and trifunctional initiators would result in diblock, triblock and star-shaped PCL molecules. Studies underway are focused on (i) the synthesis of PCL derivatives employing other heterogeneous initiators and (ii) the design of a continuous flow reactor for the scaling up of the polymer synthetic process.

References

1. El Seoud, O. A.; Heinze, T. Adv Polym Sci 2005, 186, 103.
2. Chen, G.-Q. Chem Soc Rev 2009, 38, 2434.
3. Tucker, J. L. Org Process Res Dev 2010, 14, 328.
4. Zhang, C.; Liao, L.; Gong, S. Green Chem 2007, 9, 303.
5. Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250.
6. Wiesbrock, F.; Hoogenboom, R.; Schubert, U. S. Macromol Rapid Comm 2004, 25, 1739.
7. Pon-On, W.; Meejoo, S.; Tang, I.-M. Int J Nanosci 2007, 6, 9.
8. Sosnik, A.; Gotelli, G.; Abraham, G. A.; Prog Polym Sci. doi: 10.1016/j.progpolymsci.2010.12.001
9. Perrin, D. E.; English, J. P. Polycaprolactone. In Handbook of Biodegradable Polymers; Domb, A. J.; Kost, Y.; Wiseman, D. M., Eds.; Harwood Academic Publishers, Amsterdam, The Netherlands, 1997, p 63.
10. Kumar, N.; Ravikumar, M. N. V.; Domb, A. J. Adv Drug Deliv Rev 2001, 53, 23.
11. Rathbone, M. J.; Bunt, C. R.; Ogle, C. R.; Burggraaf, S.; Macmillan, K. L.; Pickering, K. J Control Release 2002, 85, 61.
12. Sosnik, A.; Cohn, D. Polymer 2003, 44, 7033.
13. Sinha, V. R.; Bansal, K.; Kaushik, R.; Kumria, R.; Trehan, A. Int J Pharm 2004, 278, 1.
14. Sun, H.; Mei, L.; Song, C.; Cui, X.; Wang, P. Biomaterials 2006, 27, 1735.
15. Bourges, J. L.; Bloquel, C.; Thomas, A.; Froussart, F.; Bochot, A.; Azan, F.; Gurny, R.; BenEzra, D.; Behar-Cohen, F. Adv Drug Deliv Rev 2006, 58, 1182.
16. Shen, Y.; Sun, W.; Zhu, K. J.; Shen, Z. J Biomed Mater Res A 2000, 50, 528.
17. Albertsson, A.-C.; Varma, I. K. Adv Polym Sci 2002, 157, 1.
18. Altpeter, H.; Bevis, M. J.; Grijpma, D. W.; Feijen, J. J Mater Sci Mater Med 2004, 15, 175.
19. Sprockel, O. L.; Sen, M.; Shivanand, P.; Prapaitrakul, W. Int J Pharm 1997, 155, 191.
20. Carcaboso, A.; Chiappetta, D. A.; Höcht, C.; Blake, M. G.; Boccia, M. M.; Baratti, C. M.; Sosnik, A. Eur J Pharm Biopharm 2008, 70, 666.
21. Blake, M. G.; Boccia, M. M.; Carcaboso, A. M.; Chiappetta, D. A.; Höcht, C.; Krawczyk, M.; Sosnik, A.; Baratti, C. M.; Epilepsy Behav 2010, 17, 157.
22. Carcaboso, A.; Chiappetta, D. A.; Opezzo, A. W.; Höcht, C.; Fandiño, A. C.; Croxatto, J. O.; Rubio, M. C.; Sosnik, A.; Bramuglia, G. F.; Abramson, D. H.; Chantada, G. L. Invest Ophthamol Vis Sci 2010, 51, 2126.
23. González, L.; Chiappetta, D. A.; Turyn, D.; Sosnik, A. BIOOMAT 2009, First Workshop on Artificial Organs, Biomaterials and Tissue Engineering, Latin American Society of Biomaterials, Artificial Organs and Tissue Engineering (SLABO), Rosario, Argentina, August 2009.
24. Liao, L. Q.; Liu, L. J.; Zhang, C.; He, F.; Zhuo, R. X.; Wan, K. J Polym Sci Part A: Polym Chem 2002, 40, 1749.
25. Barbier-Baudry, D.; Brachais, C.-H.; Cretu, A.; Loupy, A.; Stuerga, D. Macromol Rapid Commun 2002, 23, 200.
26. Song, Y.; Liu, L. J.; Zhuo, R. X. J Biomater Sci Polym Edn 2003, 14, 241.
27. Fang, X.; Simone, C. C.; Vaccaro, E.; Huang, S. J.; Scola, D. A. J Polym Sci Part A: Polym Chem 2002, 40, 2264.
28. Moretton, M. A.; Glisoni, R.; Chiappetta, D. A.; Sosnik, A. Colloids Surf B: Biointerfaces 2010, 79, 467.
29. Antonio, C.; Deam, R. T. J Mater Process Tech 2005, 169, 234.
30. Schwach, G.; Vert, M. Int J Biol Macromol 1999, 25, 283.
31. Crescenzi, V.; Manzini, G.; Calzolari, G.; Borri, C. Eur Polym Mater 1972, 8, 449.
32. Cohn, D.; Stern, T.; Gonzalez, M. F.; Epstein J. J Biomed Mater Res 2002, 59, 273.
33. Abraham, G. A.; Marcos-Fernández, A.; San Román, J. J Biomed Mater Res A 2006, 76, 729.
34. Marcos-Fernández, A.; Abraham, G. A.; Valentín, J. L.; San Román, J. Polymer 2006, 47, 785.
35. Caracciolo, P. C.; Buffa, F.; Abraham, G. A. J Mater Sci Mater Med 2009, 20, 145.
36. Yu, Z. J; Liu, L. J Eur Polym Mater 2004, 40, 2213.
37. Liu, L. J.; Zhang, C.; Liao, L. Q.; Wang, X. L.; Zhuo, R. X. Chin Chem Lett 2001, 12, 663.
38. Zhang, C.; Liao, L.; Gong, S. Macromol Rapid Commun 2007, 28, 422.
39. Liao, L.; Zhang, C.; Gong, S. Eur Polym Mater 2007, 43, 4289.
40. Liao, L.; Zhang, C.; Gong, S. React Func Polym 2008, 68, 751.
41. Storey, R. F.; Taylor, A. E. JMC Pure Appl Chem A 1998, 35, 723.
42. Cohn, D.; Lando, G.; Sosnik, A.; Garty, S.; Levi, A. Biomaterials 2006, 27, 1718.
43. Mésangeau, C.; Yous, S.; Pérès, B.; Lesieur, D.; Besson, T. Tetrahedron Lett 2005, 46, 2465.
44. Alterman, M.; Hallberg, A. J Org Chem 2000, 65, 7984.
45. Osborn, K. R.; Jenkins, W. A. Plastic Films: Technology and Packaging Applications; Institute of Packaging Professionals/ CRC Press Ltd: Boca Raton, FL, 1992, p 226.
46. Sheikh Hasan, A.; Socha, M.; Lamprecht, A.; El Ghazouani, F.; Sapin, A.; Hoffman, M.; Maincent, P.; Ubrich, N. Int J Pharm 2007, 344, 53.
47. Zoppe, J O.; Peresin, M. S.; Habibi, Y.; Venditti, R. A.; Rojas, O. J ACS Appl Mater Interfaces 2009, 1, 1996.
48. Srivastava, R. K.; Albertsson, A.-C. Biomacromolecules 2006, 7, 2531.