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Crystallization and melting behavior of poly(ε-caprolactone-co-δ-valerolactone) and poly(ε-caprolactone-co-L-lactide) copolymers with novel chain microstructures

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ABSTRACT: Nuclear magnetic resonance spectroscopy (NMR) characterization of the statistical copolymers of this study showed that the poly(ε-caprolactone-co-L-lactide)s, with ε-caprolactone (ε-CL) molar contents ranging from 70 to 94% and ε-CL average sequence length (l_{CL}) between 2.20–9.52, and the poly(ε-caprolactone-co-δ-valerolactone)s, with 60 to 85% of ε-CL and l_{CL} between 2.65–6.08, present semi-alternating ($R \rightarrow 2$) and random ($R \sim 1$) distribution of sequences, respectively. These syntheses were carried out with the aim of reducing the crystallinity of poly(ε-caprolactone) (PCL), needed to provide mechanical strength to the material but also responsible for its slow degradation rate. However, this was not achieved in the case of the ε-caprolactone-co-δ-valerolactone (ε-CL-co-δ-VAL). Non-isothermal cooling treatments at different rates and isothermal crystallizations (at 5, 10, 21 and 37°C) were conducted by differential scanning calorimetry (DSC), and demonstrated that ε-CL copolymers containing δ-valerolactone (δ-VAL) exhibited a larger crystallization capability than those of L-lactide (L-LA) and also arranged into crystalline structures over shorter times. The crystallization enthalpies of the ε-CL-co-δ-VAL copolymers during the cooling treatments and their heat of fusion (ΔH_m) at the different isothermal temperatures were very large (i.e. $\Delta H_c > 53$ Jg^{-1}) and in some cases, unrelated to the copolymer composition. In some compositions, such as the 60 : 40, Wide Angle X-ray Scattering (WAXS) proved that that these two lactones undergo isomorphism and co-crystallize in a single cell. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42534.

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INTRODUCTION

Lactones and macrolactones are used in the chemical industry as flavors and fragrances but are also being employed in the manufacture of highly specialized biopolymers. Cyclic esters larger than five-membered rings lead to homopolymers that show a similar mechanical behavior, with good ductility and strength which resemble the properties of low density polyethylene (LDPE). δ-valerolactone,[1–4] ε-caprolactone,[5,6] ethylene brassylate,[7] ω-pentadecalactone[8–11] or hexadecalactone,[12] containing four, five, 13, 14 or 15 straight methylenes, respectively, together with an ester group (two in the case of ethylene brassylate), allow the formation of flexible semi-crystalline polymers with low melting points (<100°C) and glass transition temperatures (T_g, <–27°C) that make them easy to manipulate with thermoplastic processing techniques. Nevertheless, these polylactones degrade at a very slow rate under hydrolytic conditions, over several years, which restricts their potential applications in the biomedical field.

Poly(ε-caprolactone) (PCL) was one of the earliest polymers synthesized by the Carothers' group in the early 1930s[13] and was used extensively in the biomaterials field during the resorbable-polymer-boom of the 1970s and 1980s. Nowadays, it is still popular due to its outstanding rheological and viscoelastic properties[6] and is employed in medical devices and for tissue engineering, including among others, sutures for wound dressings, artificial blood vessels, nerve regeneration, drug-delivery devices and bone engineering applications.[14] PCL is a semi-crystalline polymer having a glass transition (T_g) at (−60)–(−65)°C and a melting point between 56 and 65°C;[5] the crystalline nature of PCL makes it easily formable at relatively low temperatures. Likewise, this polyester presents exceptional blend-compatibility, efficient processing with thermoplastic

techniques, high thermal stability[15–17] and very attractive mechanical properties, with high elongation at break values (750–1000%) and Young's Modulus from 210 to 440 MPa.[18] However, among its disadvantages are its resistance to hydrolytic degradation. PCL homopolymer biodegrades slowly and shows complete degradation after 2–4 years depending on the initial molecular weight of the device or implant.[19–22] In the hydrolytic degradation of polyesters, amorphous regions are preferentially degraded over the crystalline lamellae.[23–25] Therefore, the rate of biodegradation is highly influenced by the crystallization capability and the degree of crystallinity,[26] reaching 69% in the case of PCL.[27]

In this study, the copolymerization of ε-caprolactone with L-lactide[28,29] or δ-valerolactone[30–33] units was the strategy used to reduce the crystallinity and so improve the biodegradability of the PCL homopolymer. For this purpose, several poly(ε-caprolactone-co-L-lactide) and poly(ε-caprolactone-co-δ-valerolactone) copolymers were synthesized using triphenyl bismuth (Ph_3Bi), a catalyst that is known to favor random sequences.[34] Above their glass transition, the crystalline phase is the responsible of the mechanical properties of these low glass transition temperature's polymers and, therefore, ε-CL rich compositions were used. On the other hand, it should also be taken into consideration that their melting temperatures (T_m) should be above the body temperature (37°C), the one at which they would be employed, in order to ensure their mechanical performance during the application.

The polymers were characterized by proton and carbon nuclear magnetic resonance spectroscopy (^{1}H NMR and ^{13}C NMR) and gel permeation chromatography (GPC) measurements. In this first paper crystallization studies were carried out by means of non-isothermal cooling and isothermal experiments made on a differential scanning calorimetry (DSC) device, while wide angle X-ray diffraction (WAXRD) and Polarized Light Optical Microscopy (PLOM) techniques were also employed to complement the study. In the future, the analysis of these biomaterials will be completed after conducting mechanical characterization and in vitro hydrolytic degradation studies on the copolymers with high melting temperatures (T_m).

MATERIALS AND METHODS

Materials

ε-caprolactone monomer (assay >98%) was provided by Merck. L-lactide monomer (assay > 99.5%) was supplied by Purac Biochem (The Netherlands) while δ-valerolactone monomer (assay >98%) was provided by Tokyo Chemical Industry (Cymit Quimica). The triphenyl bismuth (Ph_3Bi) catalyst was obtained from Gelest. 1-hexanol was supplied by Sigma Aldrich.

Synthesis Procedure

Statistical copolymers from ε-caprolactone, L-lactide and δ-valerolactone were synthesized in bulk by one pot-one-step ring-opening polymerizations (ROP). The synthesis reactions were carried out in a flask immersed in a controlled temperature oil bath. In each polymerization, predetermined amounts of the different comonomers at the chosen mass feed ratio were simultaneously added and melted into the flask. 1-hexanol was also added to provide alcohol (ROH) groups in order to control the molecular weight. The flask was purged for 30 min with a nitrogen stream under the surface of the melt. The catalyst (Ph_3Bi) was then added (at 500 : 1 comonomers/catalyst molar ratio) and the magnetic stirrer maintained at 100 rpm. The ε-caprolactone-co-L-lactide polymerizations were carried out for 48 h at 130°C whereas the synthesis reactions of the ε-caprolactone-co-δ-valerolactone copolymers were conducted for 48 h at 120°C. The ε-caprolactone homopolymer was synthesized at 130°C after 24 h of reaction.

After the corresponding reaction time, the products were dissolved in chloroform and precipitated, pouring the polymer solution into an excess of methanol in order to remove the catalyst impurities and those monomers that had not reacted. Finally the product was dried at room temperature and then subjected to a heat treatment at 140°C for 1 h to ensure the complete elimination of any remaining solvent.

Methods

Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded in a Bruker Avance DPX 300 at 300.16 MHz and at 75.5 MHz of resonance frequency respectively, using 5 mm O.D. sample tubes. All spectra were obtained at room temperature from solutions of 0.7 mL of deuterated chloroform ($CDCl_3$). Experimental conditions were as follows: (a) for ^{1}H NMR: 10 mg of sample; 3 s acquisition time; 1 s delay time; 8.5 μs pulse; spectral width 5000 Hz and 32 scans; (b) for ^{13}C NMR: 40 mg, inverse gated decoupled sequence; 3 s acquisition time; 4 s delay time; 5.5 μs pulse; spectral width 18800 Hz and more than 10000 scans.

The molecular weights of the polymers were determined by GPC using a Waters 1515 GPC device equipped with two Styragel columns (10^2 -10^4 Å). Chloroform was used as eluent at a flow rate of 1 mL min^{-1} and polystyrene standards (Shodex Standards, SM-105) were used to obtain a primary calibration curve.

The crystallization behavior and the thermal properties of the polymers were studied on a DSC 2920 (TA Instruments). Samples of 6–9 mg were melted at 100°C and then quenched to −50°C at different cooling rates (5, 10, and 20°C min^{-1}) to study the crystallization process during the cooling. On the other hand, the isothermal treatments were conducted at 5, 10, 21, and 37°C for 1, 10, 30, 60, 180, 300, 600, and 1440 min. The melting temperature (T_m) and the heat of fusion (ΔH_m) were obtained from the scans completed from the corresponding isothermal temperature to 100°C at 20°C min^{-1}. The values determined from the scans which were made immediately after cooling at 40°C min^{-1} to the isothermal temperature were used as initial time values (time zero). Finally, a scan was also made at 20°C min^{-1} from −85 to 100°C to determine the glass transition temperatures (T_g) of the samples.

Polarized light optical microscopy (PLOM) was used to study the nucleation and growth of spherulites in some of the (co)polymers: the PCL homopolymer and two ε-CL-co-LA and ε-CL-co-δ-VAL copolymers with similar average sequence length of ε-caprolactone unit. The samples were melted at 180°C in an oven and then immediately put under a polarizing microscope

Table I. Characterization Data of the Different Poly(ε-Caprolactone-Co-L-Lactide) Polymeric Materials

SAMPLE	Polymer Composition[a] % molar composition		M_w ($\times 10^3$) g mol^{-1}	D	Microstructural magnitudes[b]			T_g[c] °C
	% ε-CL	% L-LA			l_{CL}	l_{LA}	R	
CL-LA 94	94.3	5.7	143.1	1.70	9.52	0.58	1.84	−57.4
CL-LA 92	91.6	8.4	131.6	1.77	6.65	0.61	1.80	−54.0
CL-LA 88	88.3	11.7	132.6	1.84	4.91	0.65	1.74	−54.6
CL-LA 83	83.3	16.7	172.9	1.92	3.54	0.71	1.69	−48.2
CL-LA 70	70.0	30.0	123.1	1.86	2.20	0.94	1.51	−32.9

[a] Calculated from ^{1}H NMR spectra.
[b] l_{CL} and l_{LA} are the CL and LA number average sequence lengths obtained from ^{1}H NMR. These values are compared to the Bernoullian random number-average sequence lengths (l_{CL}=1/LA and l_{LA}=1/CL), obtaining the randomness character value (R).
[c] Obtained from a DSC scan made at 20°C min^{-1}from −85 to 100°C

(Leica DMLM). The evolution of spherulites was followed during 20 min with images recorded at different times.

Wide angle X-ray diffraction (WAXRD) data were collected on a Bruker D8 Advance diffractometer operating at 30 kV and 20 mA. This device is equipped with a Cu tube (λ=1.5418 Å), a Vantec-1 PSD detector, an Anton Parr HTK2000 high-temperature furnace and an Anton Parr MRI-wide low-temperature chamber. The powder patterns of the high-temperature furnace were recorded in 2θ steps of 0.033° in the 10 $\leq 2\theta \leq$ 38 range, counting for 0.2 s per step, from 30 to 122°C every 2°C using a heating rate of 0.17°C s^{-1}. The powder patterns of the low-temperature chamber were recorded in 2θ steps of 0.033° in the 10 $\leq 2\theta \leq$ 38 range, counting for 0.2 s per step, from 2 to 62°C every 2°C using a heating rate of 0.2°C s^{-1}.

RESULTS AND DISCUSSION

Characterization

Tables I and II summarize the characterization data of the copolymers studied. As can be observed, the initial molecular weights (M_w) of each polymer are large, ranging from 91 to 173 kg mol^{-1} with dispersities (D) between 1.70 and 1.92. For proper evaluation of the behavior of the ε-caprolactone based copolymers, a polycaprolactone (PCL) homopolymer was also synthesized. This material has a M_w of 135 kg mol^{-1} with a dispersity of 1.74, and a glass transition temperature (T_g) at −60.4°C.

Poly(ε-caprolactone-co-L-lactide) Copolymers. The characterization data of the poly(ε-caprolactone-co-L-lactide) copolymers are gathered in Table I. This set of copolymers show glass transition temperatures (T_gs) that range from −57 to −33°C, in ascending order as the ε-CL content decreases. Their lactide molar content ranges from ∼ 6% (CL-LA 94) to 30% (CL-LA 70) with average sequence lengths of ε-CL (l_{CL}) from 9.52 to 2.20, and possess a semi-alternating distribution of sequences. The randomness character (R) value in all cases is higher than 1.50 and tends toward 2 as the ε-CL content increases.

The ε-caprolactone and L-lactide molar content and the microstructural magnitudes of the copolymers were obtained from the average dyad relative molar fractions. The lactide methine signals, centered at 5.15 ppm, and those of the α and ε methylenes of the ε-caprolactone, around 2.35 and 4.10 ppm, seen in the ^{1}H NMR spectrum (see Figure 1) were assigned to the different dyads.[28] Then, eqs. (1)–(3)[35] were employed to obtain the number-average sequence lengths (l_i), the Bernoullian random number-average sequence lengths (l_i) and the randomness character (R):

$$l_{LA}=\frac{(\text{LA-LA})+\frac{1}{2}(\text{LA-CL})}{\frac{1}{2}(\text{LA-CL})}=\frac{2(\text{LA})}{(\text{LA-CL})};\qquad l_{CL}=\frac{(\text{CL-CL})+\frac{1}{2}(\text{LA-CL})}{\frac{1}{2}(\text{LA-CL})}=\frac{2(\text{CL})}{(\text{LA-CL})} \tag{1}$$

$$(l_{CL})_{random}=\frac{1}{(\text{LA})};\quad (l_{LA})_{random}=\frac{1}{(\text{CL})} \tag{2}$$

$$R=\frac{(l_{CL})_{random}}{l_{CL}}=\frac{(l_{LA})_{random}}{l_{LA}} \tag{3}$$

where (CL) and (LA) are the ε-caprolactone and L-lactide molar fractions and (CL-LA) is the CL-LA average dyad relative molar fraction.

To confirm the semi-alternating character ($R\rightarrow 2$) of this group of copolymers, the ^{13}C NMR spectrum was recorded for CL-LA 88, a copolymer showing an R value of 1.74 in the proton nuclear magnetic resonance (^{1}H NMR). The region of β and γ methylene carbon atoms, located between 24–26 ppm,[29,36,37] was employed for obtaining the randomness character from eq. (4).

$$R=\frac{(l_{CL})_{random}}{l_{CL}}\ \text{where}\ l_{CL}=\frac{I_{\text{CL-CL-CL}}+I_{\text{LA-CL-CL}}}{I_{\text{CL-CL-LA}}+I_{\text{LA-CL-LA}}}+1 \tag{4}$$

Figure 2 shows the ^{13}C NMR spectrum of CL-LA 88 with the region of β and γ-methylene carbon atoms enlarged. CL-CL-CL, LA-CL-CL, CL-CL-LA, and LA-CL-LA triads can be assigned from left to right in both methylene signals.[37] It can be observed that the CL-CL-CL triad signals are significantly more intense than in the rest of the triads. However, for a random ($R\sim 1$) or blocky ($R\rightarrow 0$) distribution of sequences, the peaks corresponding to the other triads should be lower, primarily in

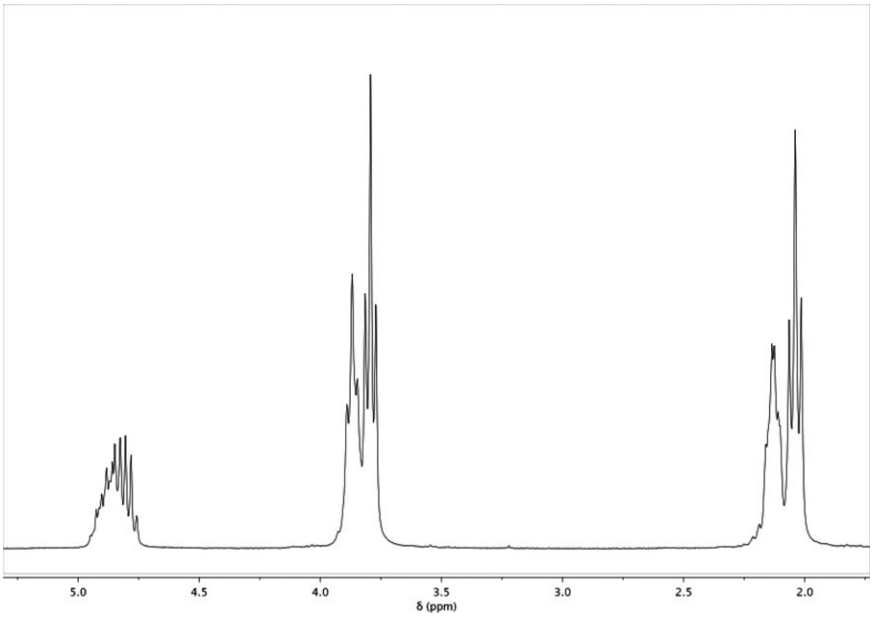

Figure 1. ^{1}H NMR spectrum of CL-LA 70.

the case of the LA-CL-LA signal, a peak which is distinguishable in the β carbon atom signal at 25.2 ppm. The calculated value of R for this copolymer was 1.85, proving again the semi-alternating chain microstructure of these poly(ε-caprolactone-co-L-lactide) polymeric materials synthesized with Ph_3Bi.

Poly(ε-caprolactone-co-δ-valerolactone) Copolymers. In the case of the poly(ε-caprolactone-co-δ-valerolactone) copolymers, the resonances for the protons of either repeat unit overlap sufficiently to prevent accurate integration of the peak areas.[31,38,39] For this reason, the molar composition and the microstructural parameters were calculated through the integration of the ^{13}C NMR spectra.

Figure 3 shows the ^{13}C NMR spectrum of CL-VAL 70, a poly(ε-caprolactone-co-δ-valerolactone) copolymer with a ε-CL molar content of 70%. The signals appearing between 21 and 174 ppm of chemical shift (δ) can be assigned to the different carbons of the repeat units as follows. The signals centered at 173.5 ppm belong to the carbonyl carbon of the ε-CL and δ-VAL units, the peaks at 64.0, 34.0, and 28.3 ppm are respectively assigned to ε-, α-, and δ-methylenes and the region 20–26 ppm contain the remaining methylene carbons. The peaks at 25.5 ppm and 24.6 correspond to the β- and γ-methylenes of the ε-CL repeat unit (δ-VAL unit does not have γ-CH_2 in its structure, see Figure 4) whereas the β-methylene of the δ-Val repeat unit give a signal at 21.4 ppm of chemical shift. The molar composition of the

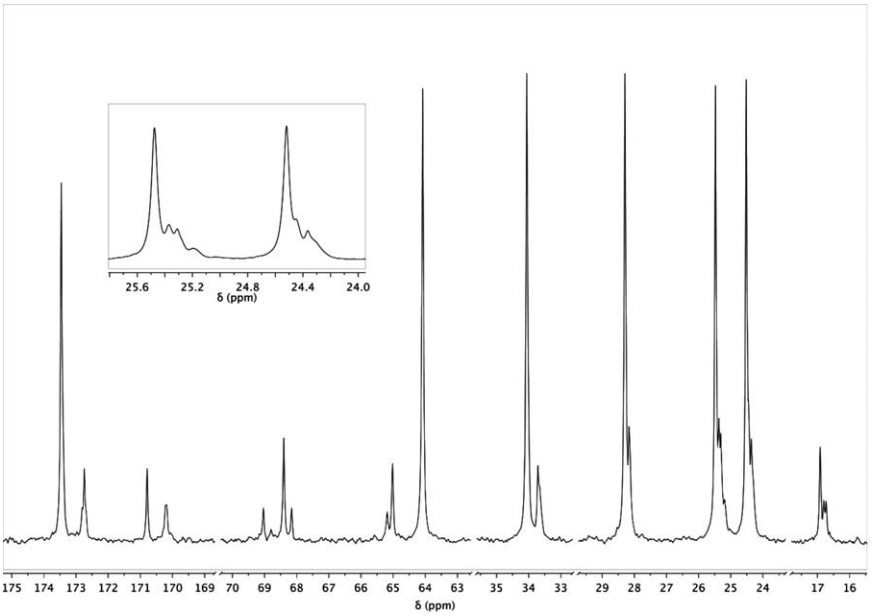

Figure 2. ^{13}C NMR spectrum of CL-LA 88; region of β and γ-methylene carbon atoms is enlarged.

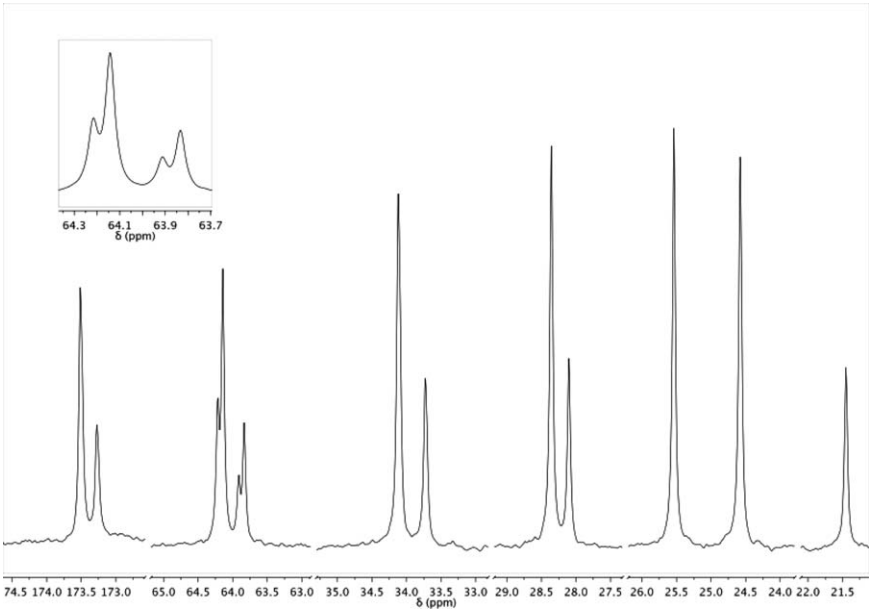

Figure 3. ^{13}C NMR spectrum of CL-VAL 70; region of ε-methylene carbon atoms is enlarged.

copolymers can be easily determined by comparing the area under the peak due to the β-carbon in the δ-VAL unit to either the area of the β-CH_2 or the γ-CH_2 of the ε-CL. The area calculated from the β-carbon of the ε-CL was reported by Storey *et al.*[31] to always be larger than that of the γ-carbon because of an added contribution from the initiator fragment. So, in this paper the calculus was made based on the ratio of the integrated areas of the γ-methylene group from the ε-CL to that of the β-CH_2 of the δ-VAL repeat unit.

In Figure 3, the ε-CH_2 region at 63.5 to 64.5 ppm is also expanded. As can be seen these signals present dyad sensitivity. Hence, the peaks at 64.22, 64.14, 63.91, and 63.83 ppm can be assigned to CL-VL, CL-CL, VL-VL, and VL-CL dyads, respectively, and the average dyad relative molar fractions calculated. This allowed the number-average sequence lengths (l_i), the Bernoullian random number-average sequence lengths (l_i), and the randomness character (R) to be obtained, using the eqs. (5–7).

$$l_{CL}=\frac{(\text{CL-CL})+\frac{1}{2}(\text{CL-VL})}{\frac{1}{2}(\text{CL-VL})}=\frac{2(\text{CL})}{(\text{CL-VL})};\qquad l_{VL}=\frac{(\text{VL-VL})+\frac{1}{2}(\text{CL-VL})}{\frac{1}{2}(\text{CL-VL})}=\frac{2(\text{VL})}{(\text{CL-VL})} \tag{5}$$

$$(l_{CL})_{random}=\frac{1}{(\text{VL})};\quad \left((l_{VL})_{random}=\frac{1}{(\text{CL})}\right) \tag{6}$$

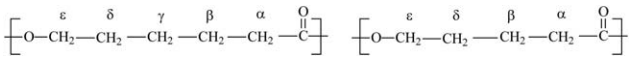

Figure 4. Scheme of the units of ε-caprolactone (left) and δ-valerolactone (right).

$$R=\frac{(l_{CL})_{random}}{l_{CL}}=\frac{(l_{VL})_{random}}{l_{VL}} \tag{7}$$

Table II summarizes the data obtained from the ^{13}C NMR, molecular weights and glass transition temperatures of the different poly(ε-caprolactone-co-δ-valerolactone) copolymers synthesized. These copolymers present ε-CL molar contents ranging from 85.3 to 60.0% (l_{CL} from 6.08 to 2.65) and show a random distribution of sequences ($R\sim1$). Owing to the similarities between the glass transition temperatures of both homopolymers (at −65°C for PCL and at −57°C for PVL[40]), the T_g values of this series of copolymers are almost equal, around −64°C.

Crystallization Studies

Non-Isothermal Crystallization During the Cooling. Several DSC cooling treatments from 100 to −50°C at rates of 5, 10, and 20°C min^{-1} were conducted successively on the polymer samples. As an illustration, Figure 5 shows the different scans of CL-LA 92.

The crystallization temperature (T_c) and the enthalpy of crystallization (ΔH_c) of each material were obtained from these scans and gathered in Table III. As can be observed not all the polymers were able to crystallize during the cooling treatments. CL-LA 83 and CL-LA 70 copolymers, with average sequence lengths of ε-CL (l_{CL}) of 3.54 and 2.20, did not exhibit a crystallization peak at any cooling rate despite the fact that, as will be seen below, crystalline domains were formed during isothermal studies. Conversely, the ε-CL sequences of the rest of poly(ε-caprolactone-co-L-lactide), within the length range of 4.91 to 9.52, were large enough to crystallize during the cooling process. Likewise, the four poly(ε-caprolactone-co-δ-valerolactone) copolymers, with l_{CL} ranging from 2.65 to 6.08, arranged into crystalline structures presenting high enthalpy of crystallization values ($\Delta H > 53$ J g^{-1} in all cases) with slight differences between them.

Table II. Characterization Data of the Different Poly(ε-Caprolactone-Co-δ-Valerolactone) Polymeric Materials

SAMPLE	Polymer Composition[a] % molar composition		M_w ($\times 10^3$) g mol^{-1}	D	Microstructural magnitudes[b]			T_g[c] °C
	% ε-CL	% δ-VL			L_{CL}	L_{VL}	R	
CL-VAL 85	85.3	14.7	90.9	1.75	6.08	1.05	1.12	−64.3
CL-VAL 76	76.1	23.9	109.7	1.76	3.94	1.24	1.06	−63.7
CL-VAL 70	70.2	29.8	94.2	1.75	3.30	1.40	1.01	−63.6
CL-VAL 60	60.0	40.0	123.6	1.77	2.65	1.77	0.94	−65.3

[a] Calculated from ^{13}C NMR spectra.
[b] l_{CL} and l_{VL} are the CL and VL number average sequence lengths obtained from ^{13}C NMR. These values are compared to the Bernoullian random number-average sequence lengths (l_{CL}=1/VL and l_{VL}=1/CL), obtaining the randomness character value (R).
[c] Obtained from a DSC scan made at 20°C min^{-1}from −85 to 100°C

As expected, a decrease in the cooling rate meant that the crystallites appeared at a higher temperature, presenting a narrower crystallization peak. At lower cooling rates, there is more time for the crystal nucleus to develop, leading to higher crystallization temperatures.[41] The differences between the respective enthalpies from the same copolymer were small, although it was noted that at 5°C min^{-1} (the slowest cooling rate) the ΔH associated to the crystallization peak was larger than those corresponding to the other cooling treatments. As an illustration, at a rate of 20°C min^{-1} the ΔH_cs of PCL homopolymer, CL-LA 92, and CL-VAL 85 were 65.4, 41.1, and 57.8 J g^{-1}, respectively, while at a rate of 5°C min^{-1} they presented slightly higher values of 68.6, 49.6, and 59.8 J g^{-1}. On the other hand, it was also observed that the changes in the crystallization temperatures were more important in the ε-CL-co-LA copolymers than in the δ-VAL based ones. For example, the T_cs at a cooling rate of 20°C min^{-1} for CL-LA 92 and CL-VAL 85 (both copolymers have an l_{CL} in the range of 6.0 to 6.7) were −1.6 and 9.8°C, respectively, whereas at 5°C min^{-1} their T_cs were 8.6 and 12.9°C.

Another aspect to take into account is that the CL-co-LA copolymers show a lower crystallization capability than the CL-co-VAL, regardless of their l_{CL} (a parameter that depends on both the composition and the randomness character). This fact can be explained by the higher T_g values of those materials containing lactide (supramolecular arrangements occur quickly if the polymer presents lower glass transition temperature, perhaps because the small rigid chains of L-lactide disrupt the crystal structure of the ε-CL domains or it could even be due to an isomorphism phenomenon between the ε-CL and δ-VAL crystal lattice. Therefore, it is worth mentioning the fact that the enthalpies associated with the crystallization of some of the poly(ε-caprolactone-co-δ-valerolactone) copolymers, such as CL-VAL 60, were surprisingly very large and unrelated to the copolymer composition. In depth analysis of these findings is discussed in the following sections.

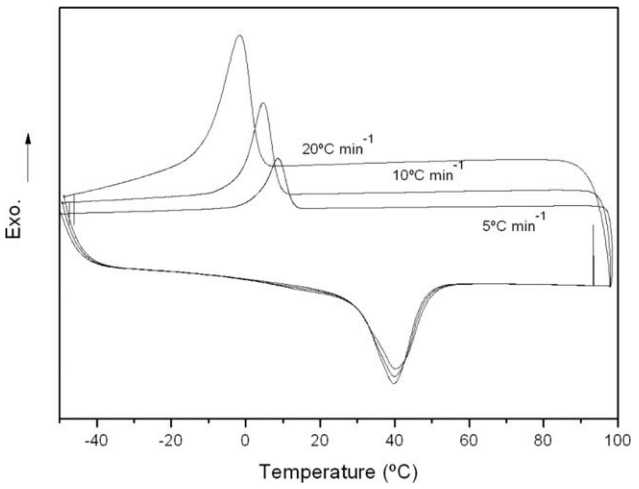

Figure 5. Crystallization process during the cooling at different cooling rates (5, 10, and 20°C min^{-1}) of CL-LA 92.

Crystallization During Isothermal Treatments. Isothermal treatments were carried out at 5, 10, 21, and 37°C for 1, 10, 30, and 60 min and 3, 5, 10, and 24 h. These temperatures were selected because the biomaterials are usually stored or used at this range of temperatures. The melting temperature (T_m) and the heat of fusion (ΔH_m) with respect to the time were obtained from the DSC scans, made from the selected isothermal temperature to 100°C.

Some of the polymers (PCL, CL-LA 94, CL-LA 92, CL-VAL 85, CL-VAL 76, and CL-VAL 70) were able to crystallize during the cooling process at 40°C min^{-1} to the isothermal temperature. Those which presented a crystallization temperature above −2°C at a cooling rate of 20°C min^{-1}, exhibited a melting peak during the scan made after the cooling to 5°C despite the fact that at higher cooling rates the crystallization temperatures are lower. From now on, the enthalpies obtained immediately after this cooling process, summarized in Table IV, will be used as initial time values of heat of fusion (time zero) in the isothermal study.

Table V summarizes the melting temperatures (T_m) of the polymers studied, which were determined at the different isothermal temperatures. As the isothermal temperature decreased, it was found that the T_m also dropped towards lower values. The growth of the crystal nucleus was less pronounced and the crystallites formed were thinner and less perfect. As can be seen, only PCL, CL-LA 94, CL-LA 92, and CL-VAL 85 were capable to form a crystalline phase at 37°C. The rest of copolymers presented T_m values around this temperature or even at lower

Table III. Characterization Data Obtained from the Cooling Treatments on the Different Poly(ε-Caprolactone-Co-L-Lactide) and Poly(ε-Caprolactone-Co-δ-Valerolactone) Copolymers

	Cooling rate at 5°C min^{-1}		Cooling rate at 10°C min^{-1}		Cooling rate at 20°C min^{-1}	
SAMPLE	ΔH (J g^{-1})	T_c (°C)	ΔH (J g^{-1})	T_c (°C)	ΔH (J g^{-1})	T_c (°C)
PCL	68.6	32.8	65.7	30.8	65.4	28.2
CL-LA 94	49.6	23.0	47.9	19.5	47.2	14.8
CL-LA 92	42.8	8.6	41.4	4.7	41.1	−1.6
CL-LA 88	34.0	−7.9	30.9	−16.2	16.4	−25.7
CL-LA 83	-	-	-	-	-	-
CL-LA 70	-	-	-	-	-	-
CL-VAL 85	59.8	12.9	58.2	11.6	57.8	9.6
CL-VAL 76	59.4	8.9	58.3	7.5	57.7	4.8
CL-VAL 70	56.7	8.5	55.0	6.3	54.0	3.0
CL-VAL 60	55.4	1.4	53.7	−1.0	53.0	−4-3

values, which will restrict its potential application in the biomedical field.

Poly(ε-caprolactone) Homopolymer. Figure 6 shows the evolution of the melting enthalpy of the poly(ε-caprolactone) homopolymer at the four isothermal temperatures. The highest values of heat of fusion (ΔH_m) were achieved at 37°C (84.3 J g^{-1} after 24 h), with a melting peak appearing at ~63°C. Using Crescenzi's[42] value of 139.5 J g^{-1} for the heat of fusion (ΔH_m) for 100% crystalline material (ΔH_m^0), the calculated crystalline fraction was 60.4%, which is in agreement with the PCL values found in literature.[27] The T_m moved towards lower values as the isothermal temperature decreased, just as in the case of the rest of copolymers in this study (see Table V). Hence, following the isothermal experiment conducted at 5°C, the T_m was located at around 58°C (5 degrees less than at 37°C) and after 24 h at this temperature the ΔH reached a final value of 77.9 J g^{-1} with an associated crystallinity of 55.8%.

Table IV. Melting Enthalpies of the Polymers Studied after Cooling at 40°C min^{-1} to the Isothermal Temperature

	ΔH_m (J g^{-1}) after cooling at 40°C min^{-1} to Isothermal Temperature[a]			
SAMPLE	T_C=5°C	T_C=10°C	T_C=21°C	T_C=37°C
PCL	66.2	64.3	55.1	-
CL-LA 94	45.5	47.0	10.0	-
CL-LA 92	30.4	1.6	-	-
CL-LA 88	-	-	-	-
CL-LA 83	-	-	-	-
CL-LA 70	-	-	-	-
CL-VAL 85	61.9	56.8	-	-
CL-VAL 76	52.7	-	-	-
CL-VAL 70	40.3	-	-	-
CL-VAL 60	-	-	-	-

[a] Obtained from a DSC scan made at 20°C min^{-1} from the isothermal crystallization temperature up to 100°C immediately after cooling at 40°C min^{-1}.

At a lower isothermal temperature that is further from the melting point of the ε-CL crystallites, the undercooling is larger and the changes in the polymer structure also occurred much more quickly owing to the more efficient nucleating abilities under those conditions. However, in the case of PCL, noteworthy differences were only observed at the initial state (time zero) and after the isothermal treatment of 1 min, that is at very short times. PCL homopolymer crystallizes very fast and at 5, 10 or 21°C the heat of fusion (ΔH_m) after "1 min" was in the range of 68 to 70 J g^{-1} while in all cases the DSC thermograms made immediately after cooling to the isothermal temperature presented a large melting peak, over 55 J g^{-1}. On the other hand the sample cooled to 37°C at 40°C min^{-1} was not capable of crystallizing during the cooling process while a melting peak of 41 J g^{-1} was found after 1 min at this temperature.

Poly(ε-caprolactone-co-L-lactide) Copolymers. The same isothermal treatments at 5, 10, 21, and 37°C were carried out for the poly(ε-caprolactone-co-L-lactide) samples. The evolution of ΔH_m against time is plotted in Figure 7. As was expected, at a larger average sequence length of ε-CL (l_{CL}) the crystallization capability of the copolymers was greater. CL-LA 94 (l_{CL}=9.52) was the copolymer that exhibited the highest value of melting enthalpy (62.1 J g^{-1} after 24 h at 21°C with a T_m at 48°C). This ΔH_m value was several J g^{-1} below than that of the PCL following the same treatment (81.9 J g^{-1} with a T_m at 59°C), proving that a 6% L-lactide content was enough to significantly alter the thermal properties of the homopolymer. On the other hand, and in general, the crystallization process of these polymeric materials was more important and progressed faster at the lowest isothermal temperature of the study (5°C), at which crystal nucleation was favored. CL-LA 83 (l_{CL}=3.54), despite not being capable of crystallizing during the cooling studies outlined in the previous section, arranged into crystalline structures under isothermal conditions at 5 and 10°C. A melting peak, at around 25°C, was found after 3 h at 5°C and after 5 h at 10°C, and reached a final value of ΔH_m of 25.5 and 17.5 J g^{-1}, respectively. On the contrary, CL-LA 70 (l_{CL}=2.20) did not exhibit a crystalline phase after any of the isothermal conditions employed in this study.

Table V. Melting Temperatures of the Polymers Studied with Respect to the Isothermal Temperature

	T_m (°C) with respect to Isothermal Temperature[a]			
SAMPLE	T_C=5°C	T_C=10°C	T_C=21°C	T_C=37°C
PCL	57.8	59.4	59.0	63.2
CL-LA 94	45.8	45.9	47.5	54.3
CL-LA 92	39.2	40.1	42.9	50.3
CL-LA 88	32.2	33.5	38.7	-
CL-LA 83	24.7	25.8	-	-
CL-LA 70	-	-	-	-
CL-VAL 85	43.6	44.0	46.8	51.1
CL-VAL 76	33.6	35.9	39.5	-
CL-VAL 70	30.9	33.3	35.5	-
CL-VAL 60	26.9	28.1	-	-

[a] Obtained from a DSC scan made at 20°C min^{-1} from the isothermal crystallization temperature up to 100°C. The values given correspond to the isothermal treatments during 24 h.

The behavior of CL-LA 94, CL-LA 92, and CL-LA 88 was quite similar at 5, 10 or 21°C: ΔH_m was almost stabilized after the first hour of the experiment and the differences between their ΔH_m values with respect to the isothermal temperature were not very large. As viewed above, higher T_m values were achieved at the highest isothermal temperatures for each of the polymers (see Table V). Figure 8 shows the evolution of the DSC thermograms of CL-LA 92 after the different isothermal treatments at 5, 10, 21, and 37°C. As can be seen, this copolymer has its T_m between 39–50°C and the final melting peak values ΔH_m, with the exception of that from the isothermal treatment at 37°C, are between 51.6 and 57.7 J g^{-1} (of these the highest value corresponds to the isotherm at 5°C). At 37°C a small melting peak does not appear until at least 10 h have passed and after 24 h at this temperature, the associated ΔH_m was only 1.9 J g^{-1}. This copolymer, with an l_{CL} of 6.65, along with CL-LA 94, was the only one that crystallized at 37°C and also had a melting peak at time zero (immediately after cooling) in the experiments at 5 or 10°C. With regard to CL-LA 94 at 37°C, it is worth mentioning that it started to crystallize after 30 min and from hour 3 to hour 24 the melting peak was almost stable and did not undergo virtually any change (ΔH_m rose from 48.4 to 53.7 J g^{-1}).

Poly(ε-caprolactone-co-δ-valerolactone) Copolymers. Figure 9 shows the evolution of the melting enthalpies of the poly(ε-caprolactone-co-δ-valerolactone) copolymers obtained at isothermal temperatures of 5, 10, 21, and 37°C. At the latter temperature the only copolymer that presented a melting peak during the experiment was that containing an 85% molar content of ε-CL, CL-VAL 85. Its T_m was centered at 51°C, which is well above the isothermal temperature (37°C), and its ΔH_m was 21.5 J g^{-1} after 24 h of treatment. This value was considerably lower than those measured after 24 h at 5, 10 or 21°C (ΔH_m was 80.5, 74.8, and 72.5 J g^{-1}, respectively). The melting of the crystal phase usually occurs over a wide range of temperatures. Therefore, at 37°C it is possible that imperfect crystallites of low T_m may not be able to form, reducing the crystallization capability of the polymer or it is possible that the time required at these conditions for the activation of the nuclei was too short (more than 24 h would be needed).

In the case of the copolymers with lower ε-CL contents, those ranging from 60 to 76%, no crystalline peaks were found at the DSC during the 24 h at 37°C. However, at an isothermal temperature of 21°C, CL-VAL 76 showed a melting peak with a final ΔH_m value of 39.6 J g^{-1} (T_m=39.5°C), whereas CL-VAL 70 had a ΔH_m of 13.8 J g^{-1} (T_m=35.5°C). On the other hand CL-VAL 60 did not crystallize at all. Referring to CL-VAL 76, its ΔH_m was practically constant from the third hour of the experiment proving that the growth of the melting peak is limited by the fraction of crystals that have a melting temperature (T_m) higher than 21°C. With respect to CL-VAL 70, the crystallization process began after 5 h and after 24 h the ΔH_m values did not attain stability yet. The nucleation occurred at a slow rate. Therefore, for this poly(ε-caprolactone-co-δ-valerolactone) copolymer, the enthalpy associated with its melting peak might be larger if the treatment had been extended for more than 24 h.

At 5 and 10°C, the four ε-CL-co-δ-VAL studied had high values of ΔH_m after 24 h, ranging from 69.8 to 80.5 J g^{-1} at 5°C and from 68.0 to 74.8 J g^{-1} at 10°C. Those copolymers with a lower average sequence length of ε-CL, such as CL-VAL 60, took longer to develop a crystalline phase and had a slightly lower final ΔH_m. However, contrary to what was expected, the differences in the ΔH_m between CL-VAL 85 (l_{CL}=6.08), CL-VAL 76 (l_{CL}=3.94), CL-VAL 70 (l_{CL}=3.30), and CL-VAL 60 (l_{CL}=2.65) were not really noteworthy despite their different copolymer composition. The melting enthalpy was in some cases very large and did not change gradually with composition. This suggests that ε-CL and δ-VAL units co-crystallize, giving rise to a conspicuous crystal phase.[43]

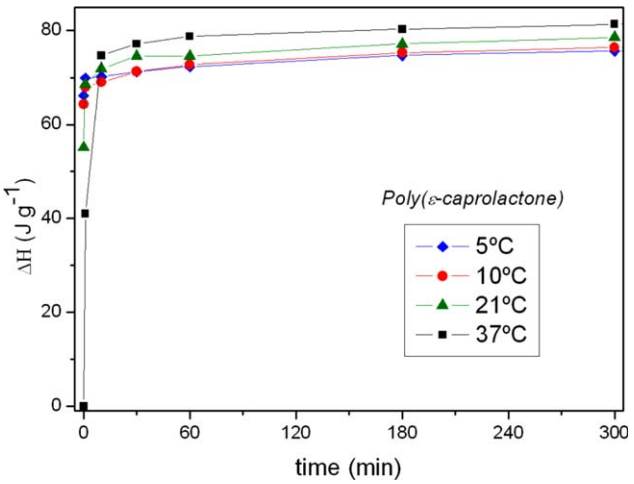

Figure 6. Melting enthalpies obtained from the isothermal treatments on poly(ε-caprolactone) at 5°C (–◆–), 10°C (–●–), 21°C (–▲–), and 37°C (–■–). The values obtained after 10 and 24 h at those temperatures are not shown. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

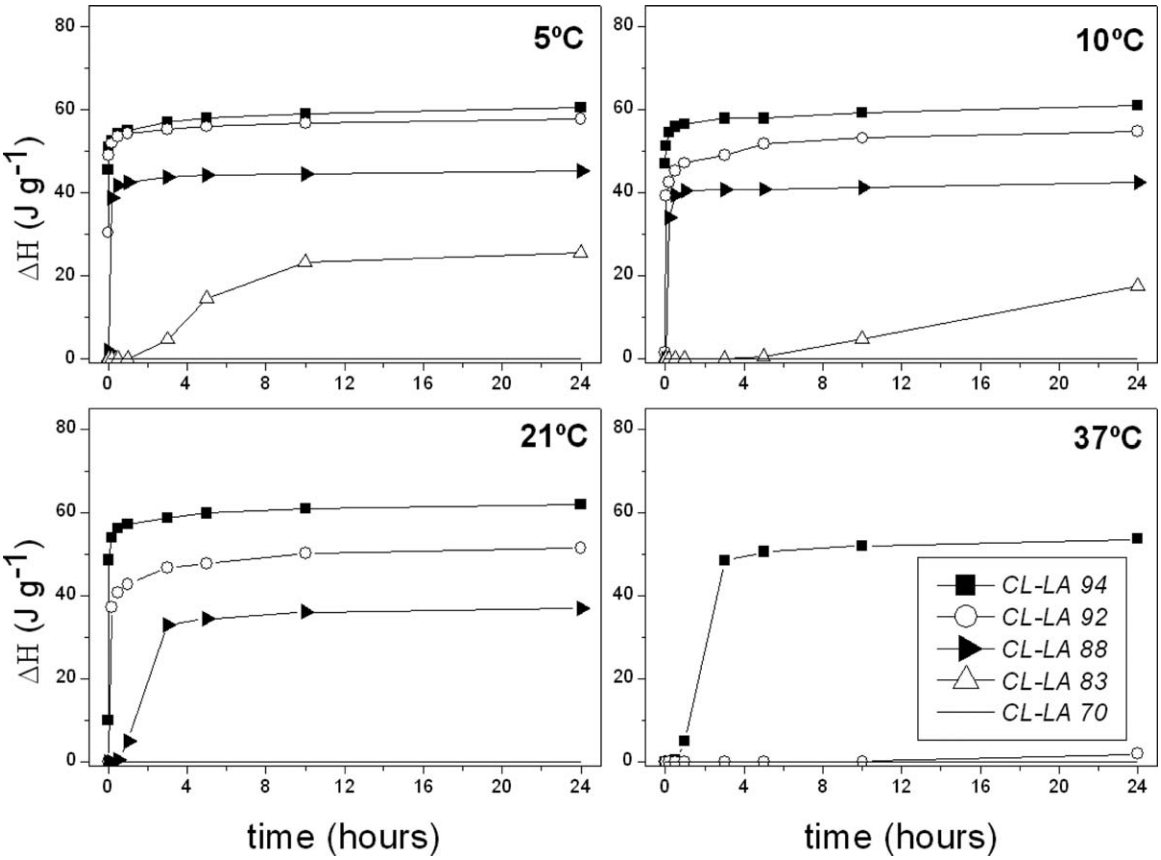

Figure 7. Melting enthalpies of the poly(ε-caprolactone-co-L-lactide) copolymers obtained after different isothermal treatments. CL-LA 94 (–■–), CL-LA 92 (–○–), CL-LA 88 (–▶–), CL-LA 83 (–Δ–), and CL-LA 70 (—).

Wide Angle X-ray Scattering (WAXS). WAXS was employed to study those poly(ε-caprolactone-co-δ-valerolactone) copolymers that exhibited an uncommon crystallization behavior in the DSC. The WAXS profiles of the poly(ε-caprolactone-co-l-lactide) will be similar to those of the PCL and it was not considered necessary their discussion.

Figure 10, three-dimensional, shows the diffraction profiles of CL-VAL 85 and CL-VAL 60, in the range of diffraction angles 2θ between 10 and 38°, in which the "z" axis represents the number of scans. These scans were made every 2°C from 30 to 122°C in the case of CL-VAL 85 and from 2 to 62°C for the ε-CL-co-δ-VAL copolymer containing 60% of ε-CL units. As can be observed, as the temperature increased the reflection intensity of the crystal bands decreases and eventually vanishes. This is the consequence of the transition from a crystalline phase to an amorphous one. These two copolymers, CL-VAL 85 and CL-VAL 60, presented a stable crystalline phase respectively until 50 and 28°C, values that are consistent with their corresponding melting temperatures (from 44 to 51°C for CL-VAL 85 and ~28°C for CL-VAL 60). On the other hand, the PCL homopolymer, whose profile is not shown, displayed a stable crystalline phase up to a higher temperature, 61°C.

Figure 11 shows the diffraction profiles of CL-VAL 85 and CL-VAL 60 together with the diffractogram of the reference homopolymer (PCL). CL-VAL 85 presented exactly the same signals as PCL at 15.0, 21.6, 22.2, 23.8, 30.0, and 36.4°, while the peaks in the $21 \leq 2\theta \leq 24°$ range were the most intense. Therefore, it can be stated that both polymers present the same crystal structure. However, this cannot be said for CL-VAL 60. Conversely, this copolymer did not exhibit the shoulder-shaped signal at 22.2° whereas the peak at 23.8 shifted to 24.2° (see the magnification in the figure). The latter peak was broader and encompassed the signals of PCL at 23.8° and that of the poly(δ-valerolactone) (PVL), centered at 24.4°.[44] Hence, it can be concluded that CL-VAL 60 presents a different crystalline phase. Moreover, the fact that the WAXRD patterns of PCL and PVL are very similar proves that the lattice parameters of both lactones are analogous and confirms that ε-CL and δ-VAL units are co-crystallizing in this copolymer composition.

The term isomorphism refers to two or more distinct substances with similar crystalline structure that crystallize together in a single crystal unit cell.[45–48] The different types of isomorphism have been classified by Natta *et al.*,[49] the subject was later reviewed by Wunderlich[50] and by Allegra *et al.*[51,52] Macromolecular isomorphism represents the statistical co-crystallization of different constitutional repeating units in a single isomorphic crystalline lattice. In a strict sense, isomorphism means that only one crystalline phase is observed, and the crystal structure is essentially the same, irrespective of the composition. On the contrary, when the reference homopolymers have different

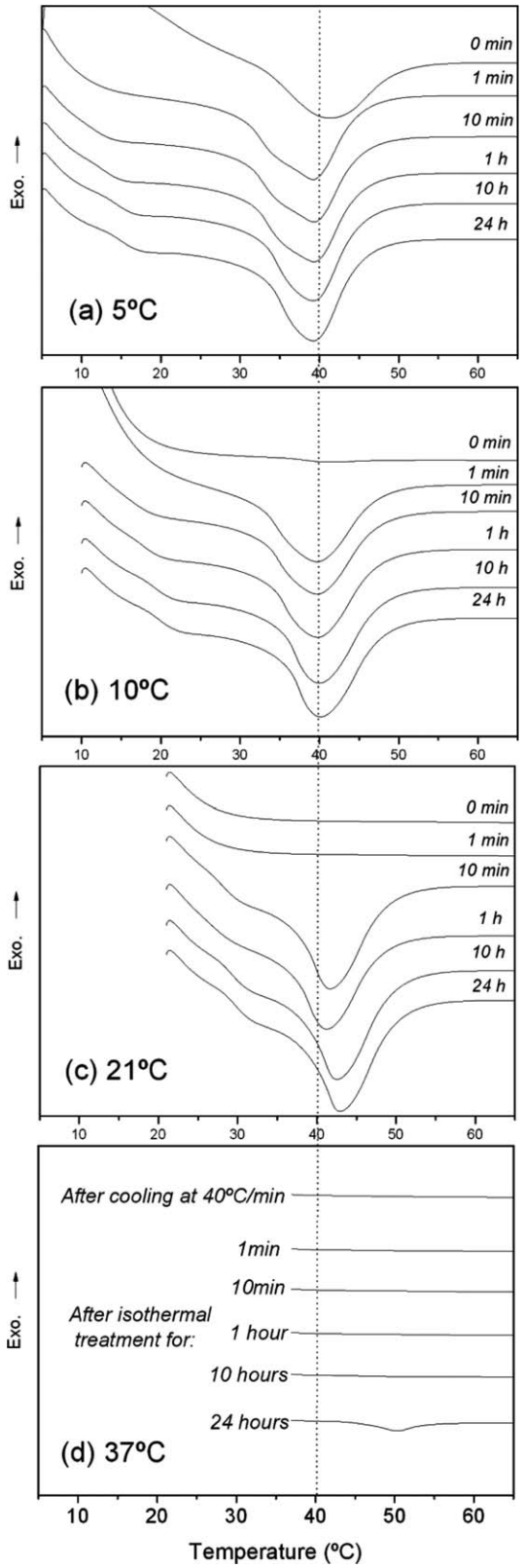

Figure 8. DSC thermograms of CL-LA 92 after different isothermal treatments at 5°C (a), 10°C (b), 21°C (c), and 37°C (d).

crystal structures, copolymers crystallize in either of the crystal lattices depending on composition (isodimorphism), and often both crystals coexist at some intermediate composition. As stated by Allegra and Bassi,[51] macromolecular isomorphism should meet several requirements: (i) the different types of monomer units must have approximately the same shape and occupy the same volume, (ii) the chain conformation of the parent homopolymers must be compatible with either crystal lattice, and (iii) the crystalline structures of parent homopolymers should be analogous in the chain conformation, as well as in lattice symmetry and dimensions. In agreement with early observations by Wunderlich,[50] PCL and other polylactones adopt polyethylene-like crystal structures, in which the length of the methylene sequences determines the packing of polyethylene.

ε-caprolactone is known to crystallize in an extended zigzag conformation and its units cells are orthorhombic,[53] with a=7.496 Å, b=4.974 Å, and c (fiber axis)=17.297 Å. δ-valerolactone, with one less methylene in its chemical structure, was also found to arrange itself into orthorhombic lattices, with parameters a=7.47 Å, b=5.02 Å, and c (fiber axis)=7.42 Å.[54] The identity of the chain conformation and the close similarity of unit-cell lateral dimensions allow both units to co-crystallize, as was seen in the 60 : 40 ε-CL-co-δ-VAL copolymer. Several other co-crystallizing copolymer systems containing ε-CL repeat units have been documented in literature. Shalaby and Kafrawy[55] prepared random poly(ε-caprolactone-co-1,5-dioxepan-2-one) copolymers, suggesting that isomorphic crystallization of these copolyesters took place. Jérome and coworkers[56] reported co-crystallization of poly(ε-caprolactone-co-2-oxepane-1,5-dione) random copolymers. Bikiaris and coworkers[57] studied the crystalline structure and crystallization kinetics of poly(ε-caprolactone-co-propylene succinate) stating that co-crystallization occurs in these copolymers to some extent. Finally, Ceccorulli *et al.*[43] investigated the co-crystallization behavior of poly(ε-caprolactone-co-ω-pentadecalactone) while Gross and coworkers with Scandola[58–60] also studied other isomorphic copolymers containing pentadecalactone units.

Polarized Light Optical Microscopy (PLOM). In the previous sections it has been demonstrated that at certain compositions of ε-CL and δ-VAL, poly(ε-caprolactone-co-δ-valerolactone) copolymers undergo isomorphic crystallization. As a result they are highly crystalline over the whole composition range studied. Nevertheless, ε-CL-co-δ-VAL copolymers also exhibited a higher crystallization capability than some poly(ε-caprolactone-co-L-lactide) copolymers with higher average sequence lengths of ε-CL. This cannot be explained by the co-crystallization phenomenon. As has been proved, CL-VAL 85, with an 85.3% of ε-CL and a l_{CL} of 6.08, is not a co-crystallizing polymer system, however it displayed a large crystallizing ability in comparison to CL-LA 92, a L-lactide based copolymer that has a higher content of ε-CL (91.6%) and a larger l_{CL} (6.65). CL-VAL 85 reached a maximum of crystallization after 24 h at 5°C, with a ΔH_m of 80.5 J g^{-1}, while it presented a crystallization peak of 59.8 J g^{-1} following a cooling treatment at 5°C min^{-1} from 100°C. Conversely, CL-LA 92 showed lower values of 57.7 J g^{-1} of ΔH_m and 49.6 J g^{-1} of ΔH_c after the same experiments in

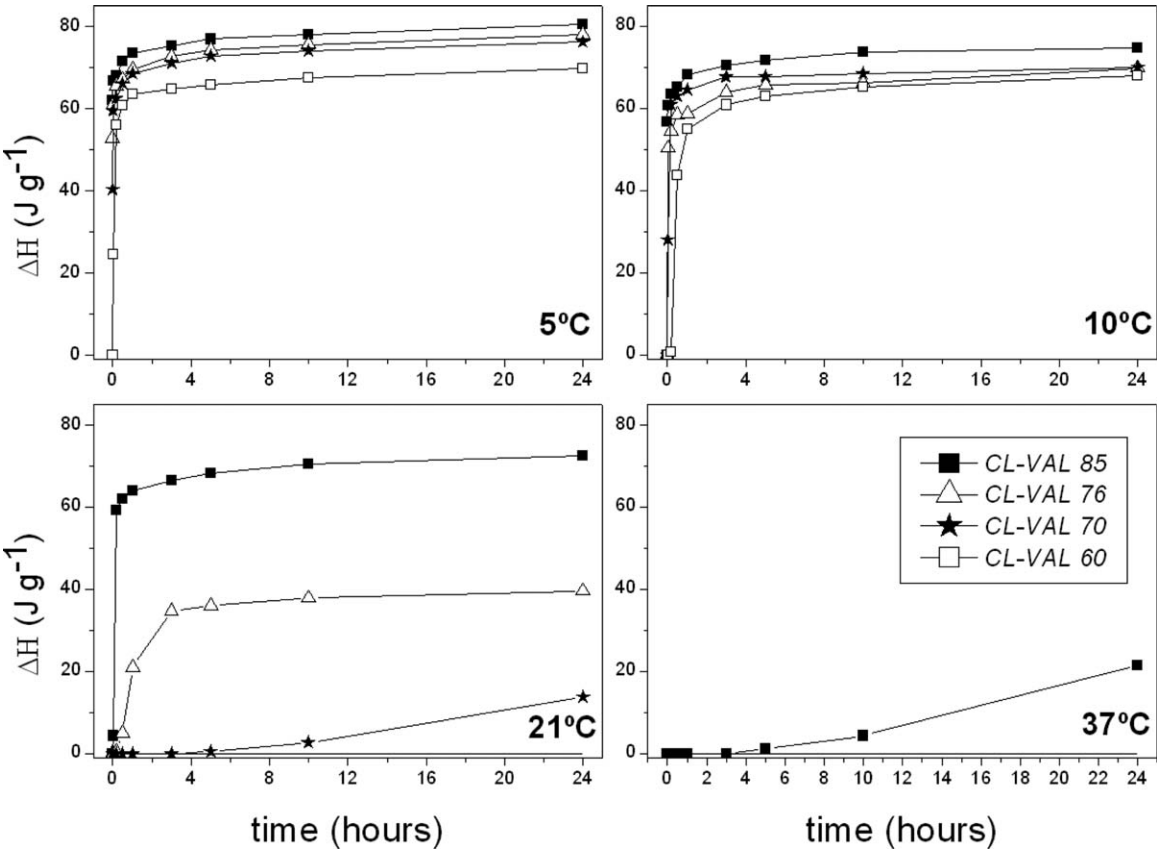

Figure 9. Melting enthalpies of the poly(ε-caprolactone-co-δ-valerolactone) copolymers obtained after different isothermal treatments. CL-VAL 85 (–■–), CL-VAL 76 (–Δ–), CL-VAL 70 (–*–), and CL-LA 60 (–□–).

the DSC. In addition, during the isothermal process at 21°C it was noted that after 1 min only CL-VAL 85 showed a melting peak, demonstrating that the supramolecular arrangements take place faster in this copolymer. In order to complete the study of crystallization of those two copolymers that have a very low T_g (−64.3°C for CL-VAL 85 vs. −54.0°C for CL-LA 92) and similar T_m (from 43 to 51°C for CL-VAL 85 vs. from 39 to 50°C for CL-LA 92), Polarized Light Optical Microscopy (PLOM) measurements were carried out

PCL, CL-LA 92, and CL-VAL 85 samples were melted in an oven and then immediately brought to the polarizing microscope, simulating the cooling to room temperature (21°C) during a thermoplastic processing. Then, images were taken at different times. Figure 12 shows PLOM micrographs of CL-VAL 85 after 6, 7, and 10 min (above) and CL-LA 92 after 9, 10, and 15 min (below) after the start of the cooling to room temperature. It was found that the nucleation and the spherulite growth began earlier in the case of CL-VAL 85, at minute 6, while the first crystal spherulites of ε-CL from CL-LA 92 were observed at 9 min. The crystalline structures of CL-VAL 85 and CL-LA 92 were stable after 10 and 15 min, respectively, while the PCL homopolymer (whose images are not shown) was already highly crystalline after 2 min.

On the basis of the DSC, WAXS, and these PLOM studies, it can be said that the crystallization of the ε-CL units was easier in the presence of δ-VAL units; both lactones have a similar structure (five straight methylenes and an ester group for ε-CL-units and four straight methylenes together with one ester group for a unit of δ-VAL). However, rigid L-lactide segments disrupt the structure of the crystal lattice of ε-CL, which decrease its crystallization capability.

CONCLUSIONS

In this work, ε-caprolactone was co-polymerized with L-lactide or δ-valerolactone monomers with the aim of reducing the crystallinity of the poly(ε-caprolactone) homopolymer, so as to improve its biodegradability properties. The poly(ε-caprolactone-co-L-lactide) and poly(ε-caprolactone-co-δ-valerolactone) copolymers were synthesized using triphenyl bismuth (Ph_3Bi) as catalyst and were characterized by nuclear magnetic resonance spectroscopy (NMR), showing respectively semi-alternating ($R \rightarrow 2$) or random ($R \sim 1$) distribution of sequences.

By means of differential scanning calorimetry (DSC), non-isothermal crystallizations were conducted at different cooling rates (at 5, 10, and 20°C min^{-1}) and several isothermal experiments (at 5, 10, 21, and 37°C) were also carried out over 24 h. ε-CL-co-LA copolymers (with ε-CL molar contents ranging from 70 to 94%) exhibited a lower crystallization capability than the ε-CL-co-δ-VAL (with ε-CL content in the range of 60 to 85%). This was observed regardless of their ε-CL average sequence length (l_{CL}), a parameter that depends on both the composition and the randomness character. In addition, supramolecular

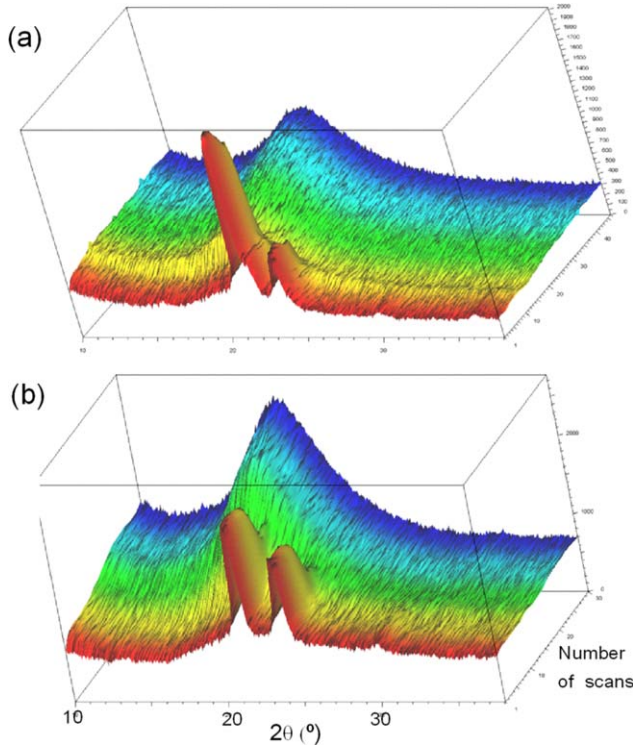

Figure 10. Three dimensional WAXS profiles of CLVAL 85 (a) and CLVAL 60 (b). "X" axis represents the diffraction angle (2θ), "Y" axis the intensity, and "Z" axis the number of scans. The scans were made every 2°C from 30 to 122°C in the case of CL-VAL 85 and from 2 to 62°C for CL-VAL 60. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

arrangements occurred slower in those copolymers containing lactide owing to their higher T_g values (∼(−64)°C for the ε-CL-co-δ-VAL and from (−57) to (−33)°C for the ε-CL-co-LA).

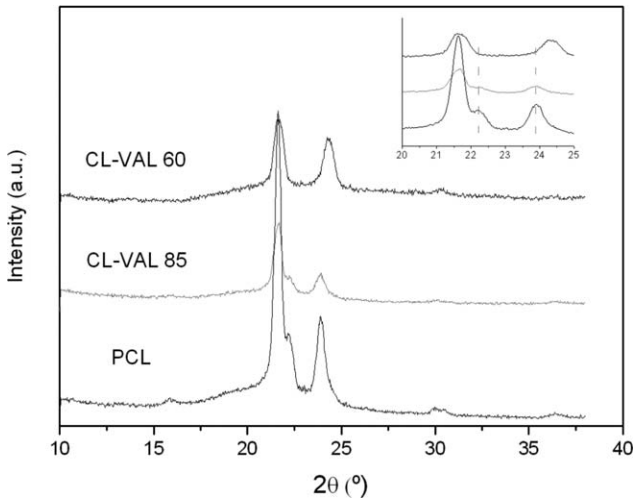

Figure 11. Initial WAXS profiles of PCL, CL-VAL 85, and CL-VAL 60 in the $10 \leq 2\theta \leq 38$ range.

Likewise, it was demonstrated that rigid L-lactide segments interfered with the structure of the crystal lattice of ε-CL, limiting the crystallization capability in CL-co-LA structures. On the other hand, crystallization of the ε-CL was easier in the presence of δ-VAL units. Furthermore, for some compositions, such as the 60 : 40 ε-CL-co-δ-VAL copolymer, it was found that ε-CL and δ-VAL undergo isomorphic crystallization. The WAXS pattern of this copolymer differed from the diffraction profiles of the PCL homopolymer and the 85 : 15 copolymer, proving that the crystal phase of the CL-VAL 60 was different. As a result, the ε-CL-co-δ-VAL copolymers were highly crystalline over a broad composition range, at the same time their crystallization and melting enthalpies were very large, unrelated to the copolymer composition. To the best of the authors' knowledge this is

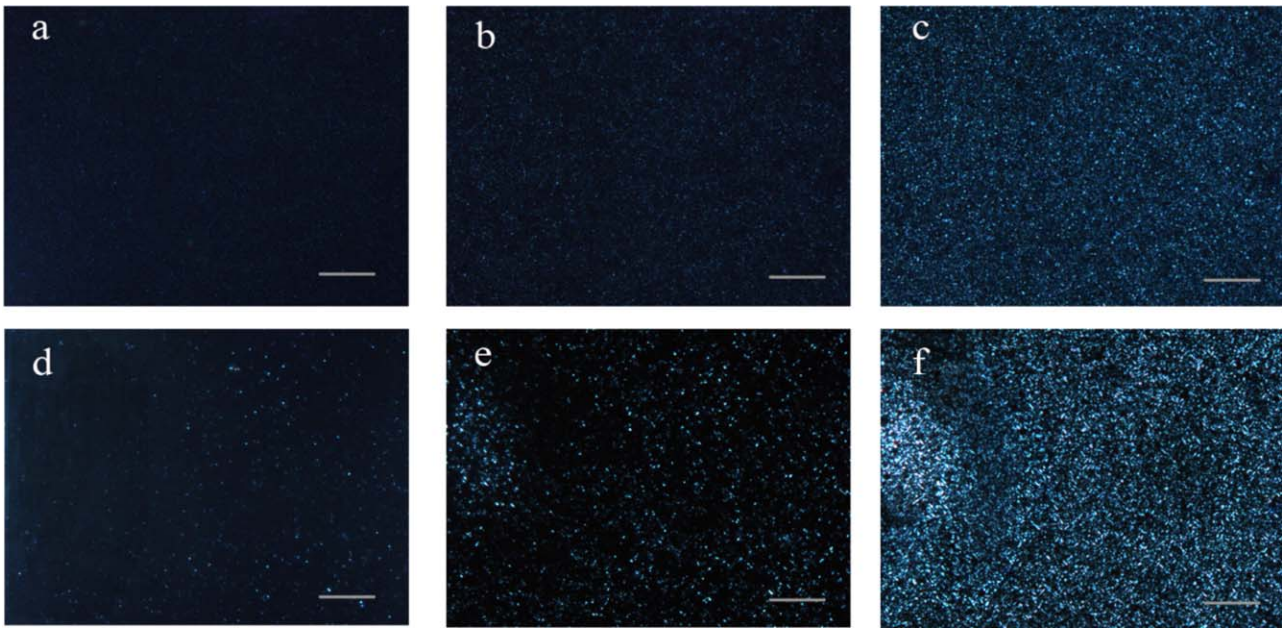

Figure 12. PLOM images of CL-VAL 85 after: (a) 6 min, (b) 7 min, and (c) 10 min; and CL-LA 92: (d) 9 min, (e) 10 min, and (f) 15 min. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the first time that this co-crystallizing system has been reported in literature.

In further studies the mechanical performance of these polymeric materials will be studied by testing their mechanical properties at room temperature (21°C) and at 37°C, human body temperature, at which these biomaterials are intended to be employed. Moreover, an in vitro hydrolytic degradation study, in phosphate buffered solution (PBS) at 37°C for a period up to 26 weeks, will be carried out so as to evaluate in depth their biodegradation mechanisms. These studies have started and will be reported on in due course.

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