

Hydrolytic Degradation of Poly(oxyethylene)–Poly-(ϵ -caprolactone) Multiblock Copolymers

SUMING LI,¹ HENRI GARREAU,¹ MICHEL VERT,¹ TSVETANKA PETROVA,² NEVENA MANOLOVA,² ILIYA RASHKOV²

¹ Centre de Recherche sur les Biopolymères Artificiels, Faculté de Pharmacie, 15 avenue Charles Flahault, 34060 Montpellier, France

² Institute of Polymers, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

Received 23 July 1997; accepted 9 September 1997

ABSTRACT: The degradation of poly(oxyethylene)–poly(ϵ -caprolactone) (POE–PCL) multiblock copolymers was investigated at 37°C in a 0.13M, pH 7.4 phosphate buffer selected to mimic *in vivo* conditions. The copolymers were obtained by coupling polycaprolactone diols and poly(ethylene glycol) diacids using dicyclohexylcarbodiimide as coupling agent. Various techniques, such as weighing, size exclusion chromatography, infrared, ¹H nuclear magnetic resonance, differential scanning calorimetry, and X-ray diffractometry, were used to monitor changes in total mass, water absorption, molar mass, thermal properties, degree of crystallinity, and composition. The results showed that introduction of POE sequences considerably increased the hydrophilicity of the copolymers as compared with PCL homopolymers. Nevertheless, the degradability of PCL sequences was not enhanced due to the phase separation between the two components. Significant morphological changes were also observed during the degradation. © 1998 John Wiley & Sons, Inc. *J Appl Polym Sci* 68: 989–998, 1998

Key words: poly(ethylene glycol); poly(ϵ -caprolactone); block copolymer; hydrolysis; degradation

INTRODUCTION

Degradable polymers are of growing interest in the field of temporary therapeutic applications, such as sustained drug delivery systems, surgical sutures, and osteosynthetic devices.^{1–3} In this area, polyester–polyether block copolymers appear very promising, especially as matrices for controlled delivery of drugs. Actually, the introduction of hydrophilic polyether blocks into degradable polyester chains is a means to enhance the hydrophilicity as compared with the parent homopolyesters. Poly(ethylene glycol) (PEG) or

poly(oxyethylene) (POE) has been used to form block copolymers with poly(lactides) (PLA) or poly(ϵ -caprolactone) (PCL), the two most frequently investigated degradable polyesters.^{4–15} PCL is a degradable polymer of great interest in the field of sustained drug delivery due to its excellent permeability to drugs.^{16,17} Nevertheless, PCL is a highly hydrophobic and crystalline polymer which degrades very slowly *in vitro* and *in vivo* as well.^{17,18} PCL–POE–PCL triblock copolymers have been investigated by several groups.^{10–12} It has been shown that the presence of POE blocks did increase the hydrophilicity and the degradation rate, although the enhanced degradability was based on inherent viscosity measurements only.

Polyether–polyester block copolymers were generally prepared by ring-opening polymerization of cyclic lactones (lactides or ϵ -caprolactone)

Correspondence to: S. Li.

Contract grant sponsor: National Science Fund of Bulgaria; contract grant number: CH 435.

Journal of Applied Polymer Science, Vol. 68, 989–998 (1998)

© 1998 John Wiley & Sons, Inc.

CCC 0021-8995/98/060989-10

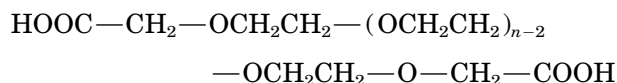
in the presence of PEG. Different catalysts such as metals (Zn), oxides (SnO, SnO₂, Sb₂O₃, PbO, and GeO₂), salts [SnCl₂, KtBuO, Sn(Oct)₂, and Ti(OBu)₄] and hydrides (NaH and CaH₂) have been used to yield block copolymers of various molar masses. Nevertheless, most of these catalysts are more or less toxic or cytotoxic.¹⁹ In order to avoid any nonbiocompatible impurities in the final product, triblock copolymers were prepared from PEG and L-lactide or ε-caprolactone in the absence of catalyst.^{9–11} The noncatalyzed polymerizations, however, had to be performed at high temperature (185°C) for long reaction times (48–72 h). We previously reported the synthesis and characterization of PCL–POE multiblock copolymers obtained by polycondensation of PEG bearing two carboxylic end groups and PCL diols in the presence of dicyclohexylcarbodiimide (DCC) as a condensing agent.²⁰ The synthesis was carried out under mild reaction conditions to yield various multiblock copolymers.

In this article, we report on the abiotic hydrolytic degradation characteristics of these original polymeric materials. Degradation was performed at 37°C in a 0.13M, pH 7.4 sodium phosphate buffer taken as a model medium of physiological fluids. Efforts were made to monitor changes of various parameters using complementary techniques.

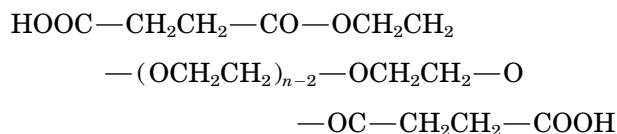
EXPERIMENTAL

Materials

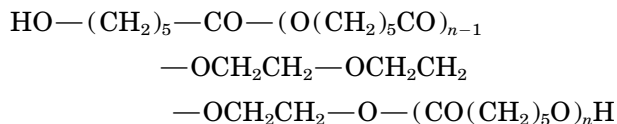
PEG₆₀₀ diacid was purchased from Fluka with the following formula:



whereas PEG₂₀₀₀ diacid was obtained by reacting PEG₂₀₀₀ diol with succinic anhydride as previously reported.²⁰ The formula of PEG₂₀₀₀ diacid is slightly different from that of PEG₆₀₀ diacid as the former is terminated at both ends with succinic half-esters as follows:



PCL₁₂₅₀ and PCL₂₀₀₀ diols were supplied by Aldrich Chemical Co. with the following formula:



Multiblock copolymers with the general formula $-(\text{POE}-\text{PCL})_n-$ were prepared by reacting equimolar amounts of PEG diacids and PCL diols as previously reported.²⁰ Typically, 1.25 g PCL₁₂₅₀ (2 mmol OH) and 0.535 g DCC (2.6 mmol) were introduced into 40 mL methylene chloride containing 0.60 g PEG₆₀₀ (2 mmol COOH) and 0.06 g dimethylaminopyridine (0.5 mmol). The mixture was stirred for 6 h at room temperature. The precipitate of dicyclohexylurea was filtered, and the filtrate evaporated to dryness. The residue was dissolved in acetone, followed by filtration and precipitation in ethanol. The recovered polymeric material was further purified by dissolution in chloroform and precipitation in ethanol. When necessary, precipitation was achieved with diethylether instead of ethanol.

For degradation studies, the copolymers were thoroughly dried before compression molding at 90°C. The circular plates of 1.5 mm thickness thus obtained were then cut into approximately 0.35-g specimens.

Measurements

Size exclusion chromatography (SEC) analysis was performed in tetrahydrofuran at room temperature with a Waters apparatus equipped with a Waters 410 differential refractometer and a PLgel 5-μm Mixed-C column. The flow rate was 1.0 mL/min. Differential scanning calorimetry (DSC) measurements were carried out at a heating rate of 10°C/min on a DuPont Instrument Series 99 Thermal Analyser. 10 mg of compound were used for each experiment. X-ray diffractometric (XRD) analysis was conducted with a Philips apparatus using Cu Kα source (0.154 nm). Infrared (IR) spectra were recorded on a Perkin-Elmer 1760 FTIR spectrometer, with the films being cast on NaCl plates from chloroform solutions. ¹H nuclear magnetic resonance (NMR) spectra were recorded at room temperature using a Bruker spectrometer operating at 250 MHz. Deuterated chloroform was used as solvent, and chemical shifts were expressed in ppm from the signal of tetramethylsilane (TMS).

Hydrolytic Degradation

For each degradation study, 20 copolymer specimens were placed into small flasks filled with 25

Table I POE-PCL Multiblock Copolymers Selected for Degradation Studies

Polymer	Diacid	Diol	OE/CL ^a	\bar{M}_n ^b	\bar{M}_w/\bar{M}_n ^b	n ^c
(POE ₂₀₀₀ PCL ₁₂₅₀) _n	PEG ₂₀₀₀	PCL ₁₂₅₀	4.7	34,000	2.2	10.5
(POE ₂₀₀₀ PCL ₂₀₀₀) _n	PEG ₂₀₀₀	PCL ₂₀₀₀	2.8	24,400	2.7	6.1
(POE ₆₀₀ PCL ₁₂₅₀) _n	PEG ₆₀₀	PCL ₁₂₅₀	1.0	16,500	2.4	8.9
(POE ₆₀₀ PCL ₂₀₀₀) _n	PEG ₆₀₀	PCL ₂₀₀₀	0.7	35,000	2.2	13.5

^a Determined by ¹H NMR.

^b Determined by SEC, laser light scattering detector (see Petrova et al.²⁰)

^c n is the average length of $-(\text{POE}-\text{PCL})_n-$ repeating units in the multiblock copolymers determined from the corresponding \bar{M}_n values.

mL of 0.13 M, pH 7.4 phosphate buffer containing 0.02% NaN₃ to prevent bacteria development. The flasks were allowed to stand in a thermostated oven for predetermined periods of time. Two specimens were withdrawn from the flasks at each degradation time and washed with distilled water. After wiping, the specimens were weighed and vacuum-dried at room temperature for 1 week.

RESULTS

Table I shows the compositional and molecular characteristics of the four copolymers considered in this study. The molar masses were not very high as the copolymers were obtained by polycondensation under mild conditions. The average length n of $-(\text{POE}-\text{PCL})_n-$ repeating units in the multiblock chains was in the 6.1 to 13.5 range. The OE/CL ratio was close to theoretical data. It is worth noting that the junctions between POE and PCL blocks are slightly different due to the different chain ends of PEG₆₀₀ and PEG₂₀₀₀ diacids, as shown above.

In the selected degradation medium, (POE₂₀₀₀-PCL₁₂₅₀)_n and (POE₂₀₀₀-PCL₂₀₀₀)_n specimens rapidly swelled and then disintegrated. However, the form of the degraded materials depended on the chain compositions. (POE₂₀₀₀-PCL₁₂₅₀)_n yielded a powder, whereas (POE₂₀₀₀-PCL₂₀₀₀)_n appeared as small pieces. In contrast, (POE₆₀₀-PCL₁₂₅₀)_n and (POE₆₀₀-PCL₂₀₀₀)_n retained their geometrical shape up to 70 weeks, the end of the experiments. These differences were assigned to the decreasing OE/CL ratio according to the following series: (POE₂₀₀₀-PCL₁₂₅₀)_n > (POE₂₀₀₀-PCL₂₀₀₀)_n > (POE₆₀₀-PCL₁₂₅₀)_n > (POE₆₀₀-PCL₂₀₀₀)_n (Table I). The two compounds deriving from PEG₂₀₀₀ seemed to degrade faster than those deriving from PEG₆₀₀. Water absorption measurements showed that after 2 weeks, (POE₆₀₀-PCL₁₂₅₀)_n and (POE₆₀₀-PCL₂₀₀₀)_n had absorbed water at the level of

32 and 14%, respectively. Beyond that, the amount of absorbed water remained almost unchanged. (POE₆₀₀-PCL₁₂₅₀)_n was more hydrophilic than (POE₆₀₀-PCL₂₀₀₀)_n due to its higher OE/CL ratio. It was not possible to collect water absorption data in the cases of (POE₂₀₀₀-PCL₂₀₀₀)_n and (POE₂₀₀₀-PCL₁₂₅₀)_n due to the early disintegration of the samples. However, it is likely that they absorbed more water than (POE₆₀₀-PCL₂₀₀₀)_n and (POE₆₀₀-PCL₁₂₅₀)_n due to their higher OE/CL ratios. Anyhow, the hydrophilicity of these copolymers was greatly enhanced as compared to PCL homopolymers, which absorbed only 1.4% of water after 63 weeks of degradation.¹⁸

Figure 1 presents the variation of weight loss during degradation. A weight loss burst of 54% was detected for (POE₂₀₀₀-PCL₁₂₅₀)_n after 2 weeks, whereas (POE₂₀₀₀-PCL₂₀₀₀)_n and (POE₆₀₀-PCL₁₂₅₀)_n lost 14 and 5%, respectively. No weight loss was observed for (POE₆₀₀-PCL₂₀₀₀)_n during the first 2 weeks. Later on, the percentage of weight loss increased almost continuously. At week 70, the weight loss attained 96, 45, 27, and 20% for (POE₂₀₀₀-PCL₁₂₅₀)_n, (POE₂₀₀₀-PCL₂₀₀₀)_n, (POE₆₀₀-PCL₁₂₅₀)_n, and (POE₆₀₀-PCL₂₀₀₀)_n, respectively. Therefore, the weight loss depended on the composition of the copolymers. The higher the OE/CL ratio, the larger the weight loss. Under similar conditions, a PCL homopolymer lost only 3.4% after 63 weeks.¹⁸

The evolution of SEC chromatograms of (POE₂₀₀₀-PCL₂₀₀₀)_n is shown in Figure 2(A). The molar mass distribution was initially monomodal, but the presence of oligomeric species at higher elution times was detected. During the first 11 weeks, the chromatogram did not change significantly. However, the release of oligomers caused a depletion in the low molar mass range of the peak, in agreement with mass loss data. Afterwards, the chromatogram shifted slowly but continuously to lower molar masses. Similar changes were observed for (POE₂₀₀₀-PCL₁₂₅₀)_n. The two

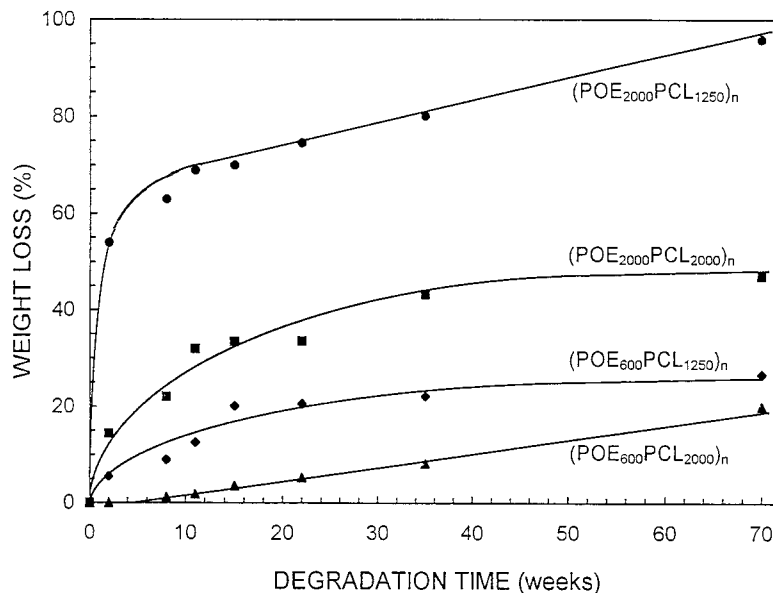


Figure 1 Weight loss of $(\text{POE}_{2000}\text{PCL}_{1250})_n$, $(\text{POE}_{2000}\text{PCL}_{2000})_n$, $(\text{POE}_{600}\text{PCL}_{1250})_n$, and $(\text{POE}_{600}\text{PCL}_{2000})_n$ with degradation.

other copolymers $(\text{POE}_{600}\text{PCL}_{1250})_n$ and $(\text{POE}_{600}\text{PCL}_{2000})_n$ exhibited initially monomodal and rather narrow molar mass distributions [Fig. 2(B)]. In contrast to $(\text{POE}_{2000}\text{PCL}_{2000})_n$, the SEC molar mass of the two latter compounds decreased from the very beginning. On the other hand, the molar mass distribution became larger during degradation, especially beyond 35 weeks. The decrease of peak molar mass after 70 weeks was about 25, 38, and 41% for $(\text{POE}_{2000}\text{PCL}_{2000})_n$, $(\text{POE}_{600}\text{PCL}_{2000})_n$, and $(\text{POE}_{600}\text{PCL}_{1250})_n$, respectively. Data were not available for $(\text{POE}_{2000}\text{PCL}_{1250})_n$ at this time due to the lack of material.

Thermal characteristics of the copolymers were investigated by DSC. A second heating was performed after quenching of the first melt in order to observe glass transition and crystallization phenomena. Figure 3(A) shows comparatively the thermograms of the starting products PEG_{2000} , PCL_{2000} , and of the copolymer $(\text{POE}_{2000}\text{PCL}_{2000})_n$. All these compounds appeared semicrystalline. PEG_{2000} exhibited a melting temperature (T_m) at 47°C. At the second run, a glass transition (T_g) was detected at -55°C, which was immediately followed by a sharp crystallization peak (T_c) at -45°C and by a melting peak at 44°C. T_m detected at the second run was several degrees below that obtained at the first run because of the difference in crystallization histories. Similarly, PCL_{2000} exhibited $T_m = 56^\circ\text{C}$ at the first run and $T_g = -67^\circ\text{C}$, $T_c = -55^\circ\text{C}$, and $T_m = 47^\circ\text{C}$ at the second run. In contrast, the copolymer presented two melting

peaks $T_{m1} = 30^\circ\text{C}$ and $T_{m2} = 48^\circ\text{C}$, which were tentatively assigned to POE and PCL blocks, respectively. Melting temperatures of both blocks were lower than those of the starting homopolymers. At the second run, T_g was detected at -59°C and T_c at -47°C. The fact that only one T_g was detected between those of the two components indicated compatibility in the amorphous state. T_c of the copolymer was also between those of the starting homopolymers. Moreover, the T_{m1} peak detected at 32°C became more intense than the T_{m2} peak detected at 43°C, thus suggesting a higher crystallizability of PEG_{2000} as compared to PCL_{2000} blocks.

Figure 3(B) presents the thermograms of $(\text{POE}_{2000}\text{PCL}_{2000})_n$ after 2, 8, and 70 weeks of degradation. The higher melting peak T_{m2} , which was assigned to PCL blocks, remained at 48°C during the first 15 weeks. Beyond this, it increased slowly to attain 51°C at the end of 70 weeks. The area of the peak that reflected the melting enthalpy ΔH also increased [Fig. 3(B)]. The lower melting peak T_{m1} due to POE blocks decreased from 30 to 20°C during the first 15 weeks, and then increased to 34°C after 70 weeks. It is also of interest to note that the peak area of POE blocks first decreased and then increased during the first run, but it remained almost constant for the second run. T_g of the copolymer only slightly decreased from -59 to -61°C in the meantime. T_c increased from initial -47 to -44°C at week 4, then slowly

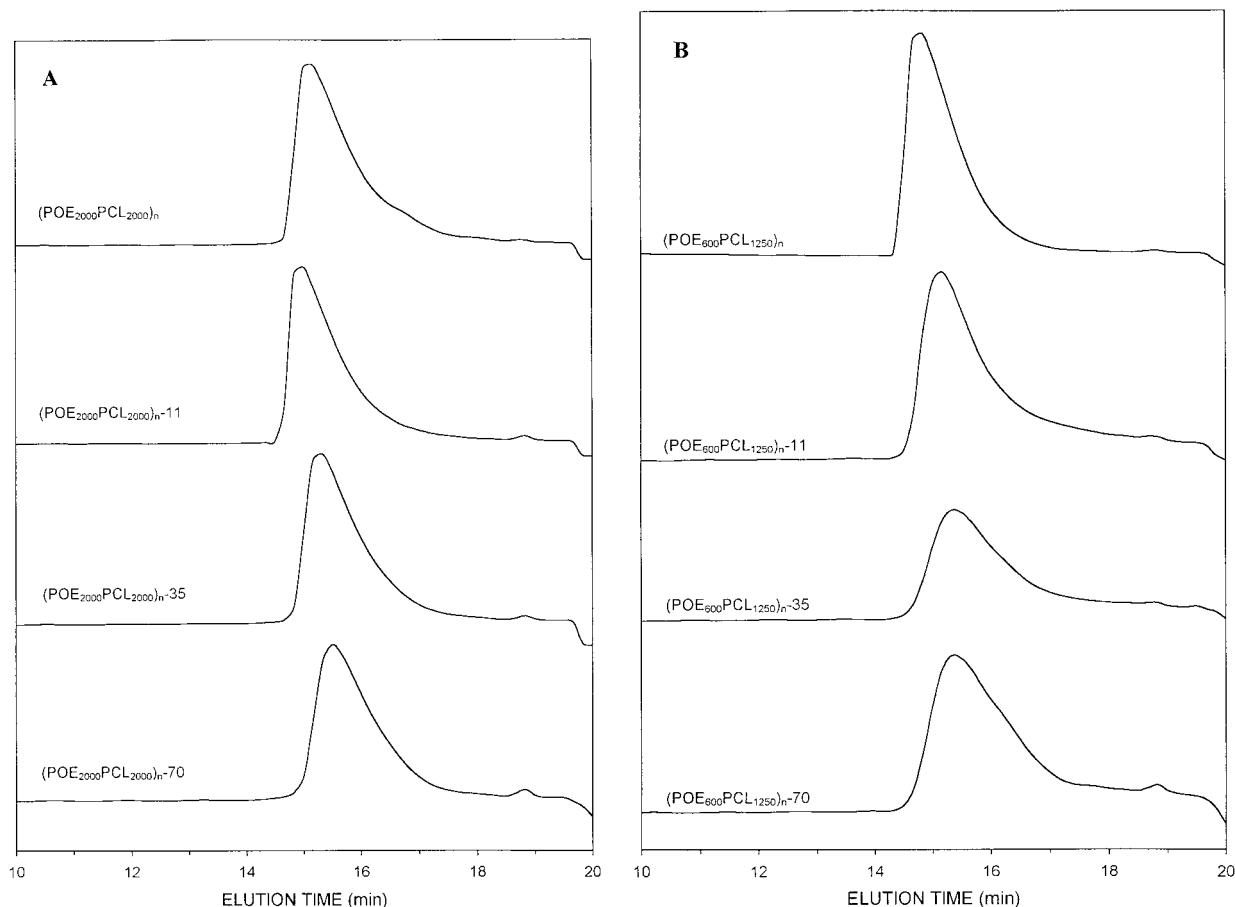


Figure 2 (A) SEC chromatograms of $(\text{POE}_{2000}\text{PCL}_{2000})_n$ after 0, 11, 35, and 70 weeks of degradation. (B) SEC chromatograms of $(\text{POE}_{600}\text{PCL}_{1250})_n$ after 0, 11, 35, and 70 weeks of degradation.

decreased to -48°C at the end of 70 weeks. On the other hand, a small exothermal peak following the main crystallization peak at -47°C was detected beyond 8 weeks. After 70 weeks, this peak became more intense and appeared at -40°C , which could be tentatively attributed to the subsequent crystallization of amorphous areas and/or crystallite defects.

As in the case of $(\text{POE}_{2000}\text{PCL}_{2000})_n$, the copolymer $(\text{POE}_{2000}\text{PCL}_{1250})_n$ presented also two distinct crystalline domains (Table II). Similar T_g , T_c , T_{m1} , and T_{m2} changes were observed during the degradation period. In contrast, $(\text{POE}_{600}\text{PCL}_{1250})_n$ and $(\text{POE}_{600}\text{PCL}_{2000})_n$ exhibited only one melting peak, with PEG₆₀₀ blocks being unable to crystallize. In both cases, the following T_m increase was detected during the 70 weeks degradation period: from 43 to 51°C for $(\text{POE}_{600}\text{PCL}_{1250})_n$ and from 45 to 53°C for $(\text{POE}_{600}\text{PCL}_{2000})_n$. T_g remained almost unchanged, while T_c decreased from -40 to -45°C for $(\text{POE}_{600}\text{PCL}_{1250})_n$ and from -45 to -48°C for $(\text{POE}_{600}\text{PCL}_{2000})_n$ (Table II).

Figure 4 presents XRD spectra of the starting macromonomers PEG₂₀₀₀ and PCL₂₀₀₀ and of the copolymer $(\text{POE}_{2000}\text{PCL}_{2000})_n$ before and after degradation. PCL₂₀₀₀ showed an intense peak at $\theta = 10.7^\circ$ and two smaller ones at $\theta = 10.9^\circ$ and 11.8° , whereas PEG₂₀₀₀ showed two main peaks at $\theta = 9.4^\circ$ and 11.5° . All these peaks were present in the spectrum of the copolymer, with the peak of PCL at 11.8° being overlapped with that of PEG at 11.5° to yield a large peak. Beneath diffraction peaks typical of PCL and POE crystalline phases, a broad diffusion zone characteristic of the amorphous phase was observable in the diffractogram.

After 2 weeks of degradation, the intensity of the peaks characteristic of POE crystalline structures greatly diminished (Fig. 4). Between 8 and 35 weeks, they almost disappeared. In contrast, at the end of 70 weeks, these peaks appeared again, in agreement with the increase of T_{m1} in DSC thermograms. The degree of crystallinity deduced from the XRD spectra decreased from the initial 31 to 18% after 2 weeks, corresponding to

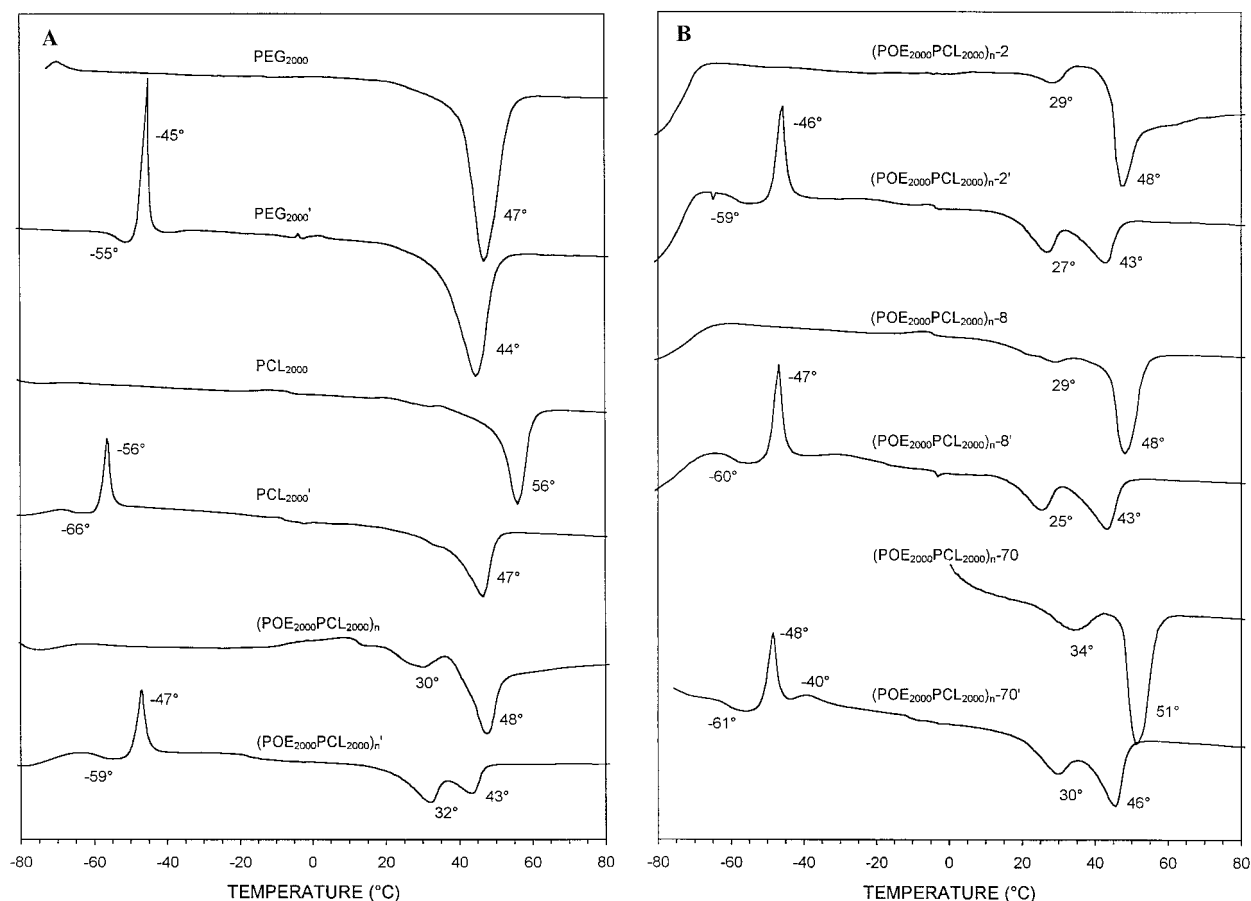


Figure 3 (A) DSC thermograms of PEG₂₀₀₀, PCL₂₀₀₀, and (POE₂₀₀₀PCL₂₀₀₀)_n (: second heating). (B) DSC thermograms of (POE₂₀₀₀PCL₂₀₀₀)_n after 2, 8, and 70 weeks of degradation (: second heating).

the diminution of the POE crystalline zone. It remained rather low between 2 and 35 weeks and significantly increased up to 39% after 70 weeks (Table III).

(POE₂₀₀₀PCL₁₂₅₀)_n showed similar diffractograms with the presence of diffraction peaks typical of both POE and PCL crystallites. Its crystallinity decreased from initial 31% to as low as

Table II Thermal Property Changes of the Multiblock Copolymers with Degradation

Polymer	(POE ₂₀₀₀ PCL ₁₂₅₀) _n				(POE ₂₀₀₀ PCL ₂₀₀₀) _n				(POE ₆₀₀ PCL ₁₂₅₀) _n			(POE ₆₀₀ PCL ₂₀₀₀) _n			
	Time (Weeks)	T_g^a (°C)	T_c^a (°C)	T_{m1}^b (°C)	T_{m2}^b (°C)	T_g (°C)	T_c (°C)	T_{m1} (°C)	T_{m2} (°C)	T_g (°C)	T_c (°C)	T_m (°C)	T_g (°C)	T_c (°C)	T_m (°C)
0		-56	-46	34	41	-59	-47	30	48	-59	-40	43	-61	-45	45
2		-59	-47	34	45	-59	-46	29	48	-60	-40	48	-60	-45	49
4		-59	-44	32	47	-58	-44	21	49	-60	-40	48	-60	-44	49
8		-60	-47	31	47	-60	-47	29	48	-60	-42	50	-61	-45	51
15		-60	-48	15	48	-60	-47	20	48	-61	-43	50	-61	-45	48
22		nd ^c	nd	nd	nd	-60	-47	32	49	-60	-43	51	-61	-46	50
35		-60	-46	34	47	-60	-47	34	50	-60	-43	51	-61	-45	52
70		nd	nd	nd	nd	-61	-48	34	51	-60	-45	51	-62	-48	53

^a Determined from the second heating on DSC.

^b Determined from the first heating on DSC.

^c nd, not determined.

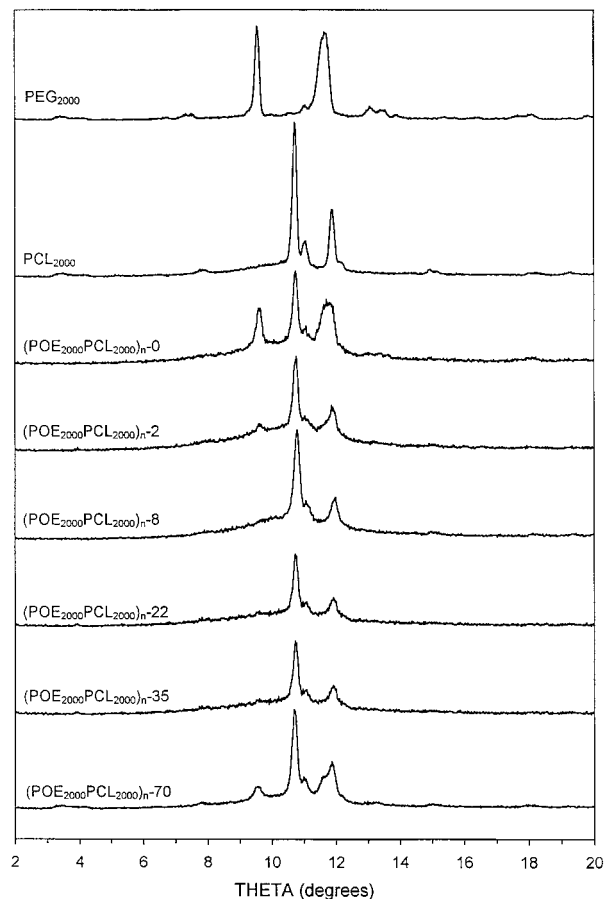


Figure 4 X-ray diffractograms of PEG_{2000} , PCL_{2000} , and $(\text{POE}_{2000}\text{PCL}_{2000})_n$ after 0, 2, 8, 22, 35, and 70 weeks of degradation.

12% after 8 weeks. At week 35, the crystallinity of $(\text{POE}_{2000}\text{PCL}_{1250})_n$ was back to 32% and the reappearance of small POE diffraction peaks was also detected, as in the case of $(\text{POE}_{2000}\text{PCL}_{2000})_n$ after 70 weeks. Insofar as $(\text{POE}_{600}\text{PCL}_{1250})_n$ and $(\text{POE}_{600}\text{PCL}_{2000})_n$ are concerned, only PCL diffraction peaks were observed, in agreement with the presence of one melting peak on DSC thermo-

grams. $(\text{POE}_{600}\text{PCL}_{1250})_n$ showed initially lower crystallinity than the three others since POE_{600} blocks cannot crystallize, and PCL_{1250} blocks had lower crystallizability than PCL_{2000} . In contrast to $(\text{POE}_{2000}\text{PCL}_{1250})_n$ and $(\text{POE}_{2000}\text{PCL}_{2000})_n$, no crystallinity decrease was observed for $(\text{POE}_{600}\text{PCL}_{1250})_n$ and $(\text{POE}_{600}\text{PCL}_{2000})_n$. An important increase of crystallinity was detected at the end of 70 weeks (Table III).

Figure 5 showed the IR spectra of $(\text{POE}_{2000}\text{PCL}_{2000})_n$ after 0, 11, and 70 weeks of degradation. Three main bands can be distinguished in the $3000\text{--}1500\text{ cm}^{-1}$ range: the carbonyl stretching at 1725 cm^{-1} and the C—H stretching band at 2943 cm^{-1} of PCL blocks, and the C—H stretching band at 2867 cm^{-1} due to both PCL and POE blocks. No major changes were observed for these bands during the 70-week degradation period, although the band at 2867 cm^{-1} slightly diminished as referred to the band at 2943 cm^{-1} , suggesting a decrease in POE content. In contrast, the band around 3520 cm^{-1} significantly increased, which corresponded to the formation of hydroxyl and carboxyl end groups due to PCL chain cleavage. Similar features were observed for the three other compounds.

Compositional changes were also monitored by ^1H NMR. The OE/CL ratio was calculated from the signals typical of PCL and POE blocks on the spectra. The results are presented in Table IV. During the first 2 weeks, the OE/CL ratio dramatically decreased from 4.7 to 2.8 for $(\text{POE}_{2000}\text{PCL}_{1250})_n$. Beyond, it continued to decrease and reached 1.3 after 35 weeks. In the case of $(\text{POE}_{2000}\text{PCL}_{2000})_n$, the decrease of OE/CL ratio was slower than for $(\text{POE}_{2000}\text{PCL}_{1250})_n$. From the initial 2.8, the ratio decreased to 1.7 at the end of 70 weeks. Insofar as the two other copolymers $(\text{POE}_{600}\text{PCL}_{1250})_n$ and $(\text{POE}_{600}\text{PCL}_{2000})_n$ are concerned, compositional changes were also detected, but to a less extent (Table IV). In all cases, there

Table III Crystallinity^a Changes of the Copolymers with Degradation

	Time (Weeks)					
	0	2	8	22	35	70
$(\text{POE}_{2000}\text{PCL}_{1250})_n$	31	24	12	nd ^b	32	nd
$(\text{POE}_{2000}\text{PCL}_{2000})_n$	31	18	24	19	24	39
$(\text{POE}_{600}\text{PCL}_{1250})_n$	20	28	18	27	26	40
$(\text{POE}_{600}\text{PCL}_{2000})_n$	33	33	36	38	38	46

^a Determined by X-ray diffraction.

^b nd, not determined.

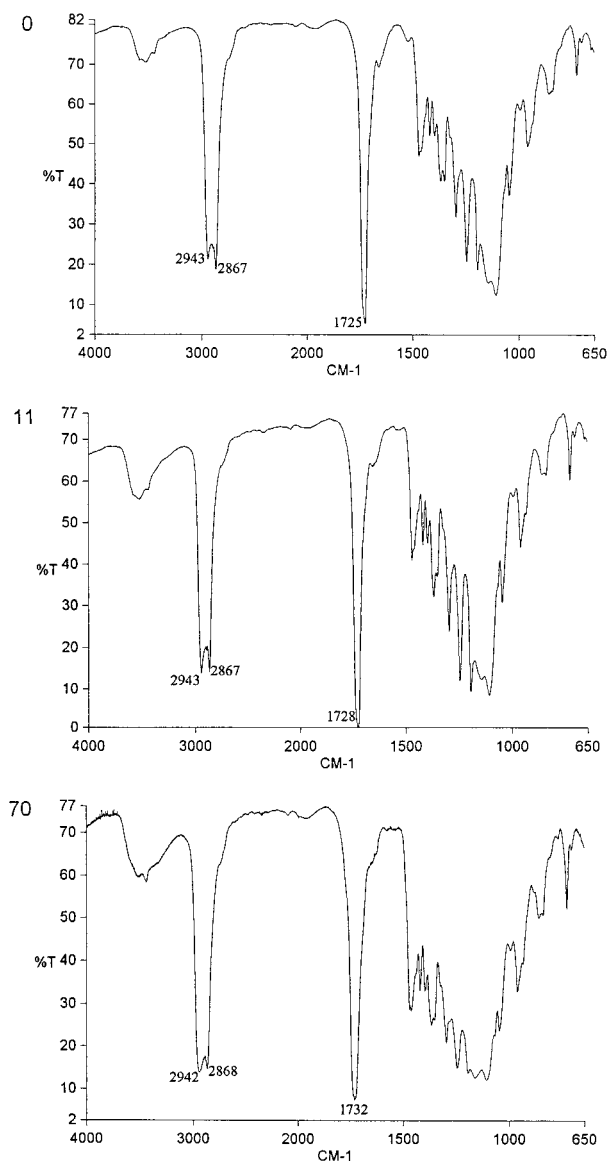


Figure 5 IR spectra of $(\text{POE}_{2000}\text{PCL}_{2000})_n$ films after 0, 11, and 70 weeks of degradation.

still remained rather large amounts of POE segments.

DISCUSSION

In literature, only a few authors examined the hydrolytic degradation of PCL–POE block copolymers. Wang and Qiu investigated the *in vitro* degradation (pH 6.5, 37°C) of a series of PCL–POE block copolymers obtained by ring-opening polymerization of ϵ -caprolactone in the presence of PEG_{6000} using tetra-*n*-butyl titanate as a catalyst.¹² These copolymers were likely to have a

triblock structure, although the authors did not mention this point. A steady decrease of inherent viscosity $[\eta]$ was detected. The higher the POE content in the copolymer, the faster the $[\eta]$ decrease. On the other hand, the CL/OE ratio was found to increase continuously. The authors suggested a two-step degradation process, as follows: ester bonds are first broken hydrolytically and, then, free POE segments can leach out of the bulk material.

Recently, Cerrai et al. prepared various PCL–POE block copolymers by reacting ϵ -caprolactone with PEG_{9200} , PEG_{20000} , and PEG_{35000} without catalyst.^{10,11} All the copolymers were semicrystalline. PCL blocks crystallized in all cases, whereas central POE blocks crystallized only when POE content in the copolymer was superior to 58% (in mole) as deduced from DSC and XRD data.¹⁰ On the other hand, these copolymers exhibited good cyto- and hemocompatibility.¹¹ Biodegradation assays were carried out in the presence or in the absence of fibroblast cell populations. From $[\eta]$ measurements, the authors concluded that the higher the hydrophilicity of the material, the faster the $[\eta]$ decrease rate.¹¹ The amount of the final degradation product, 6-hydroxyhexanoic acid, depended on both the hydrophilicity and lateral PCL block length.

Our results agree with these literature data despite the multiblock nature of the copolymers. From water absorption and weight loss data, it can be concluded that weight loss rate increases with the OE/CL ratio and thus with the hydrophilicity, as follows: $(\text{POE}_{600}\text{PCL}_{2000})_n < (\text{POE}_{600}\text{PCL}_{1250})_n < (\text{POE}_{2000}\text{PCL}_{2000})_n < (\text{POE}_{2000}\text{PCL}_{1250})_n$. The early weight loss resulted mainly from the release of initially present low molar mass species or POE-rich ones, especially in the case of $(\text{POE}_{2000}\text{PCL}_{1250})_n$. In fact, the multiblock chains can be terminated with two PCL segments, with one PCL and one POE segment, or with two POE segments. Hydrophilicity or solubility should be very different, depending on the nature of the two end blocks. For example, chains ended with two POE blocks are much more hydrophilic than those ended with two PCL blocks.

Weight loss data account well for the compositional changes as determined by ^1H NMR and suggest that weight loss resulted from the solubilization of POE-rich segments. It is noteworthy that the POE content of the copolymer was still rather high at the end of 35 or 70 weeks, suggesting a random chain cleavage along PCL blocks. In other words, no preferential cleavage occurred at ester–ether junctions. This is in contrast to the conclu-

Table IV OE/CL Ratio^a Changes of the Copolymers with Degradation

	Time (Weeks)					
	0	2	15	22	35	70
(POE ₂₀₀₀ PCL ₁₂₅₀) _n	4.7	2.8	nd ^b	nd	1.3	nd
(POE ₂₀₀₀ PCL ₂₀₀₀) _n	2.8	2.1	1.9	1.8	1.7	1.7
(POE ₆₀₀ PCL ₁₂₅₀) _n	1.0	0.9	0.7	0.7	0.6	0.6
(POE ₆₀₀ PCL ₂₀₀₀) _n	0.7	0.7	0.6	0.6	0.5	0.4

^a Determined by ¹H NMR.^b nd, not determined.

sion of Kissel et al.¹³ that hydrolytic cleavage of PLA–POE–PLA triblock copolymers proceeded preferentially at ester–ether junctions. This conclusion was only based on a rapid increase in LA/OE ratio and a decrease in molar mass at the early stages of degradation.¹³ However, the rapid initial loss of POE detected by Kissel et al. can also be related to the solubilization of initially present POE-rich chains rather than a preferential cleavage at ester–ether junctions. The molar mass of POE blocks in degradation studies of Kissel et al. was 10,000 and the initial POE contents were as high as 48 and 52%. Therefore, the presence of initially soluble copolymer chains should be possible. Moreover, their conclusion cannot explain why the LA/OE ratio tended to a limit beyond 3 weeks.

SEC data showed a rather limited molar mass decrease during the 70-week degradation period, which is comparable to PCL homopolymers.¹⁸ This can be related to the phase separation phenomenon between POE and PCL blocks, as suggested by Shah et al. in the case of PLA–POE–PLA triblock copolymers.²¹ The large amounts of water absorbed by the copolymers were probably located in the POE swollen phase. Degradation of PCL blocks proceeded very slowly as in the case of PCL homopolymers.

For (POE₂₀₀₀PCL₂₀₀₀)_n and (POE₂₀₀₀PCL₁₂₅₀)_n, both POE and PCL blocks are long enough to crystallize separately and yield distinct crystalline domains (Figs. 3 and 4). Nevertheless, there exists an amorphous phase where POE and PCL blocks are present. In the degradation medium, water absorption and swelling destroyed POE crystalline domains of (POE₂₀₀₀PCL₂₀₀₀)_n and (POE₂₀₀₀PCL₁₂₅₀)_n after a maximum of 2 weeks. Therefore, all POE blocks were in highly swollen amorphous state and were rather mobile. The higher mobility of POE blocks allowed PCL blocks to better crystallize. That is probably why T_m of PCL blocks increased during degradation (Table II), as

shown by (POE₆₀₀PCL₂₀₀₀)_n and (POE₆₀₀PCL₁₂₅₀)_n which contained amorphous POE blocks.

When the degradation products of (POE₂₀₀₀PCL₂₀₀₀)_n and (POE₂₀₀₀PCL₁₂₅₀)_n are withdrawn from the phosphate buffer and dried at room temperature, POE blocks can hardly crystallize because they are attached to crystalline PCL blocks. Therefore, T_{m1} and melting enthalpy due to POE blocks decreased at intermediate degradation times, in agreement with the disappearance of POE diffraction peaks and with the decrease of crystallinity. However, after the first melting on DSC, all PCL and POE blocks became mobile since they were in an amorphous state. As POE₂₀₀₀ blocks have higher crystallizability than PCL₂₀₀₀ and PCL₁₂₅₀ ones, POE blocks crystallized more than PCL blocks during the second run [Fig. 3(B)]. At the later stages of degradation, POE₂₀₀₀ blocks within (POE₂₀₀₀PCL₂₀₀₀)_n and (POE₂₀₀₀PCL₁₂₅₀)_n appeared slightly crystalline, as shown by the first run of DSC and by XRD spectra. This phenomenon probably resulted from the higher chain mobility generated by PCL degradation and was in good agreement with the significant crystallinity increase in this period. Last but not least, both T_c and T_g changes were rather limited, in contrast to T_m and crystallinity, which were more sensitive to degradation or molar mass decrease.

The situation of (POE₆₀₀PCL₂₀₀₀)_n and (POE₆₀₀PCL₁₂₅₀)_n was less complex since only PCL blocks can crystallize within the copolymer matrices. T_m and crystallinity increased during degradation because of further crystallization of PCL blocks as in the cases of (POE₂₀₀₀PCL₂₀₀₀)_n and (POE₂₀₀₀PCL₁₂₅₀)_n. T_g and T_c did not change very much during the 70-week degradation period.

CONCLUSION

Most of the degradation characteristics of POE–PCL multiblock obtained by step growth polymer-

ization of complementary bifunctional macromonomers are in good agreement with those of PCL-POE-PCL triblock copolymers reported in literature. Introduction of POE sequences did increase the hydrophilicity and decrease the crystallinity of the copolymers as compared with PCL homopolymers. Water absorption and weight loss rates were considerably increased. Nevertheless, molar mass decrease was very slow due to the phase separation between POE and PCL blocks. In fact, chain cleavage of PCL blocks proceeded very slowly, as in the case of PCL homopolymers. No preferential cleavage at ester-ether junctions was observed. The mobility of the POE blocks appeared enhanced on swelling in the aqueous medium and allowed further crystallization of PCL blocks. Degradation properties of these multi-block copolymers can be modulated by varying the lengths of both POE and PCL blocks, a finding of great importance for applications in the field of sustained drug delivery.

The authors are indebted to Ms. Sylvie Hunger and Mr. Xavier Dumont for technical aids and to Ms. Sylvie Tixier for helping editing the manuscript. The authors are also indebted to the National Science Fund of Bulgaria for financial support (Contract CH 435).

REFERENCES

1. S. J. Holland, B. J. Tighe, and P. L. Gould, *J. Controlled Release*, **4**, 155 (1986).
2. R. L. Dunn, in *Biomedical Applications of Synthetic Biodegradable Polymers*, J. O. Hollinger, Ed., CRC Press, Boca Raton, 1995, pp. 17-31.
3. S. M. Li and M. Vert, in *Degradable Polymers: Principles and Applications*, G. Scott and D. Gilead, Eds., Chapman & Hall, London, 1995, pp. 43-87.
4. K. J. Zhu, X. Z. Lin, and S. L. Yang, *J. Appl. Polym. Sci.*, **39**, 1 (1990).
5. H. R. Kricheldorf and J. Meier-Haack, *Makromol. Chem.*, **194**, 715 (1993).
6. X. M. Deng, C. D. Xiong, L. M. Cheng, and R. P. Xu, *J. Polym. Sci., Part C: Polym. Lett.*, **28**, 411 (1990).
7. Z. Jedlinski, P. Kurcok, W. Walach, H. Janeczek, and I. Radecka, *Makromol. Chem.*, **194**, 1681 (1993).
8. H. Younes and D. Cohn, *J. Biomed. Mat. Res.*, **21**, 1301 (1987).
9. P. Cerrai, M. Tricoli, L. Lelli, G. D. Guerra, R. Sbarbati Del Guerra, M. G. Casone, and P. Giusti, *J. Mat. Sci.: Mat. Med.*, **5**, 308 (1994).
10. P. Cerrai, G. D. Guerra, L. Lelli, M. Tricoli, R. Sbarbati Del Guerra, M. G. Casone, and P. Giusti, *J. Mat. Sci.: Mat. Med.*, **5**, 33 (1994).
11. R. Sbarbati Del Guerra, C. Cristallini, N. Rizzi, R. Barsacchi, G. D. Guerra, M. Tricoli, and P. Cerrai, *J. Mat. Sci.: Mat. Med.*, **5**, 891 (1994).
12. S. G. Wang and B. Qiu, *Polym. Adv. Technol.*, **4**, 363 (1993).
13. Y. X. Li, C. Volland, and T. Kissel, *J. Control. Rel.*, **32**, 121 (1994).
14. I. Rashkov, N. Manolova, S. M. Li, J. L. Espartero, and M. Vert, *Macromolecules*, **29**, 50 (1996).
15. S. M. Li, I. Rashkov, J. L. Espartero, N. Manolova, and M. Vert, *Macromolecules*, **29**, 57 (1996).
16. C. G. Pitt, A. R. Jeffcoat, R. A. Zweidinger, and A. Schindler, *J. Biomed. Mat. Res.*, **13**, 497 (1979).
17. C. G. Pitt, M. M. Gratzl, A. R. Jeffcoat, R. A. Zweidinger, and A. Schindler, *J. Pharm. Sci.*, **68**, 1534 (1979).
18. S. M. Li, J. L. Espartero, P. Foch, and M. Vert, *J. Biomater. Sci.: Polym. Ed.*, **8**, 165 (1996).
19. M. C. Tanzi, P. Verderio, M. G. Lampugnani, M. Resnati, E. Dejana, and E. Sturani, *J. Mat. Sci.: Mat. Med.*, **5**, 393 (1994).
20. T. Petrova, N. Manolova, I. Rashkov, S. M. Li, and M. Vert, *Polym. Int.*, in press.
21. S. S. Shah, K. J. Zhu, and C. G. Pitt, *J. Biomater. Sci.: Polym. Ed.*, **5**, 421 (1994).