Thermal Degradation of Two Classes of Block Copolymers Based on Poly(lactic-glycolic acid) and Poly(ε-caprolactone) or Poly(ethylene glycol)

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Summary: Thermodegradative investigations of two classes of multi-block copolymers containing poly(D,L-lactic-glycolic acid) (PLGA) and either poly(ethylene glycol) (PEG) or poly(ε-caprolactone) diol-terminated (PCDT) segments were performed. In particular, the influence of the type and length of the segments as well as of the molar ratio between the D,L-lactic acid (LA) and glycolic acid (GA) residues was investigated at 180°C in air by viscometry, FT-IR analysis and isothermal thermogravimetry. The thermal oxidative degradation of these materials is largely affected by the LA/GA ratio, a higher LA content generally imparting higher stability. The FT-IR analysis suggests that, depending on the composition of the PLGA segments, degradative processes are triggered which can lead to a preferential degradation of the blocks.

Introduction

Poly(lactic-glycolic acid) (PLGA) belongs to a family of biocompatible and bioerodible polymers currently employed in the biomedical field as surgical materials, matrices for bone reparation, scaffolds for tissue regeneration, drug delivery systems [1-5] *etc.* Polymers with variable lactic acid (LA) over glycolic acid (GA) molar ratios, or containing D,L-lactic acid mixtures, can be prepared to modulate the properties of these materials and to optimise their performance in view of the specific involved applications. To that purpose, PLGA have also been copolymerised with other polymers [4,6]. Such materials are often subjected to thermal treatments, for instance during moulding or sterilisation, which can induce polymer degradation, thus affecting both their mechanical properties and their performance in vivo [7-11]. Therefore, the knowledge of their calorimetric properties and thermal stability is of great

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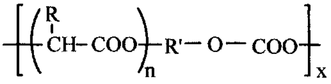
interest from the technological point of view.

In recent years we have developed a procedure to synthesise poly(ester-carbonate)s with variable structures. In particular, our attention has focused on two classes of multi-block copolymers containing segments of poly(D,L-lactic-glycolic acid) and of diol-terminated poly(ε-caprolactone) (PCDT) or poly(ethylene glycol) [12-14]. The copolymers thus obtained (PLGA-PCDT and PLGA-PEG, respectively) contain blocks linked to each other through carbonate or ester linkages:



$$\left[\left(\overset{\mathrm{R}}{\overset{|}{\mathrm{CH}}}-\mathrm{COO}\right)_n-\mathrm{R'}-\mathrm{O}-\mathrm{COO}\right]_x$$

where:

$R = H$ or CH_3

$R' = \left[(CH_2)_5\text{-}COO\right]_a CH_2\text{-}CH_2\left[OCO-(CH_2)_5\right]_b$ in **PLGA-PCDT**

$R' = -CH_2-\left(CH_2OCH_2\right)_m-CH_2-$ in **PLGA-PEG**

Previous investigations showed that semicrystalline or amorphous materials endowed with different calorimetric properties and susceptibility to hydrolytic degradation can be obtained varying the copolymer composition [15-16]. More recently, their thermal stability was also studied by TGA, from room temperature to 650°C, both under nitrogen and air flow [17]. It was concluded that PLGA-PCDT and PLGA-PEG do not exhibit any noticeable weight loss at temperatures lower than about 200–250°C. However, processes that lead to polymer degradation might be active at those temperatures even if they could not be detected by TGA for the absence of appreciable volatilisation under the analytical conditions adopted (scanning rate = 20°C/min, flow rate = 20 ml/min). Therefore, the aim of this paper is to report the results of more extensive studies on the thermal stability of the above copolymers. To that purpose they were annealed in air at 180°C and their behaviour was monitored by isothermal TGA, viscometry and FT-IR analysis. For comparison, the homopolymers constituting the blocks were also investigated by the same techniques.

Experimental Part

Instruments

TGA analysis was run by a Mettler TC11 Thermal Analyser Processor equipped with a Mettler TG50 microbalance, heating samples of about 20 mg into alumina crucibles at 180 °C under air flow (10 ml/min). The FT-IR spectra were recorded on a Jasco 5300 FT-IR spectrophotometer by casting from chloroform on KBr windows. Viscometric determinations were performed in chloroform at 30°C by means of Ubbelohde viscometers.

Materials

PCDT oligomers, PEO and high molecular weight PLGA50/50 ($\overline{M}_w$= 50,000-75,000), PLGA75/25 ($\overline{M}_w$= 75,000-120,000) and PCL ($\overline{M}_w$ = 65,000, $\overline{M}_n$ = 42,500) were purchased from Aldrich Co. PLGA oligomers, PLGA-PCDT, PLGA-PEG and PLA-PEG block-copolymers were synthesised as previously described [12-14].

Film preparation

Materials used for viscometric and FT-IR studies were films obtained by casting from chloroform solutions (c = 70 mg/ml). Each film was prepared pouring exactly 1 ml of solution into a 15 x 100 mm test tube and allowing the solvent to evaporate first at room pressure and then at 0.1 mmHg up to constant weight. For each material a number of replicate films were prepared. Samples of the desired material were annealed in an oven at 180°C. At intervals (after 15, 30, 60, 120 or 240 minutes), they were withdrawn from the oven, put in a desiccator, allowed to cool to room temperature and analysed.

Results and Discussion

Copolymers with different LA/GA ratios and different segment lengths were investigated to analyse the influence of structure on the degradative behaviour of the materials. Segments of poly(D,L-lactic acid) (PLA) and of PLGA with two LA/GA molar ratios typically employed in the biomedical field (50/50 and 75/25) were considered. For every ratio, PCDT segments with molecular weight 530, 1250 and 2000, respectively, or PEG segments having molecular weight 2000 were used. The composition of the copolymers investigated and the molecular weight of segments are summarised in Table 1. The molecular weight values were obtained by size exclusion chromatography (SEC) using a polystyrene calibration curve.

Table 1. Molecular weight characterisation of block copolymers.

Code	Starting oligomers				Block copolymers			
	PLGA		Diol		$[\eta]$[a]	$\overline{M}_n$[b]	$\overline{M}_w$[c]	D[d]
	M_r[e]	$\overline{M}_n$[f]	Type	$\overline{M}_n$	(dl/g)	$x10^{-3}$	$x10^{-3}$	
PLGA50/50 - PCDT530	1:1	1920	PCDT	530	0.40	8.4	31.5	3.7
PLGA50/50 - PCDT1250	1:1	1920	PCDT	1250	1.20	22.0	114.7	5.2
PLGA50/50 - PCDT2000	1:1	1920	PCDT	2000	0.82	27.0	113.7	4.2
PLGA75/25 - PCDT530	3:1	2830	PCDT	530	0.81	18.0	97.1	5.4
PLGA75/25 – PCDT1250	3:1	2830	PCDT	1250	1.49	26.6	133.7	5.0
PLGA75/25 – PCDT2000	3:1	2830	PCDT	2000	1.45	22.8	123.9	5.4
PLGA50/50-PEG2000	1:1	1920	PEG	2000	1.55	197	370	1.9
PLA-PEG2000	-	3050	PEG	2000	1.63	119.5	301.2	2.5

[a] Intrinsic viscosity in chloroform at 32 °C.

[b] Number-average molecular weight evaluated by SEC using polystyrene narrow standards.

[c] Weight-average molecular weight evaluated by SEC using polystyrene narrow standards.

[d] Polydispersity index $\overline{M}_w/\overline{M}_n$.

[e] LA:GA molar ratio.

[f] Determined by end-group titration.

Isothermal TGA

The copolymers containing PCDT or PEG segments of molecular weight 2000 were analysed by isothermal TGA in air, at 180°C, for 240 min. The traces of PLGA-PCDT2000 copolymers are reported in Figure 1 along with those of the corresponding homopolymers. PLGA75/25 and PLGA50/50 exhibit comparable weight loss (WL) while PCL is more stable. Interestingly, the volatilisation rate of PLGA75/25-PCDT2000 is very similar to that of PCL, whereas it is much higher in PLGA50/50-PCDT2000. Figure 2 shows the results obtained for the copolymers with PEG and parent homopolymers. PEO undergoes rapid degradation when heated in air, in agreement with data reported in literature [18]. PLGA-PEG copolymers show a higher WL than PLGA-PCDT, but it is less remarkable than in PEO. In addition, while the WL of PLA-PEG2000 increases almost linearly with time, a more complex trend is exhibited by PLGA50/50-PEG2000, suggesting that different degradative processes are active in these materials. Again, the copolymer with a lower LA content degrades faster, even if the difference becomes less pronounced with time. Therefore in both families of copolymers the thermoxidative stability seems to be enhanced by the presence of a higher LA content.

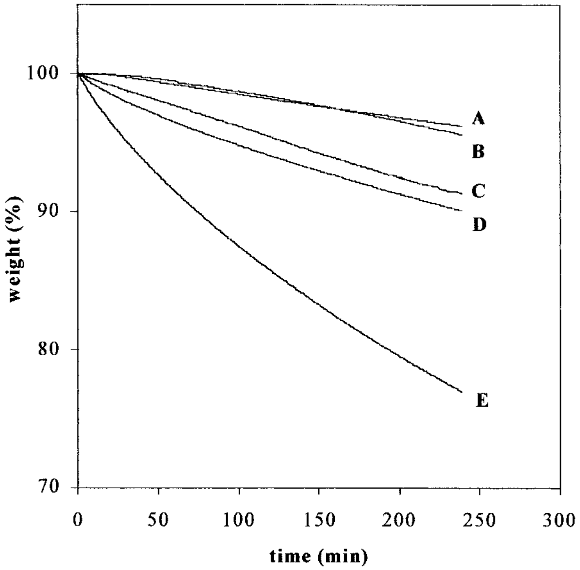


Figure 1. Weight percentage *vs.* heating time at 180°C in air for PLGA75/25-PCDT2000 (A), PCL (B), PLGA50/50 (C), PLGA75/25 (D) and PLGA50/50-PCDT2000 (E).

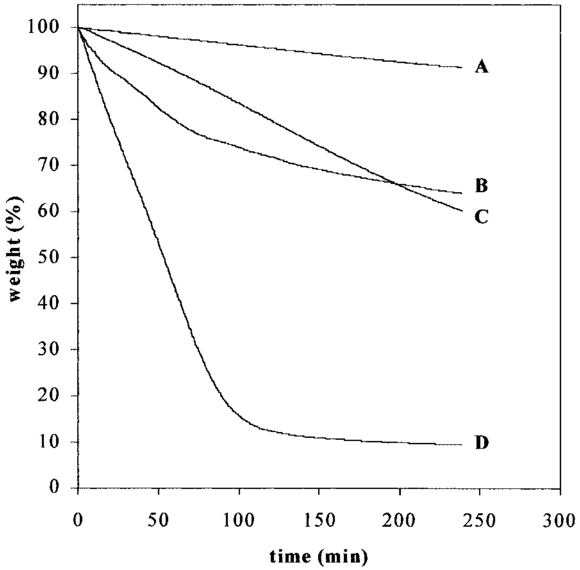


Figure 2. Weight percentage *vs.* heating time at 180°C in air for PLGA50/50 (A), PLGA50/50-PEG2000 (B), PLA-PEG2000 (C) and PEO 200,000 (D).

Viscometric investigations

The molecular weight of copolymers was monitored as a function of the heating time by viscometry. Films of these materials obtained by casting from chloroform were heated in air at 180°C for different periods of time, then they were dissolved in chloroform and their η_{sp}/c was determined. The results are shown in Figure 3 for PLGA-PCDT copolymers and parent homopolymers. Surprisingly, the viscosity of PLGA75/25, PLGA50/50 and PCL exhibits a maximum after around 15 min and then gradually decreases. In contrast, the viscosity of all PLGA-PCDT copolymers strongly decreases in the first 30 minutes and then reaches a plateau. It may be noticed that higher viscosity drops are exhibited by PLGA50/50 copolymers. It was impossible to measure the viscosity of PLGA50/50-PCDT1250 and PLGA50/50-PCDT2000 for t = 240 min since they could not be dissolved. Most probably some degree of crosslinking occurred in the above materials upon heating. A comparison of the FT-IR spectra of crosslinked (t = 240 min) and un-crosslinked (t = 120 min) materials did not allow to gather evidences about the crosslinking mechanism.

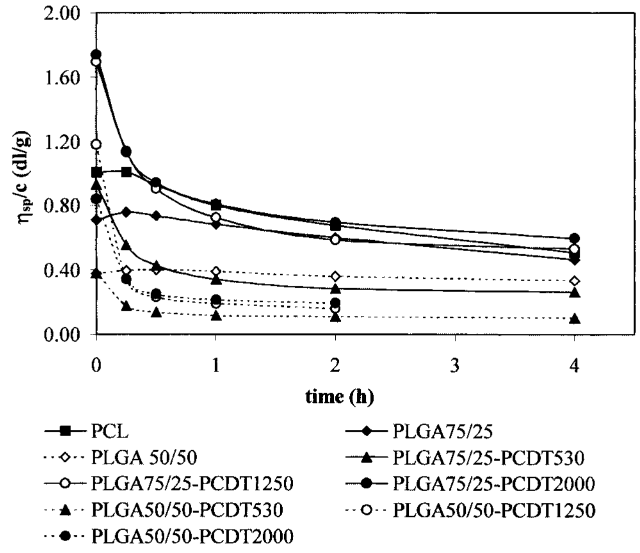


Figure 3. Viscosity *vs.* heating time for PLGA-PCDT copolymers treated at 180°C in air.

The initial increase in viscosity found for commercial homopolymers might be explained supposing that volatile products are already present in these samples and are lost owing to the high temperature. Alternatively, degradative reactions leading to the simultaneous formation of higher molecular weight chains and volatile oligomers might occur, as reported by Watchsen *et al.* for oligomeric PLLA [20]. To assess the presence of volatile products, films of the commercial samples were dried *in vacuo* at 0.1 torr and 50°C for 1 week, then their viscosity was determined. A slight increase in viscosity was observed but it was lower than in heated samples, therefore neither hypothesis could be discarded.

An appreciable WL does not accompany the viscosity decrease in PCL even if elimination of caprolactone has been reported for PCL pyrolised by mass spectrometry [21].

The PLGA75/25-PCDT copolymers are more stable than PLGA50/50-PCDT. Anyway, all multiblock copolymers, when heated at 180°C, undergo a dramatic viscosity drop in spite of the relatively good stability exhibited by the polymers constituting their blocks. This behaviour is probably the consequence of the weakness of chemical bonds linking the segments, which are bound each other alternatively through an ester and a carbonate group. The blocks being themselves polyesters, it seems unlikely that the introduction of a further ester function can affect the stability so dramatically and therefore it seems reasonable to suppose that the carbonate groups constitute "weak points" where degradative phenomena can start.

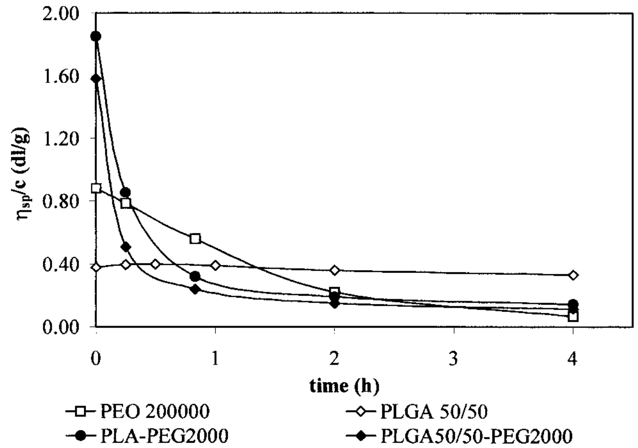


Figure 4. Viscosity *vs.* heating time for PLGA-PEG copolymers treated at 180°C in air.

A similar trend is observed for PLGA-PEG copolymers (Figure 4). The viscosity of PEO decreases considerably and almost linearly over the first two hours, but a much more rapid drop is exhibited by PLA-PEG2000 and PLGA50/50-PEG2000. As in the case of PLGA-PCDT, it is initially more pronounced for the copolymer with the higher GA content.

Nevertheless, while in that case relatively high viscosity values are found for the PLGA75/25-PCDT copolymers even after four hours, in this case the viscosity of both copolymers is drastically reduced within the first hour. This is probably a consequence of the higher susceptibility to thermoxidative degradation of the PEG segments compared to the PCDT segments and it is in agreement with the findings of thermogravimetric analysis.

FT-IR analysis

FT-IR spectra of films treated at 180°C were recorded to monitor possible modifications of polymer structure, which might provide some insight into the mechanism of polymer degradation. PLGA and PCL spectra of samples annealed at 180°C for 240 min are superimposible on those of original polymers. The same happens with PLGA75/25-PCDT but not with PLGA50/50-PCDT copolymers. In the latter, in fact, there are evidences for a preferential degradation of PLGA in comparison with the PCDT segments. For instance, as reported in Figure 5, in PLGA50/50-PCDT2000 the intensity of the PLGA carbonyl band (band A, 1760 cm^{-1}) decreases with the heating time compared to that of PCDT (band B, 1726 cm^{-1}). In PLGA75/25-PCDT2000 no evidence for such preferential degradation of PLGA segments is found, the relative height of the bands being unaffected by heating.

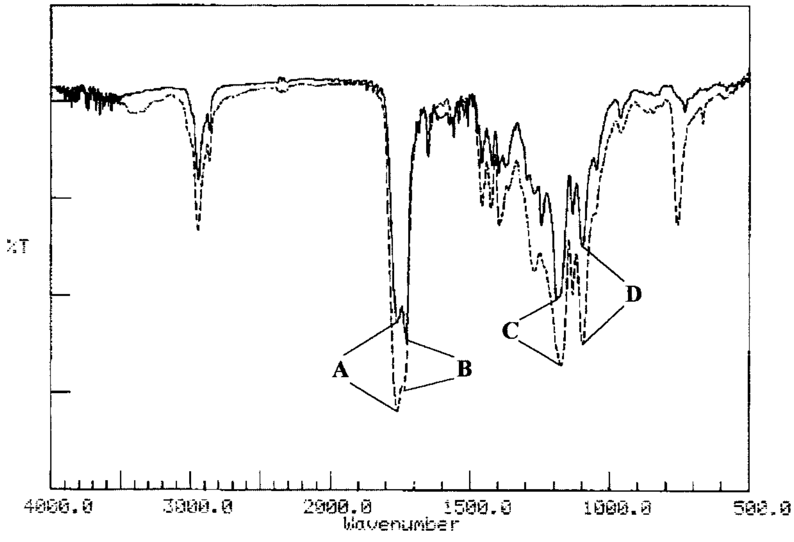


Figure 5. FT-IR spectrum of native PLGA50/50-PCDT2000 (broken line) and of the same polymer after heating in air at 180°C for 4 hours (solid line).

In the copolymers containing shorter PCDT blocks only a single carbonyl band is observed at 1760 cm^{-1}, and therefore it is unsuitable to monitor degradative phenomena. To that purpose, however, the bands located at 1175 cm^{-1} (band C, CO-O stretching of PCDT and PLGA) and 1095 cm^{-1} (band D, O-C-C stretching of PLGA) can be considered. If their relative intensity in samples heated for 240 min is compared with that of the unheated samples, it can be observed that, while in all PLGA75/25-PCDT copolymers no appreciable difference exists, in the PLGA50/50-PCDT samples the intensity of the band at 1095 cm^{-1} decreases relative to that at 1175 cm^{-1} after the thermal treatment. Therefore the FT-IR investigations demonstrate that in the PLGA50/50-PCDT multi-block copolymers the PLGA50/50 segments have a greater susceptibility than the PCDT segments towards thermoxidative degradation.

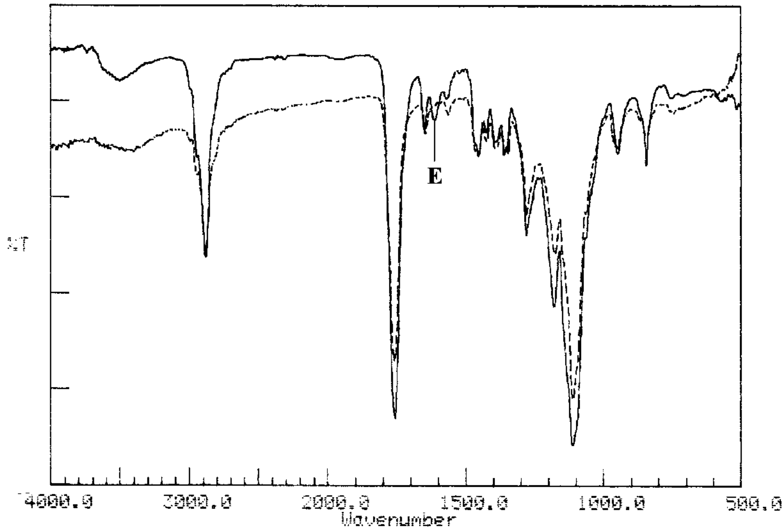


Figure 6. FT-IR spectrum of native PLGA50/50-PEG2000 (broken line) and of the same polymer after heating in air at 180°C for 4 hours (solid line).

A different behaviour can be inferred from the analysis of the spectra of PLGA-PEG copolymers. The most important modification in the spectrum of PLGA50/50-PEG2000 after thermal treatment is the appearance of an absorption at 1613 cm^{-1} (band E in Figure 6). This may suggest that PEG segments degrade forming vinyl ether end-groups, in agreement with the mechanism proposed for the degradation of ethylene glycol based polyesters and copolyesters [19]. No evidence for the presence of such functions can be found in the spectrum of thermally treated PLA-PEG2000, which presents the same bands as untreated PLA-PEG2000. Therefore it is evident that, as in the case of PLGA-PCDT, the LA/GA ratio has a large influence on the degradation mechanism of these copolymers.

Conclusions

The isothermal investigations run in air at 180°C on the PLGA-PCDT and PLGA-PEG copolymers showed that these materials undergo degradative processes which are largely affected both by the type of segments and by the LA/GA ratio. In general, the stability is higher for the PLGA-PCDT copolymers and it increases with the LA content. A rapid molecular weight drop, which may be a consequence of the weakness of carbonate bonds connecting the blocks, takes place in all copolymers upon heating. The FT-IR analysis suggests that, depending on the composition of the PLGA segments, the degradative processes can lead to a preferential degradation of the blocks. Further studies will be necessary to elucidate how the LA/GA ratio can so largely affect the thermodegradative behaviour of these materials.

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