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High-performance liquid chromatographic determination of some of the hydrolytic decomposition products of poly(α-hydroxyacid)s

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Abstract

An HPLC procedure is described for the separation and identification of some hydrosoluble by-products resulting from the hydrolytic degradation of poly(α-hydroxyacid)s having biomedical interest: poly(L-lactide), poly(DL-lactide), poly(glycolide) and poly(lactide-co-glycolide). Peak identification was performed by comparing the respective retention times with those of pure standards. It was observed that optimum shape and separation of peaks are considerably affected by the composition of the mobile phase, consisting of acetonitrile (A) and a 0.006 *M* K_2HPO_4 buffer (B), and, in particular, its pH and A:B ratio, which had to be adjusted to around 5.8 and 75:25 (v/v), respectively. Under the investigated experimental conditions (aqueous suspension, 100°C for 12 h under stirring), poly(L-lactide) is quite stable, poly(glycolide) degrades easily to glycolic acid, whereas poly(DL-lactide) and poly(DL-lactide-co-glycolide) exhibit intermediate behaviour. Upon hydrolytic decomposition, these poly(α-hydroxyacid)s yield not only the corresponding acids, but also their linear dimers and, possibly, trimers, tetramers and higher oligomers.

Keywords: Poly(α-hydroxy acid); Poly(lactide); Poly(glycolide); Poly(lactide-co-glycolide)

1. Introduction

Among the poly(α-hydroxyacid)s, poly(lactic acid) and stereocopolymers, poly(glycolic acid) and poly(lactic acid-co-glycolic acid) are the most studied and used synthetic biodegradable, biocompatible, bioresorbable polymers in the medical and pharmaceutical fields [1,2].

In particular, they have found wide acceptance, or are being developed, as materials for surgical sutures, osteosynthesis and drug carriers in controlled release systems [3,4]. This stems from their versatility, intrinsic mechanical properties, and degradation behaviour in aqueous environments such as the body fluids, which proceeds through a simple hydrolytic mechanism and yields a series of by-products that are eventually metabolized to carbon dioxide and water or excreted via the kidneys [5].

The degradability of these materials, which are generally prepared by catalytic ring opening polymerization of the cyclic dimers of the corresponding acids [6–9], has been extensively studied, either in vivo or in vitro [10–12]; however, at least to the best of our knowledge, degradation rate and mechanism have so far been investigated by following the fate of the solid component, that is monitoring the time-dependent changes of its physico–mechanical properties, molecular mass, structure, morphology, etc. [13–20]. In contrast, little or no attention has been

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devoted to the hydrolytic by-products that the substrate releases into the mother liquor.

The knowledge of both the type and amount, as well as evolution in time of the hydrosoluble decomposition products of the system, is important for at least two reasons: first, because it leads to a better understanding of degradation kinetics and mechanism; second, because these hydrosoluble species could affect, depending on their nature and concentration, the reaction of the living tissue [21]. A recent paper describes a study on the hydrolytic degradation of poly(lactide-co-glycolide) by monitoring not only the time changes of the solid phase, but also the degradation products in degradation medium. However, the investigation is limited to the determination of the amounts of lactic and glycolic acids by titration [22].

This work describes a simple and rapid high-performance liquid chromatography (HPLC) procedure for the identification and quantitative determination of most of the soluble species resulting from the hydrolytic decomposition of the above mentioned materials under controlled conditions.

The application of this method to investigate degradation rate and mechanism will be reported in a subsequent paper.

2. Experimental

2.1. Chemicals

Pure DL-lactide (3,6-dimethyl-1,4 dioxane-2,5-dione), 98% purity, was purchased from Purac Biochem (Gorinchem, Netherlands). Glycolide S (1,4-dioxane-2,5-dione), poly(L-lactide) (Resomer L 210, intrinsic viscosity (I.V.) in $CHCl_3$ at 35°C=3.6 dl/g), poly(DL-lactide) (Resomer R 207, I.V.=3.6 dl/g), poly(glycolide) (Resomer G 205, I.V.=1.5 dl/g), poly(DL-lactide-co-glycolide), 85:15 (mol/mol) (Resomer RG 858, I.V.=1.4 dl/g) were purchased from Boehringer (Ingelheim, Germany). The above polymers were used as received for degradation studies. Pure DL-lactic acid, 96% purity, was obtained by hydrolysis, at 90°C for 20 h, of DL-lactide. Pure glycolide was obtained either by sublimation at 120°C under vacuo or by crystallization from chloroform of the corresponding commercial product. Monobasic potassium phosphate was obtained from Carlo Erba (Milan, Italy). Acetonitrile and water for HPLC were obtained from Merck (Darmstadt, Germany).

2.2. HPLC apparatus

The HPLC instrument used was a Varian (Palo Alto, CA, USA) Model 5560, equipped with a Rheodyne (Cotati, CA, USA) 7125 injection valve and a 10-μl loop, a diode-array Varian Polychrome 9060 detector, a DS 651 data station and a Spectra-Physics (San Jose, CA, USA) SP 4270 integrator. The analytical column was a 5-μm Varian Bondesil SAX (25 cm×4.6 mm I.D.), code 1215-7033.

2.3. Preparation of the standard solutions and of the HPLC eluent

The standard solutions of glycolic acid, lactic acid and their corresponding linear dimers, were prepared by dissolving the acids (1000 ppm, w/v) in a water–acetonitrile (25:75, v/v) mixture at room temperature. The resulting solutions were stored at 3°C under dry, inert atmosphere. Under these conditions, glycolic and lactic acids and the linear dimer of lactic acid are stable for weeks, whereas the linear dimer of glycolic acid lasts unaltered only for days (both linear dimers tend to decompose into the corresponding monomeric acids). The reference samples for the identification of the linear dimers of glycolic and lactic acids (see Section 3.1) were prepared as follows: 1 g of glycolide or lactide was dissolved in 100 ml of water under stirring, at 50°C for 20 min in the case of glycolide and at 90°C for 30 min in the case of lactide, respectively. Under these conditions, it was found (^{13}C NMR) that the cyclic dimers of the acids transform quantitatively into the corresponding linear dimers. After rapid cooling at room temperature, the water solution was extracted with ethyl acetate (three times with 50 ml ethyl acetate each time) and then the organic phase was eliminated by distillation until dry. The residue consisted of colorless dendritic crystals, melting at 104.8°C (differential scanning calorimetry) in the case of dimer of glycolic acid, and of a viscous oil in the case of dimer of lactic acid. The purity of both compounds

was estimated higher than 98%, based on the area fractions of the relevant HPLC peaks.

2.4. Hydrolytic decomposition of the poly(α-hydroxyacid)s

A 0.25-g quantity of each polymer was finely ground (particle size in the 0.5–1 mm range) in order to minimize any morphological effect of the starting materials, then suspended in 25 ml of water and finally submitted to a thermal treatment at 100°C for 12 h under reflux and stirring. The suspension was let to settle at room temperature, then an aliquot of the supernatant liquid was drawn and diluted with acetonitrile (75%, v/v). This represents the hydrolytic polymer solution.

2.5. HPLC analysis

A 10-μl volume of the respective hydrolytic polymer solutions, or an equivalent volume of the standard solutions, or a standard mixture obtained by mixing known volumes of the standard solutions of the acids and their linear dimers, was injected into the chromatograph by means of a sample loop. The HPLC eluent was obtained by mixing (75:25, v/v) two solutions, A and B, respectively; A was pure acetonitrile and B was a 0.06 *M* solution of KH_2PO_4 in water; the resulting solution keeps unchanged for weeks at room temperature. The chromatographic conditions were: flow-rate, 1 ml/min; column temperature, 30°C; detector wavelength, 210 nm.

The analytes in the standard mixture and in the various hydrolytic solutions were identified by comparing the retention times of the relevant peaks with those of the corresponding standards injected separately. No distinction could be made between D-lactic acid and L-lactic acid.

Quantitative determination of each compound was effected by the external standard chromatographic method, i.e. by comparison of peak areas obtained with the sample and the standard solutions.

2.6. NMR analysis

For NMR analysis, the samples of DL-lactic acid, DL-lactide, glycolic acid, glycolide and their presumed linear dimers, obtained as described in Section 2.3, were dissolved (1–1.5 g/ml) in deuterated acetone at room temperature.

The ^1H and ^{13}C NMR spectra were acquired on a Bruker AC-200 spectrometer, equipped with an Aspect 3000 computer, operating at 200.13 and 50.32 MHz, respectively. For the ^1H spectra the following conditions were used: pulse angle=15°, pulse width=1 μs, delay between two successive pulses=1 s; for each measure 32 free induction decays were recorded at room temperature. For the ^{13}C spectra, after some trials, the following conditions were found to be optimum: pulse angle=15°C, delay between two successive pulses=30 s, number of free induction decays=512. The reference signal was that of tetramethylsilane.

3. Results and discussion

3.1. Identification of the linear dimers of glycolic and lactic acids

The ^1H NMR spectrum of the presumed linear dimer of glycolic acid shows three peaks at 4.22, 4.68 and 7 ppm, respectively; the peaks at 4.22 and 4.68 ppm exhibit the same area. In addition, the areas of the four signals in the ^{13}C spectrum, centered respectively at 60.64, 60.99, 169.25 and 172.93 ppm, also tend to be the same. The presumed linear dimer of lactic acid shows five ^1H signals at 1.3, 1.4, 4.3, 5.0 and 7.5 ppm, and six ^{13}C signals at 17.1, 20.52, 67.2, 69.2, 172.6 and 175.1 ppm.

The FT-IR spectrum of the presumed dimer of glycolic acid shows remarkable differences compared to the spectra of glycolic acid and glycolide and, in particular (Fig. 1): a split absorption band (3409 and 3456 cm^{-1}) in the zone of O-H stretching, and the presence of both a carboxyl stretching absorption band at 1734 cm^{-1} and a carbonyl stretching absorption band at 1762 cm^{-1}. The spectrum of the presumed linear dimer of lactic acid is closer to that of lactic acid and lactide; on the other hand differences do exist, especially in the zone of carbonyl and carboxyl stretching frequencies (Fig. 2). GC–MS fragmentation patterns of the presumed linear dimers, treated with trimethylchlorosilane, are compatible with the presence of molecular ions having mass 263 and 291 in the case of glycolic acid

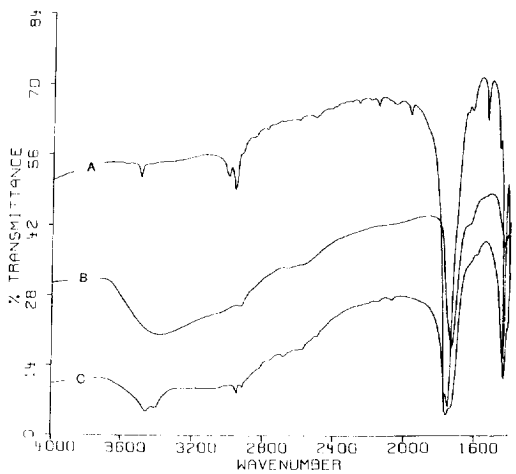


Fig. 1. FT-IR spectra (Nicolet 20SXB) of (A) glycolic acid, (B) glycolide and (C) linear dimer of glycolic acid (KBr discs).

and lactic acid derivatives respectively, which correspond to the masses of the fully silylated compounds, minus a methyl group. Direct determination of molecular mass by vapor pressure osmometry (Hewlett-Packard instrument Mechrolab, acetonic solutions) gave the following values: found 135 g/mol (theoretical 134 g/mol) and found 160 g/mol (theoretical 162 g/mol) for the presumed linear dimers of glycolic acid and lactic acid respectively.

Based on the above results, we can safely state that the analyzed compounds are actually linear dimers of glycolic and lactic acids having the following molecular structures, respectively (Scheme 1).

The ^{13}C NMR signals at 60.64, 60.99, 169.25 and 172.93 ppm, present in the spectrum of the linear dimer of glycolic acid, have been tentatively assigned to the methylene carbon (2), the methylene carbon (4), the carbonyl carbon (3) and the carboxyl carbon (1), respectively. In the case of the linear dimer of lactide, the signals at 17.1, 20.52, 67.2, 69.2, 172.6 and 175.1, have been assigned respectively to the methyl carbon (2), the methyl carbon (5), carbon (4), carbon (1), the carbonyl carbon (3) and the carboxyl carbon (6).

3.2. HPLC determination of the hydrosoluble hydrolytic decomposition products of poly(α-hydroxyacid)s

As Fig. 3 shows, under the above reported experimental conditions, apart from some peaks that appear outside the zone of interest and are due to the injection solvent, the HPLC chromatogram of a standard mixture of DL-lactic acid, glycolic acid and their linear dimers, shows symmetrical and well resolved peaks, having reproducible retention times, thus making possible the attribution of the various peaks by matching their retention times with those of the standards and allowing qualitative and quantita-

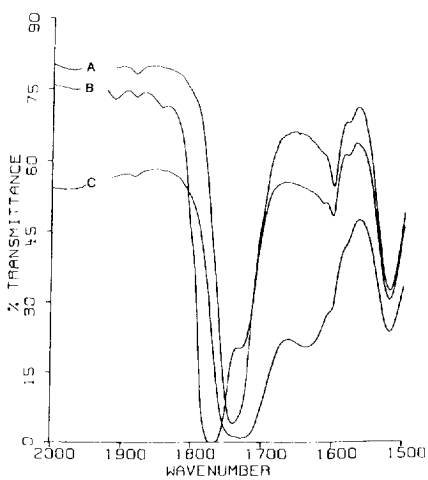
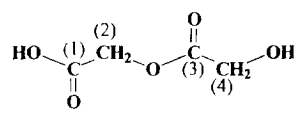
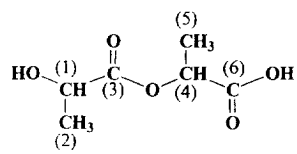


Fig. 2. FT-IR spectra (Nicolet 20SXB) of (A) DL-lactic acid, (B) DL-lactide and (C) linear dimer of DL-lactic acid (2.5%, w/v, chloroform solutions in NaCl capillary cells).



linear dimer of glycolic acid



linear dimer of DL - lactic acid

Scheme. 1. Molecular structures of the linear dimers of glycolic and lactic acid.

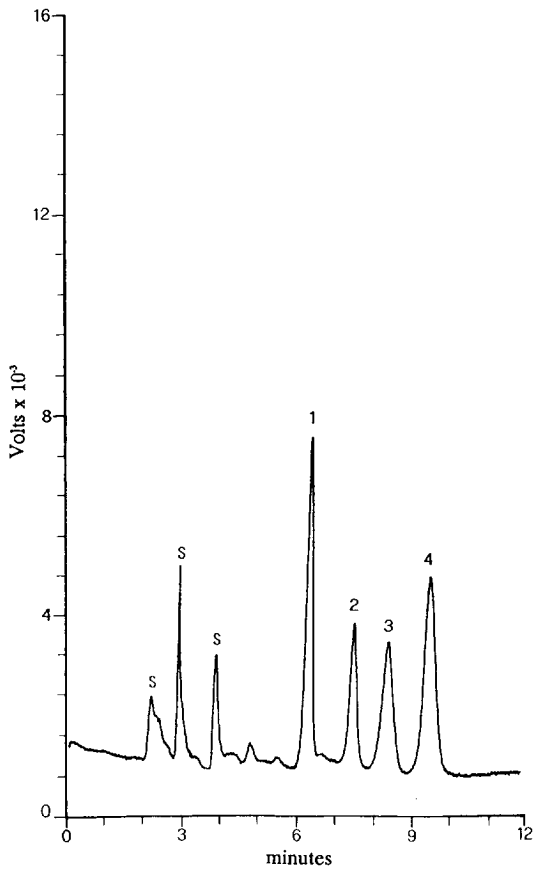


Fig. 3. HPLC chromatogram of a standard mixture of (1) linear dimer of lactic acid, (2) DL-lactic acid, (3) linear dimer of glycolic acid, (4) glycolic acid. (S) Peaks present in the solvent used for sample injection. Injected amount of each component, about 5 μg. See text for HPLC operating conditions.

tive analysis of the various analytes. In relation to this, the composition of the mobile phase is particularly critical; actually, the concentration of the buffer component and thus the pH of the resulting solutions can lead to considerably different chromatographic profiles: when the eluent composition is acetonitrile (A)–0.06 *M* KH_2PO_4 (B) (75:25, v/v) and the pH is 5.8, it is possible to obtain the optimum profile depicted in Fig. 3. When the composition is changed to A–B–water (75:12.5:12.5, v/v) and the pH is 6.1, a chromatogram is observed characterized by a poor resolution and a considerable broadening of the various peaks which, in addition, show unsymmetrical shapes. Finally, an eluent resulting from A–B–water (50:25:25, v/v) (pH 5.6), leads to a chromatogram where the various peaks appear very sharp and symmetrical, but tend to be much less resolved than in the optimal case; in particular, the peaks relevant to DL-lactic acid and the linear dimer of glycolic acid tend to merge into a single peak. It is believed that the former, undesirable situation, likely arises from the role the H^+ ions play in affecting certain ionic equilibria: when the pH is higher than 6, the H^+ concentration is insufficient to shift the acid–base equilibrium of the analytes having acid nature towards the associated form: $RCOO^- + H^+ \rightarrow RCOOH$. This results in peak broadening or even splitting due to the simultaneous occurrence of the analyte in its associated and dissociated forms. On the other hand, when the concentration of the organic component is relatively low, an insufficient resolution of the peaks is observed, even if they are characterized by symmetrical and narrow shapes.

It is important to note that a concentration of acetonitrile higher than 75% (v/v) in the mobile phase should be avoided as it would bring about the precipitation of the buffer salt and thus considerable damage to the HPLC instrument, pump, valves and column in particular.

Also, it is advisable that the sample solutions and the eluent have about the same concentration of acetonitrile (75%, v/v). Actually, when the acetonitrile concentration is different, some spurious peaks appear on the chromatogram, probably due to a lack or excess of the buffer salt in the mobile phase, which could cause difficulties in the correct integration of peak areas and lead to systematic errors in the quantitative determination of some analytes.

Figs. 4–7 show the chromatograms of the solutions resulting from the hydrolytic decomposition of poly(glycolide), poly(L-lactide), poly(DL-lactide) and poly(DL-lactide-co-glycolide), respectively. The normalized yields of the hydrosoluble species deriving from the above reported hydrolytic polymer treatment (see Section 2.4), are reported in Table 1. As can be seen, if we exclude poly(L-lactide), which appears to be quite stable under the investigated degradation conditions, the other polymers release, in addition to the expected final degradation products, namely lactic acid or glycolic acid, a considerable amount of other by-products, some of which were identified as the linear dimers of the acids, whereas

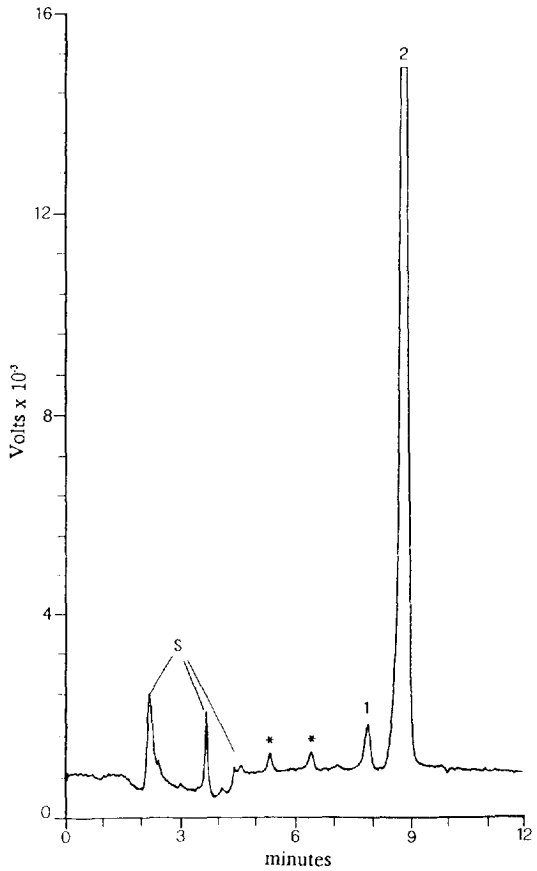


Fig. 4. HPLC chromatogram of the hydrolytic decomposition solution obtained from poly(glycolide) (Resomer G 205). (1) Linear dimer of glycolic acid, (2) glycolic acid, (*) unidentified peaks. (S) Peaks present in the solvent used for sample injection. See text for HPLC and hydrolysis conditions.

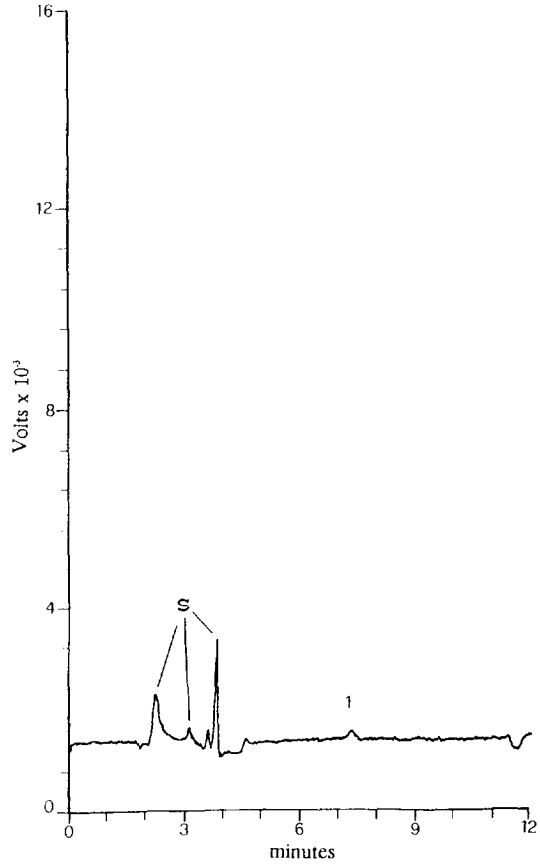


Fig. 5. HPLC chromatogram of the hydrolytic decomposition solution obtained from poly(L-lactide) (Resomer L 210). (1) DL-Lactic acid. (S) Peaks present in the solvent used for sample injection. See text for HPLC and hydrolysis conditions.

others might be tentatively identified, based on their retention times, as linear trimers, tetramers or higher oligomers.

Peaks S on chromatograms are not due to a particular eluent component, since the eluent chromatogram is perfectly flat. The peaks appear in any case when the sample solvent, either consisting of pure water, or acetonitrile, or the 75:25 (v/v) acetonitrile–water mixture is added to the mobile phase. Thus, the occurrence of these peaks is simply due to the well known fact that the injection of a solute disturbs the steady-state distribution of the UV-adsorbing component of the mobile phase. It is also known that this generally causes the appearance of multiple peaks in the chromatogram. Sample solvents were not identical with eluents for practical reasons. The use of sample solvents identical with eluents might have helped minimize the occurrence of system peaks; on the other hand, they appear outside the zone of interest. Finally, we cannot exclude displacement effects or interactions between sample components and eluent components, but these should be reasonably limited to the oligomer components we have not tried to identify.

3.3. Precision

The precision of the method was evaluated, under reproducibility conditions, on the basis of twelve

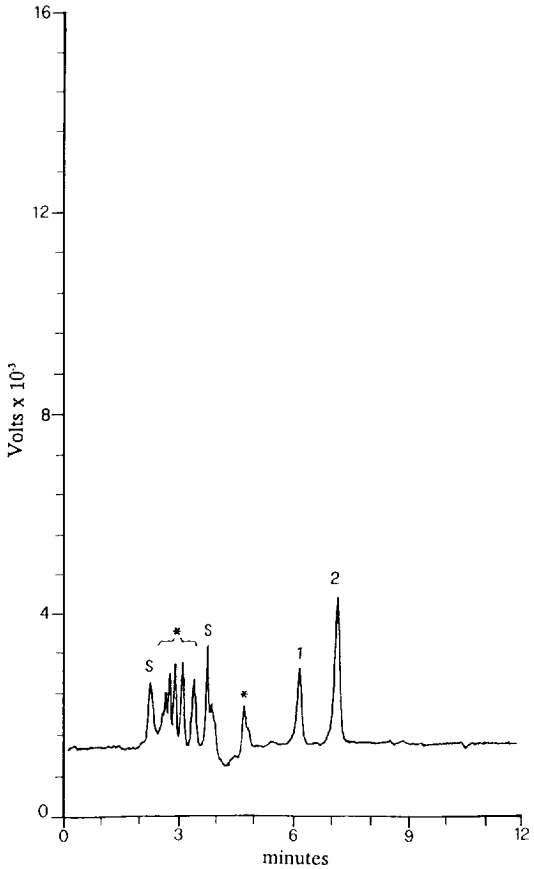


Fig. 6. HPLC chromatogram of the hydrolytic decomposition solution obtained from poly(DL-lactide) (Resomer R 207). (1) Linear dimer of lactic acid, (2) DL-lactic acid, (*) unidentified peaks. (S) Peaks present in the solvent used for sample injection. See text for HPLC and hydrolysis conditions.

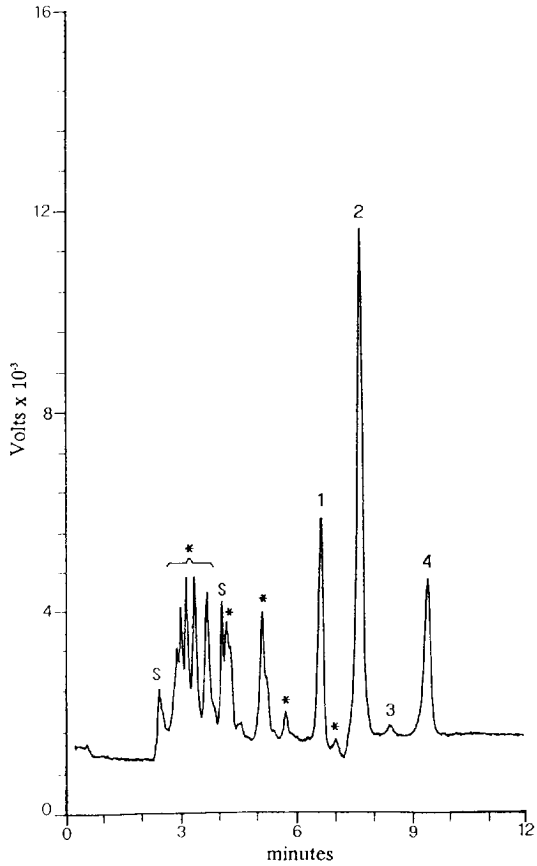


Fig. 7. HPLC chromatogram of the hydrolytic decomposition solution obtained from poly(DL-lactide-co-glycolide) (Resomer RG 858). (1) Linear dimer of lactic acid, (2) DL-lactic acid, (3) linear dimer of glycolic acid, (4) glycolic acid, (*) unidentified peaks. (S) Peaks present in the solvent used for sample injection. See text for HPLC and hydrolysis conditions.

independent runs performed on standard solutions containing about 1 mg/ml DL-lactic acid. Statistical treatment of experimental data gave the following results: standard deviation (S.D.)=0.0027, repeatability value (95% probability level) (R)= 0.0076. In order to check the linear range of the experimental setup, a series of five calibration standards was made with different concentrations of DL-lactic acid (0.1–1.5 mg/ml). A linear correlation was found by plotting the peak-area ratio y of the various solutions to that of a 1 mg/ml standard solution of DL-lactic acid, vs. the analyte concentration x, expressed in mg/ml (each run was duplicated and the data averaged). The parameters of the relevant linear equation: $y=a+bx$ were respectively $a=-4.17\times10^{-3}$ and $b=0.9938$ and the linear correlation coefficient r was 0.9995. As to the hydrolytic decomposition solutions, the precision of the method was simply evaluated based on duplicate runs performed at the concentration levels of the various components resulting from the treatment described in Section 2.4. The differences between duplicates were within the following values corresponding to the given concentration ranges of the various analytes: DL-lactic acid (0.4–1.5 mg/ml)=1.1–1.5%; glycolic acid (0.2–2.5 mg/ml)=2.4–0.5%; linear dimer of lactic acid (0.1–0.25 mg/ml)=3.2–5%; linear dimer of glycolic acid (0.02–0.08 mg/ml)=10%. The

Table 1
Normalized yields of hydrosoluble, hydrolytic decomposition by-products of poly(α-hydroxyacid)s.

Polymer	By-product (mol-%)			
	Lactic acid	Linear dimer of lactic acid	Glycolic acid	Linear dimer of glycolic acid
Poly(L-lactide)	1.0	N.D.		
Poly(DL-lactide)	12.4	1.2		
Poly(glycolide)			90.0	0.9
Poly(DL-lactide -co-glycolide)	51.0	3.4	86.7	1.4

See text for hydrolytic decomposition and HPLC conditions. N.D. = below detection limits.

detection limit for DL-lactic acid was estimated to be around 0.02 mg/ml.

3.4. Preliminary considerations on the degradability of the investigated poly(α-hydroxyacid)s

Glycolide and lactide, that are possibly incorporated as impurities in the corresponding polymers, cannot be determined using the present HPLC conditions, as the degradation rate of these components in aqueous media is faster than their elution time. Table 1 reports the normalized yields of the hydrosoluble, hydrolytic decomposition by-products of the investigated polymers (the quoted values are referred to the content of the corresponding repeating units in the starting polymer). Judging from the amount and nature of the hydrolytic decomposition by-products, it can be anticipated that the investigated materials exhibit a considerably different degradation rate and, perhaps, mechanism. As mentioned above, poly(L-lactide) is quite stable (1% degradation); on the contrary, poly(DL-lactide) decomposes more readily (13.6% degradation) into lactic acid, passing through a series of intermediates such as possibly oligomers and linear trimer, and, certainly, linear dimer compounds. This different behaviour is likely to be connected with the different stereoregularity of the starting products, which leads either to semicrystalline (46% crystallinity by WAXS) poly(L-lactide) or totally amorphous poly(DL-lactide). On the other hand, the 60% crystalline poly(glycolide) shows the fastest degradation rate (90.9% degradation), whereas the amorphous poly(lactide-co-glycolide) exhibits a behaviour which is intermediate between that of poly(glycolide) and poly(DL-lactide) (54.4% degradation of lactide units and 88.1% degradation of glycolide units). It is interesting to note that poly(lactide-co-glycolide) gives a hydrolytic decomposition solution in which the proportion of glycolic acid is far larger than expected based on simple stoichiometric considerations. In fact, the glycolide/lactide molar ratio in the starting copolymer is 0.176, whereas the glycolic acid to lactic acid ratio in the decomposition solution is 0.285. Thus, the glycolide moiety of the macromolecule is clearly intrinsically more prone to hydrolytic decomposition than the lactide segment. In any case, the hydrolytic degra-

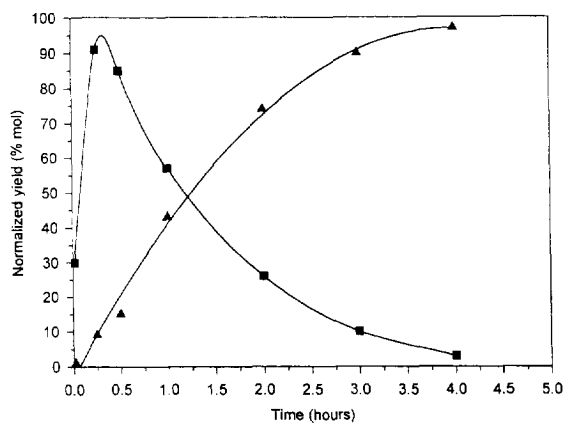


Fig. 8. Hydrolytic decomposition of glycolide (0.1%, w/w aqueous solution, 90°C under stirring). Normalized yield (actual yield related to the maximum theoretical yield based on the initial amount of glycolide) of hydrolytic decomposition by-products as a function of treatment time. (■) Linear dimer of glycolic acid; (▲) glycolic acid.

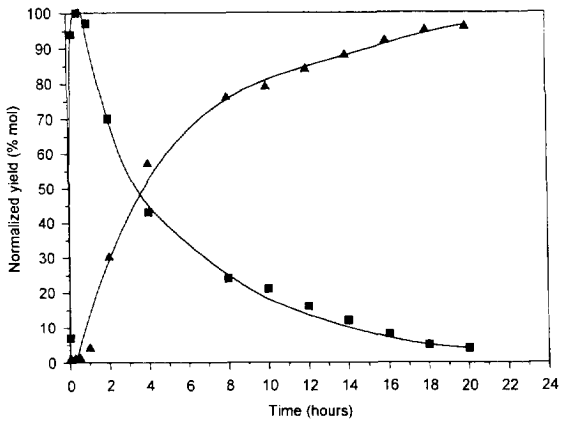


Fig. 9. Hydrolytic decomposition of DL-lactide (0.1%, w/w aqueous solution, 90°C under stirring). Normalized yield (actual yield related to the maximum theoretical yield based on the initial amount of DL-lactide) of hydrolitic decomposition by-products as a function of treatment time. (■) Linear dimer of lactic acid; (▲) DL-lactic acid.

dation entails a series of intermediate products, among which the linear dimers of the α-hydroxy-acids have been clearly identified.

It is also worth mentioning that the degradability of the studied poly(α-hydroxyacid)s seems to parallel that of the corresponding cyclic dimers. In fact, we found that, when starting with 0.1% (w/w) aqueous solutions of the cyclic dimers at 90°C, glycolide transforms quantitatively into glycolic acid in 4 h, while DL-lactide takes about 20 h. In both cases the transformation proceeds through the formation of the corresponding linear dimers (Fig. 8 and Fig. 9), probably according to the following reaction scheme (Scheme 2).

Obviously, in the case of substrates having different morphology and/or crystallinity, such as e.g. poly(L-lactide) and poly(DL-lactide) the diffusion rate of the reactive permeant into the polymer bulk and the mechanical resistance of the material to hydrolytic attack, could play the predominant role.

As already mentioned, a detailed study of the degradation mechanism and kinetics of poly(α-hydroxyacid)s in aqueous media will be reported in a forthcoming paper.

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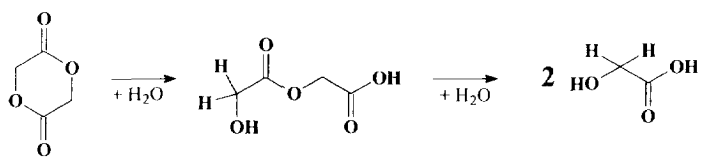
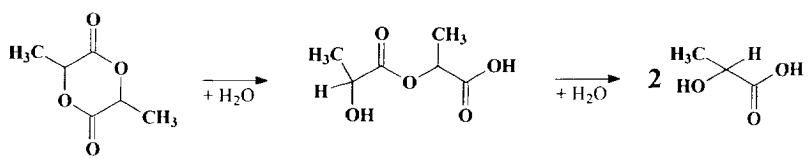


glycolide — linear dimer of glycolic acid — glycolic acid



DL - lactide — linear dimer of DL - lactic acid — DL - lactic acid

Scheme. 2. Reaction scheme of the hydrolysis of glycolide and lactide.

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