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New Insights on the Degradation of Bioresorbable Polymeric Devices Based on Lactic and Glycolic Acids

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Abstract: This contribution recalls some recent advances in the understanding of the mechanisms of degradation of bioresorbable polymers of the poly(α -hydroxy acid) type derived from lactic and glycolic acids, which are receiving increasing interest for their potential for osteosynthesis. First, the various polymers are introduced and the field of applications is delimited. It is confirmed that degradation proceeds faster in amorphous domains than in crystallites. It is also shown that degradation proceeds faster in the center than at the surface, although this feature is not predominant in the case of semicrystalline lactic acid stereocopolymers. Of special interest are the findings that quenched compounds can crystallize at body temperature during degradation and that highly crystalline degradation residues can remain *in situ* for several years. Data show that osteosynthesis with bioresorbable plastics might become a reality for reasonably loaded bones, provided the peculiarities of polymers are taken into account by surgeons.

This contribution is aimed at presenting some recent advances in the understanding of the mechanism of degradation of bioresorbable polymers of the poly(α -hydroxy acid) type derived from lactic (LA) and glycolic (GA) acids, two well known metabolites. These polymers are receiving an increasing interest in the field of therapeutic applications because of their remarkable biocompatibility and their versatility.¹ The latter is primarily due to the poly(α -hydroxy acid)-type backbone, which allows property adjustments either by the combination of lactic and glycolic repeat units via copolymerization or by the combination of L- and D-isomers of chiral lactic acid (L-LA and D-LA respectively) by stereocopolymerization or both.² The degradation behaviors of these polymers depend upon many factors whose contributions are still poorly identified, mostly because it is difficult to take into account all of them in modelization experiments.

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For the sake of clarity, we will first delimit the domain of this discussion and then we will consider the case of those LA/GA polymers which might fulfil the requirements for safe internal fixation of bone fragments normally submitted to loads and stresses.

In the field of poly(α -hydroxy acids), difficulties start at the stage of the naming of the polymers. So far, no rule has been accepted and several systems are used in the literature. This situation has been the source of many misunderstandings. Table 1 recalls the acronyms we have introduced in order to name the polymers after the composition of the monomer feed which is known to be close to chain composition from ¹H NMR investigations.³ These acronyms are those used in this presentation.

Copolymerization with other monomers is also feasible. However, in most of the cases reported in literature, these monomers do not yield metabolites as ultimate degradation products, a peculiarity which can be regarded as a shortcoming from a basic point of view. At the moment, bioresorbable thermoplastic devices based on LA/GA-type

Table 1. Chemical structure and acronyms of poly(α -hydroxy acids) derived from lactic and glycolic acids

<i>Chemical structure</i>	<i>Acronyms</i>
$-\text{[O}-\text{CH}_2-\text{CO}-]_n-$	PGA poly(glycolic acid)
$\begin{array}{c} \text{H} \\ \\ -\text{[O}-\text{C}^*-\text{CO}-]_n- \\ \\ \text{CH}_3 \end{array}$	PLA100 (poly(L-lactic acid))
$\begin{array}{c} \text{H} \\ \\ -\text{[O}-\text{C}^*-\text{CO}-]_n-\text{O}-\text{CH}_2-\text{CO}-]_q- \\ \\ \text{CH}_3 \end{array}$	PLA (100- <i>Y</i>) GA <i>Y</i> ($Y = q/(n+q)$) (L-LA/GA copolymers)
$\begin{array}{c} \text{H} \qquad \qquad \text{CH}_3 \\ \qquad \qquad \\ -\text{[O}-\text{C}^*-\text{CO}-]_n-\text{O}-\text{C}^*-\text{CO}-]_p- \\ \qquad \qquad \\ \text{CH}_3 \qquad \qquad \text{H} \end{array}$	PLA <i>X</i> ($X = 100n/(n+p)$) (LA stereocopolymers)
$\begin{array}{c} \text{H} \qquad \qquad \text{CH}_3 \\ \qquad \qquad \\ -\text{[O}-\text{C}^*-\text{CO}-]_n-\text{O}-\text{C}^*-\text{CO}-]_p-\text{O}-\text{CH}_2-\text{CO}-]_q- \\ \qquad \qquad \\ \text{CH}_3 \qquad \qquad \text{H} \end{array}$	PLA <i>X</i> GA <i>Y</i> ($X = 100n/(n+p+q)$) ($Y = 100q/(n+p+q)$) (terpolymers)

polymers are being studied for many applications and in various sizes and shapes.⁴ They can be made glassy or rubbery at human body temperature, and can be processed by dry or wet spinning, casting, hot-pressing, or compression moulding followed by machining. Systems such as massive implants, films, fibers, microparticles, nano-particles, etc., have been described in the literature. In the field of controlled drug delivery, implants and particulates are extensively investigated, especially the latter which can be directly injected using syringes. In this field, mechanical strength is not requested except, maybe, for needle-like implants. In contrast, osteosynthesis requires devices with suitable initial properties and degradation characteristics which are adapted to fracture loading and healing time, two parameters which depend very much upon the type of bone (cancellous or cortical) and on local stresses.

Clinical studies have been reported where PGA and PGA/LA sutures were used for the repair of tendons, ligaments and dislocations of joints.⁴ Symphysis disruptions in rhesus monkeys,⁵ severely dislocated mandibular fractures in humans⁶ and femoral osteotomies in rabbits⁷ have also been synthesized with sutures. Successful healings have been reported after plating of fractures in the

human maxillofacial sphere⁸ as well as for long bones in small animals such as beagle dogs.⁹ For those bones submitted to significant load or stress, mechanical resistance is desired and this situation is generally associated with a 3–4 month healing time. In order to fulfil these requirements and thus upgrade the bioresorbable polymeric devices, several ways have been considered: machining as-polymerized ultra high molecular weight compounds¹⁰ or using compression moulding to minimize thermal degradation¹¹ improves processing conditions.¹² With the same goal, totally bioresorbable composite materials have been proposed which are based on the combination of a bioresorbable reinforcement and a bioresorbable matrix. Although some inorganic fibers of the phosphate-type have been experimented,¹³ the most attractive composite systems are at the moment the PGA/PLA ones which combine PGA fibers or threads with matrices of semicrystalline PLA *X* polymers,¹⁴ and the self-reinforced PGA/PGA ones which combine PGA threads with sintered PGA matrices.¹⁵ Both systems have good initial mechanical properties but the latter has a shorter lifetime because of the use of PGA for the matrix. Furthermore, the matrix of these self-reinforced

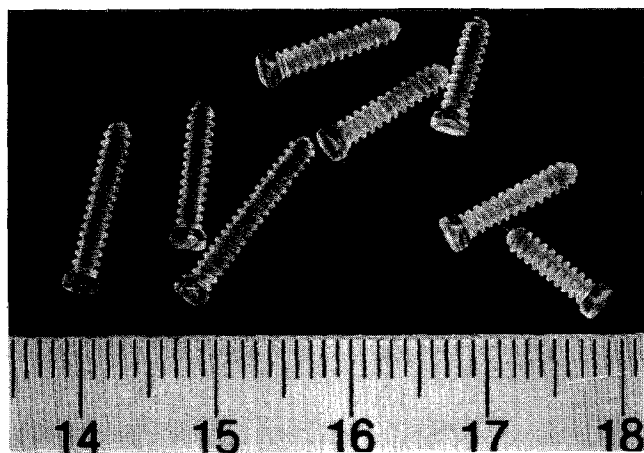


Fig. 1. PLA85GA15 screws of various dimensions processed by injection moulding (from PHUSIS, France).

systems can only be sintered because one cannot take advantage of a difference of melting points between matrix and fibers to process the matrix from the melt, as is the case for PGA/PLA composites. It is now possible to process bone plates, rods and screws of various dimensions by injection moulding with minor changing of the molecular weights of the parent polymers (Fig. 1).

Only semicrystalline members of the poly(α -hydroxy acids) family (PGA, GA-rich and L-LA-rich PLA X GA Y copolymers, and PLA X stereocopolymers with $X > 92$) have acceptable initial mechanical properties at body temperature. However, among these members, only those of the PLA X type seem to retain their strength for periods of time basically long enough to allow the synthesis of reasonably stressed bone fractures.¹⁶ So far, no one knows what 'reasonably' means and this should be a source of concern for those who would like to use such materials for bone surgery.

In spite of the rather large number of animal and human clinical experiments carried out with LA/GA polymers so far, one of the most striking features is certainly the existence of remarkable discrepancies between data obtained apparently under similar conditions, according to the literature. There are many reasons for this. Some of them are well known. For instance, macromolecular science tells us that polymeric compounds are poorly defined because of their molecular weight polydispersity and of the presence of more or less active additives or impurities. In the case of LA/GA polymers, the situation is complicated by the presence of chiral repeat units in the main chain, except for PGA itself, and by the fact that corresponding macromolecules are heat-, water- and radiation-sensitive. In 1981, we underlined for

Table 2. Factors which can affect the degradation of biodegradable polymers *in vitro* and *in vivo*

Chemical structure
Chemical composition
Distribution of repeat units in multimers
Presence of ionic groups
Presence of unexpected units or chain defects
Configurational structure
Molecular weight
Molecular weight distribution (polydispersity)
Presence of low molecular weight compounds (monomer, oligomers, solvents, initiators, drugs, etc.)
Processing conditions
Shape
Sterilizing process
Morphology (amorphous versus semicrystalline, presence of microstructures, presence of residual stresses)
Annealing
Storage history
Site of implantation
Adsorbed and absorbed compounds (water, lipids, ions, etc.)
Physicochemical factors (ion exchange, ionic strength, pH)
Physical factors (shape and size changes, variations of diffusion coefficients, of HHB, mechanical stresses, stress and solvent-induced crackings, etc.)
Mechanism of hydrolysis (enzymes versus water)

the first time that compounds with the same name can exhibit dramatically different properties.¹⁷ Ten years later, the same message can be addressed because the literature is still somewhat confusing in so far as lifetimes are concerned. The situation is even worse than ten years ago because some of the members of the poly(α -hydroxy acid) family are now commercially available and thus accessible to anyone. This should be regarded as positive for the reproducibility of experiments. However, one must keep in mind that history is a very important parameter for polymer properties and that the same batch of polymer can lead to devices with totally different biological behavior properties after processing and conditioning. Table 2 shows a list of the factors which determine and thus can affect the behavior of poly(α -hydroxy acids) *in vivo* and *in vitro*.¹⁸

If one refers to the literature, there is no example of an investigation of the degradation mechanism of LA/GA polymers where authors have tried to take into account the existence of this list and of the corresponding consequences. The degradation mechanism of GA-based sutures has been extensively investigated and is quite well understood.¹⁹ It is far from being the case for PLA massive devices.

In an attempt to fill this gap, we undertook four years ago a detailed investigation of the degradation of LA/GA polymers, starting from the fact that this

Table 3. PLA *X* polymers of interest for bone fracture internal fixation which were compared

Polymer	% Gross composition of the monomer feed			<i>Mw</i> ^c	<i>I</i> = <i>Mw</i> / <i>Mn</i>	Characteristics
	<i>L-LA</i>	<i>D-LA</i>	<i>GA</i>			
PLA96	96	4	0	100000	1.7	Made amorphous ^a
PLA100A	100	0	0	130000	1.8	Made amorphous ^a
PLA100C	100	0	0	130000	1.8	Semicrystalline ^b

^a By fast cooling of the mould and after X-ray diffraction.

^b After annealing for 2 h at 130 °C.

^c From SEC.

degradation is purely hydrolytic, at least until soluble degradation by-products are released, and that comparison between the various members must be done on the basis of coordinated monitoring of degradation effects by various techniques applied to comparable specimens with the same history.²⁰ One of the most striking features which has been found is the fact that degradation is faster in the center of massive devices. A similar feature has already been observed for poly(orthoesters) containing acidic or acid-generating additives.²¹ This surface/center differentiation accounted well for several features of partially degraded amorphous members, namely bimodal molecular weight distributions in the absence of semicrystalline morphology,²⁰ heterogeneous aspects of the cross-sections of partially degraded massive implants *in vitro* and *in vivo*²² and time- and polymer composition-dependent secondary inflammatory reactions related to the release of soluble degradation by-products.²³ Another finding of interest was that intrinsically amorphous devices, i.e. devices made of polymers which are unable to crystallize because of the irregular structure of the macromolecules, can undergo dramatic morphological changes when degradation produces crystallizable macromolecule fragments.

In the last part of this contribution, we would like to show some recent data obtained on those members of the poly(α -hydroxy acid) family which, we believe, are better recommended for bone fracture internal fixation because they are semicrystalline.

Table 3 shows the compounds which were selected among the crystallizable PLA *X* stereocopolymers, namely PLA100 and PLA96, the latter being less crystalline because of the presence of a small amount of *D-LA* repeat units in an (*L-LA*)-rich polymer backbone.

PLA96 and PLA100 powdered polymers were

processed to specimens of similar sizes (15 mm \times 10 mm \times 2 mm), machine-cut from compression-moulded round plates (75 mm diameter, 2 mm thickness) and made either amorphous by quenching (PLA100A and PLA96) or semicrystalline (crystallinity higher than 70% according to X-ray diffraction) by annealing (PLA100C). All the specimens were allowed to age in 0.13 M pH = 7.4 phosphate buffer solution (PBS) at 37 °C for periods of time up to 2 years. Various techniques were used to compare the effects of morphology on the mechanism of hydrolytic degradation for these specimens: weighing, SEC, potentiometry, cryometry, enzymatic assay of the *L*-lactic acid formed, X-ray scattering and DSC.²⁰ All sets of data have been reported in detail elsewhere.²⁴ Here, we will mention only those which are of interest for the typical problems of application to bone fracture fixation.

PLA100 is an intrinsically semicrystalline poly(α -hydroxy acid). Its ability to crystallize is related to the stereo-ordered chains composed of *L*-lactic acid repeat units. The morphology of PLA100 crystallites has been discussed in the literature. However, the correlation between molecular structures, crystalline morphologies and degradation behaviors is still poorly understood, although the fact that many factors can contribute has been known for a long time, including the effects of enantiomeric purity of PLA100 chains¹⁷ and the presence of residual monomer as noted recently.²⁵

The degradation behaviors of PLA100A and PLA100C in pH = 7.4 PBS will be discussed together for direct comparison. PLA100 is known to be very resistant to hydrolysis compared to other members of the poly(α -hydroxy acid) family.¹⁷ In the buffered medium, the initially amorphous PLA100A specimens stayed transparent for 18 weeks and then turned whitish. At week 40, cross-sections appeared white from surface to center.

Furthermore, they showed evidence for faster central degradation, the outer layer being dense whereas the center was porous. Large cracks became visible at the surface beyond week 50. From week 70 to the end of the experiment (110 weeks), the recovered specimens were brittle and contracted. The initially semicrystalline, and thus opaque, PLA100C specimens became also gradually whitish. At week 40, the specimens were totally white and were brittle. Small cracks appeared at the surface. In contrast to PLA100A, the size and shape of PLA100C specimens did not change during ageing. Measurements of weight loss, lactic acid release and pH changes agree well, showing that the release of lactic acid started earlier for PLA100C than for PLA100A (12 weeks compared to 31 weeks). Nevertheless, at the end of two years, much more lactic acid had been released from PLA100A specimens than from PLA100C.

The storage modulus, E' , was used as a means of reflecting the change of mechanical properties with the degradation time. Initially E' was slightly higher for PLA100C specimens than for PLA100A ones. However, the decrease of mechanical properties occurred earlier for PLA100C than for PLA100A. Indeed, E' started decreasing after 3 weeks for PLA100C specimens whereas the PLA100A ones retained the initial value for 12 weeks. It was no longer possible to measure E' beyond week 31 for PLA100A due to the swelling of the specimens and beyond week 50 for PLA100C because of brittleness. After 7 months, the two sets of specimens still exhibited some mechanical strength and E' values were approximately 20% and 40% of the initial values, respectively. Although the tensile strength could not be measured correctly on the tiny specimens used, it was concluded that internal fixation devices made of PLA100A and PLA100C should be able to keep a large part of their initial mechanical properties for 3–4 months.

Size-Exclusion Chromatography (SEC) measurements confirmed that degradation is faster in the central part of the specimens and that crystallites are much more resistant to degradation than amorphous microdomains, a finding which agrees well with the normal behavior of semicrystalline polymers in general. However, we have found that initially amorphous PLA100A specimens progressively crystallized during ageing in aqueous media, as revealed by X-ray diffraction measurements (Table 4).

In contrast, X-ray spectra of semicrystalline PLA100C did not change significantly with the

Table 4. Changes of crystallinity for PLA100A quenched specimens allowed to age in pH = 7.4 PBS at 37 °C

Degradation time (weeks)	0	18	31	40	70	90
Crystallinity (%)	0	4	17	19	37	49

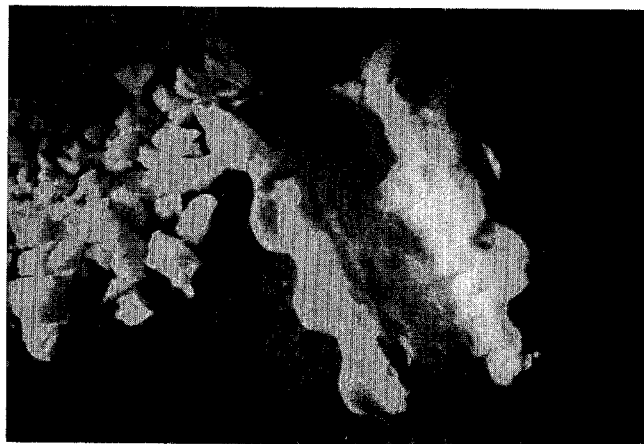


Fig. 2. PLA96 injection-moulded screw allowed to age for 40 weeks in a pH = 7.4 phosphate buffer solution.

ageing time, in agreement with the high degree of crystallinity of the specimens from the very beginning.

Amorphous PLA96 specimens also crystallized during their ageing in pH = 7.4 PBS. Figure 2 shows a picture of a PLA96 injection moulded screw which was allowed to age for 40 weeks in PBS. The screw was extremely brittle in the center whereas the outer layer was still rigid and mechanically resistant.

The findings described in this paper can be regarded with interest in so far as bone fracture fixation is concerned. They bring new information on the behavior of devices made of semicrystalline PLA X stereocopolymers in aqueous media. However, one must keep in mind that bioresorbable devices like plates, screws, nails, etc., are supposed to work in various environments. Whereas a plate is going to be in contact with the bone one side, a screw will be surrounded by bone and thus somewhat protected from body fluids and a nail will be largely surrounded by bone marrow. Accordingly, one can predict that differences will be still observed between devices of different shapes and submitted to contact with body fluids under different conditions. Considering the research that is being devoted to LA/GA polymers throughout the world, it is likely that in the foreseeable future bioresorbable devices of this type will be in everyday

use in bone surgery, provided that the limitations of the materials are known and respected.

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