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Bioresorbability and biocompatibility of aliphatic polyesters

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The field of biodegradable polymers is a fast growing area of polymer science because of the interest of such compounds for temporary surgical and pharmacological applications. Aliphatic polyesters constitute the most attractive family among which poly(α-hydroxy acids) have been extensively studied. In the past two decades, several excellent reviews have been published to present the general properties of aliphatic polyesters. The aim of this paper is to complete the information collected so far with a special attention to the complex phenomena of biodegradability and biocompatibility. Indeed, the degradation of a polymer leads to the delivery of low molecular weight degradation by-products whose effects on the host body have to be considered. The consequences of the absence of standard terminology are first discussed with respect to words such as biodegradable and bioresorbable. Poly(α-hydroxy acids) derived from lactic and glycolic acids are then introduced in order to make easier the critical discussions of the following problems from literature data: biocompatibility, biodegradability, bioresorbability, mechanism of hydrolysis (enzymatic *vs* simple chemistry), polymodality of molecular weight distributions during degradation and the effects of the presence of oligomers. Finally, some specific comments are made on other aliphatic polyesters such as poly(hydroxy butyrate) and poly(β-malic acid).

1. Introduction

Soon after synthetic polymers were invented, about 50 years ago, the medical profession realized that this new class of materials may have a potential for a variety of therapeutic and technical uses. Isotonic aqueous polyvinylpyrrolidone (PVP) was used as a plasma expander during World War II, for example, and although this compound was far from ideal, it was used for years before substitutes were proposed [1].

Since then, the list of polymers evaluated with respect to the concept of biomaterials has grown rapidly [2]. However, the number of compounds having reached the stage of clinical and commercial applications is still small.

Basically, one can distinguish polymers used for prosthetic purposes from those whose contribution is required for a limited period of time, especially the healing time. For thousands of years in the past, stable materials have been used without distinction between permanent and time-limited applications. However, it has been realized progressively that materials, and especially polymers capable of degrading in the body, could be of special interest for temporary therapeutic applications either in medicine, or in surgery, or in drug delivery. Compounds derived from biopolymers like animal sinews a long time ago, or catgut denatured collagen more recently, have been considered because they were easily available. The discovery of fibre forming properties and of hydrolysability of high molecular mass polyglycolic acid (PGA), obtained by ring opening polymerization of glycolide cyclic diester (GA), was the first step towards the development of synthetic biodegradable and bioresorbable polymers with no structural features in common with natural biopolymers [3, 4].

Since then many other polymers have been identified as degradable in model aqueous media or in animal bodies [5–9]. However, the family of aliphatic polyesters appears at the moment to be the most attractive and promising one. This statement is supported by the number of scientific papers and patents in which aliphatic polyesters have been mentioned.

Several pertinent reviews have been issued during the past years where the degradation and the properties of biodegradable or potentially biodegradable polymers are considered [6–9]. However, it is of value to point out immediately that most reports of polymer degradation in the presence of body fluids or tissues are qualitative and confined to evaluation from a single point of view. In most cases, the origin and the specifications of these polymers are not mentioned. There are actually many other reasons for the lack of conclusive information about biocompatibility and biodegradability of polymers which can intentionally undergo chain scissions in the body. Literature in this domain can be split into two parts. The first part groups polymers aimed at surgical applications, as is the case for compounds which are involved in suture materials, in osteosynthesis devices, in bone augmentation, in bone restoration, and so on. The second

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group concerns polymers aimed at pharmaceutical applications as is the case for compounds considered to make drug delivery devices and to achieve rate-controlled release, targeting, drug-protection and host-protection.

The gap still exists between these two classes of application, although it is foreseeable that in the future medicated biodegradable devices will bridge this gap for the good of patients.

Before considering the various aspects of the subject, we would like first to comment on some generalities, particularly the meaning of words like bioabsorbable, bioerodible, biodegradable and bioresorbable, which are going to be used in the paper and which are often used misleadingly in the literature. We also comment on some general features which have been considered to limit the scope of the paper.

In this review, "bioabsorbable" will be reserved for solid polymeric materials or devices which can dissolve in body fluids without any polymer chain cleavage or molecular mass decrease. This acceptation agrees well with the meaning of absorption phenomena in physical chemistry. "Biodegradable" will be reserved for solid polymeric devices which break down to macromolecule degradation with dispersion in an animal body but no proof for elimination from the body (this definition excludes environmental, fungi or bacterial biodegradation). In contrast, "bioresorbable" will be applied to solid materials which can degrade and further resorb *in vivo*, i.e. which are eliminated through natural pathways either because of simple filtration of degradation by-products or after their metabolization. Bioresorption is thus a concept which reflects total elimination of the initial foreign material and of degradation by-products with no residual side-effects. The use of the word "bioresorbable" assumes that elimination is shown conclusively. "Bioerodible" will be exclusively used with reference to surface degradation in agreement with the usual meaning of "erosion". The prefix "bio" will thus be considered as reflecting phenomena which result from the contact with living elements such as tissues, cells or fluids. Accordingly, water in body fluids and enzymes will be both considered as biological elements capable of degrading macromolecules regardless of the mechanism by which degradation occurs. In other words, biodegradation will be reserved for both enzymatic and non-enzymatic degradation *in vivo*, or because of cell activity in cell cultures, whereas degradation will be used for *in vitro* experimentation using aqueous model media.

The family of aliphatic polyesters is very large. Compounds of this type can be synthesized either by ring opening polymerization of heterocyclic monomers with one ester bond at least in the cycle, or by step-growth polymerization of hydroxy acids, or of dialcohol and diacids.

Table I presents some of the members of the family which have been mentioned in the literature as degradable, as biodegradable, or, for some of them, as bioresorbable.

We have been interested in bioresorbable polymers for many years and the need for concentrating our investigations to a limited number of compounds appeared early to us. Our choice was guided by the need to take into account the properties which are required when one really wants to reach the stage of clinical applications. Indeed, medical applications must always be in mind as the final goal in one way or another if one wants to talk in terms of "biomaterials". A list of the prerequisites of bioresorbable polymers is given in Table II. Of course, such a list includes general prerequisites of any biomaterial. It has to be completed by more specific ones, which are related to

TABLE I Aliphatic polyesters (and their copolymers with other cyclic monomers of the series) known as degradable, biodegradable or bioresorbable

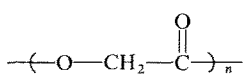
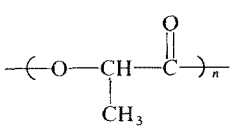
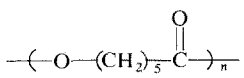
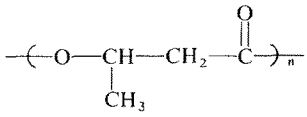
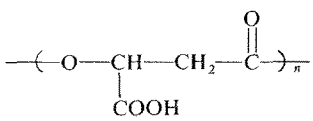
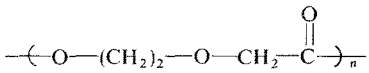
Precursors	Polymers	Acron.	Structure	Ref.
glycolide	Poly (glycolic acid)	PGA		3, 4
lactides	Poly (lactic acids)	PLA		10
ε-caprolactone	Poly (ε-caprolactone)	PCL		11
β-butyrolactone	Poly (hydroxy butyrate)	PHB		12
β-benzyl-β-malolactone	Poly (β-malic acid)	PMLA		13
1,4-dioxane-2-one	Poly (*p*-dioxanone)	PDS		14, 15

TABLE II General prerequisites of bioresorbable polymers

Biocompatibility	concerns:
	polymers
	leacheable:
	oligomers
	residual monomers
	degradation by-products
	shape
	surface properties
	degradation characteristics
Biofunctionality	depends on:
	physical properties
	mechanical properties
	biological properties
Stability	required at the following stages:
	processing
	sterilization
	storage
Bioresorbability	assumes:
	degradability
	controlled degradation rate
	resorption of degradation products

the various time-limited applications (bone fracture internal fixation, filling of bone defects, bone augmentation, skin dressings, sutures, vitreous humour substitutes, drug delivery, etc.). It is of value to point out that some of these prerequisites are difficult to accommodate, such as stability to processing, sterilization and storage on the one hand, which assume chemical stability, and biodegradability on the other hand, which assumes chemical instability. From the literature one can easily see that it is almost impossible to discuss biocompatibility and bioresorbability, or even biodegradability only of all the aliphatic polyesters with respect to these prerequisites because of the lack of information.

As mentioned above, aliphatic polyesters derived from glycolic and lactic acids were proposed as biodegradable polymers for biomedical applications in the 1960s. Since then a great deal of work has been done and new members (poly(ε-caprolactone), polydioxanone, poly(β-malic acid), etc.) have joined the family of aliphatic polyesters. An excellent review has been issued recently by Holland *et al.* [16] which deals with polymers for biodegradable medical devices with special attention to the potential of polyesters as controlled macromolecular release systems. As these authors and others [6–9, 17] have reviewed the literature and various aspects of the degradation of polyesters, we will not reconsider these topics in detail here. Although members of the aliphatic polyester family have reached the stage of commercialization either as sutures or as devices for bone surgery in different countries, there are still controversies and discrepancies about their behaviour and their fate when they are in contact with living tissues. This situation results mostly from the fact that polymers, in general, and aliphatic polyesters in particular, are poorly defined chemicals as compared with low molecular mass organic compounds or with biopolymers such as natural proteins or polynucleotides. As sources of modulation of polymer properties, let us mention factors like molecular mass and molecular mass distributions, which are most frequently mentioned in the literature together with chemical composition for copolymers. However, these factors are far from being the only perturbing ones. The presence of low molecular mass compounds, such as oligomers, residual monomers, residual solvents, adsorbed atmospheric water and heat-induced or radiation-induced degradation products, can also cause significant changes of the intrinsic properties of a polymer. The configurational structure is also a critical factor for optically active compounds, as has been shown in the case of lactic acid stereocopolymers and lactic–glycolic copolymers with respect to applications in bone surgery [18]. Therefore, discrepancies found in the literature could arise because the investigations reported for polymeric materials identified by the same name were actually done with different compounds if one refers to the science of synthetic polymers. Furthermore, properties like biocompatibility and biodegradability are generally discussed by considering polymeric materials aimed at different applications. Polymeric systems designed for bone fracture internal fixation require good mechanical properties and thus impose the use of very pure polymers. In contrast, polymers for drug delivery systems are processed in the presence of solvents and combined with low molecular mass drugs, which can be regarded as additives, with consequences which are predictable from polymer science and from the behaviour of normal plastic materials.

During the past decade we have been studying poly(α-hydroxy acids) for various applications ranging from bone fracture internal fixation, filling of bone defects or bone reconstruction, to drug delivery from implants or microparticles starting from the same homemade compounds.

Accordingly, we have felt that the confrontation of our data on homemade poly(α-hydroxy acids) with those reported in the open literature might improve the present understanding of biocompatibility and bioresorbability of aliphatic polyesters in living tissue and will perhaps help people to select a methodology for the investigation of these properties with respect to real therapeutic applications.

After introducing poly(α-hydroxy acids), we consider separately some of the aspects of biocompatibility and bioresorbability of these polymers before commenting briefly on some of the other aliphatic polyesters in the light of the recent research. The separation of biocompatibility and bioresorbability is artificial and was done for the sake of clarity. Actually, both phenomena are very much dependent on each other.

2. Poly(α-hydroxy acids)

Poly(α-hydroxy acids) constitute a class of polymers represented by the general formula $-(-O-CHR-CO-)-_n$. Among the whole family, members composed of constitutive repeating units with R=H (glycolic acid) or R=CH_3 (lactic acid) are known to be bioresorbable. For lactic acid-containing polymer chains, the presence of a methyl group as a side

chain generates an asymmetric carbon atom and thus chirality at the level of each repeating unit. The presence of repeating units with *L*- and *D*-opposite configurations has been shown to provide a worthwhile means of adjusting physical and mechanical characteristics and *in vivo* resorption rates of stereocopolymers of lactic acid (PLA *X*) [17]. Similar adjustments can be achieved through the respective amounts of glycolic and lactic units in *L*-lactic/glycolic copolymers or in glycolic/*L*-lactic/*D*-lactic terpolymers (PLA *X* GA *Y*). The various members of the series are presented in Table III together with the keys used for acronyms. For the sake of clarity, polymer chains are identified in this text by using acronyms where *X* is the percentage of *L*-lactic acid present in the monomer feed whereas *Y* is the percentage of glycolic acid and $100 - (X + Y)$ the percentage of *D*-lactic acid whenever these two moieties are present in the feed. LA and GA mean lactic and glycolic constitutive repeating units respectively. This nomenclature may appear unusual with respect to the literature. However, it has been introduced for applications of poly(α-hydroxy acids) in bone surgery and shows the great advantage of reflecting immediately the gross composition of the polymers [9]. As mentioned above, this nomenclature is based on the composition of the feed. However, we know from nuclear magnetic resonance (NMR) data that the averaged composition in LA- and GA-containing polymer chains of our homemade compounds is close to that of the feed [20] probably because of transesterification reactions [21]. Furthermore, no configuration enrichment occurs during polymerization in the case of lactic acid stereocopolymers polymerized by using zinc powder as the initiator [19].

3. Biocompatibility

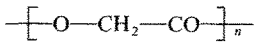
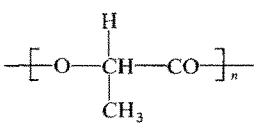
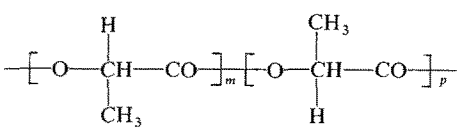
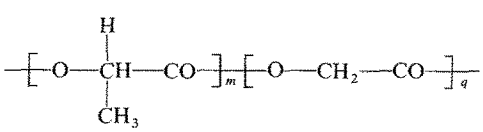
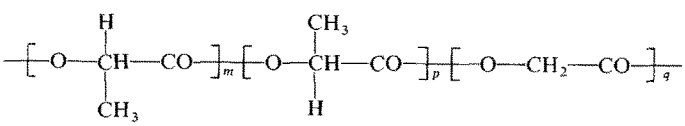
Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific application [22]. Biocompatibility is generally evaluated through the fate of test animals, histologic and pathologic examinations of surrounding tissues and host responses such as immunogenic, carcinogenic and thrombogenic responses. However, interactions between materials and tissues involve complex phenomena where either tissue or material can adversely affect the other.

In the field of biostable materials, the goal is primarily one of minimizing and adjusting material–tissue interactions so that the effects of the living environment on the material are acceptable for long-term therapy.

In the field of biodegradable materials, the situation is the opposite, as the material is the source of degradation by-products which are able to strongly interact with living systems. From this view point, biodegradable and bioresorbable polymers must be regarded as much closer to pharmacology than to materials science.

With respect to biocompatibility, choosing poly(α-hydroxy acids) which derive from metabolites as potential bioresorbable compounds has been of special interest from the beginning. Indeed, it was likely that

TABLE III Bioresorbable polymers derived from lactic acids and glycolic acid

Poly(glycolic acid)	
	PGA
Homopoly(*L*-lactic acid)	
	PLA 100
Stereocopolymers of *L*- and *D*-lactic acids	
	PLA *X* $(X = 100m/(m + p))$
Copolymers of glycolic and *L*-lactic acid	
	PLA $(100 - Y)$ GA *Y* $(Y = 100q/(m + q))$
Terpolymers of glycolic and *L*- and *D*-lactic acids	
	PLA *X* GA *Y* $(X = 100m/(m + p + q))$ $(Y = 100q/(m + p + q))$

degradation products will be the metabolites themselves, since this type of polymer is obtained by ring opening polymerization, a method which yields well-defined repeating unit enchainments, and it could be assumed that their behaviour with respect to living media will depend primarily on their chemical nature. However, chemistry and physical chemistry of polymers can depend on many other structural factors such as those recalled above. Therefore, polymers derived from glycolic and chiral lactic acids, or from other metabolites of the hydroxy acid type, are compounds much more difficult to define from a structural point of view than it has usually been believed [17]. Indeed, low molecular mass compounds such as residual monomers and oligomers, or impurities such as residual solvents, oxidation side-products, absorbed atmospheric water, etc., can be present and are far from being under control. Furthermore, physical factors like crystallinity and morphology also contribute [17]. Therefore, we have all the ingredients to account for discrepancies and controversies present in the literature. This statement is true for both biocompatibility and bioresorbability, as both properties depend very much on the same factors. With these remarks and all their possible consequences on the interpretation of experimental data in mind, one can now examine the literature.

From a general point of view it is remarkable that the main features related to biocompatibility and bioresorbability, or bioresorbable aliphatic polyester of the poly(α-hydroxy acid)-type, have been recognized from the beginning.

In 1966, histopathological examination of implanted poly(*L*(+)lactic acid) (PLA 100) samples showed that the polymeric mass disappeared from the implantation sites with only the mildest and most transient of inflammatory responses [23]. Let us recall the findings of the authors to support this statement. Kulkarni *et al.* [23] wrote:

"The gross evaluation of the results of the polylactic acid implants in 18 guinea pigs for six weeks showed no inflammatory reaction on the skin, although the powder or the films could be palpated in the implanted areas. The inflammatory response during the first week was very mild in that the reactive zone was limited to only a thin layer of polymorphonuclear leukocytes, occasional lymphocytes, and a few eosinophils. At the end of this period some oedema of the tissue by the early formation of giant cells of the foreign body reaction was seen. At the end of two weeks, the powder enmeshed in the connective tissues was seen to elicit marked fibroblastic activity. The gradual ingrowth of the tissue fibres in and around the powder was seen after four weeks with formation of a firm sheet of connective tissues, similar to surgical scar tissue, whereas the original birefringency of the polymer faded away. Strikingly, there were no indications of inflammatory reaction from the implants made, thus giving evidence of inertness and tissue receptivity. Polylactic acid films gave evidence of change in the physical state. From original thin and transparent form, they changed to opaque and swollen state until the end of four weeks. In sequence with the change in the films, there was corresponding change in the pocket wall. Although there was a fine collagen fibre layer formed at the end of two weeks, the inflammatory response was entirely absent. There was active fibroblastic proliferation at the end of four weeks, along with the appearance of some vascular channels. At the end of six weeks, the wall of the cavity showed localized proliferation of the fibroblasts. This might be due to the swelling of the film or formation of the roughened surface due to degradative erosion".

The same authors reported results of investigations of the route of elimination. As they did not find significant radioactivity in the faeces or urine during a three-month period nor in any of the vital organs at death, they concluded that the degraded polymer had possibly been eliminated through the CO_2 in the respiration. Since then, these findings have been completed without any dispute [24–27]. In 1971, Kulkarni confirmed the minimal inflammatory responses for both poly(*L*-lactic acid) (PLA 100), and poly(*D*-lactic acid) (PLA O) [23]. Cutright *et al.* [28] reported data on mandibular fracture reduction in monkeys using transosseous ligatures with poly(lactic acid) suture materials. Animals were sacrificed from 2 to 12 weeks. After 12 weeks, early features of bony union appeared and the sutures became infiltrated by cellular connective tissue with fibroblasts, endothelial cells, mononuclear phagocytes and giant cells. Sutures were progressively replaced by bands of young collagen and vascular connective tissue. The tissue reaction was limited to the immediate perisutural area.

In 1972, Getter *et al.* [29] found that scattered inflammatory cells infiltrated the fibrous tissue surrounding poly(lactic acid) bone plates. Inflammatory reaction remained low all along the observation period up to complete degradation of plate and screws after 40 weeks.

As for polymers derived from glycolic acid, work had been in progress for a decade but data on the behaviour of poly(glycolic acid) only appeared in the open literature in the early 1970s [4]. According to the authors who contributed to the development of bioresorbable PGA sutures, PGA exhibited a lower degree of tissue inflammation than catgut, being similar in this respect to Dacron aromatic polyester fibres, polyolefinic and the other inert "non-degradable" sutures. For PGA, at 90 days, the subcutaneous implant site appeared as a faint darkened area only about one-third of its original size and, after two years, it could not be distinguished from the surrounding tissues.

At this time many papers reported clinical investigations of PGA sutures. Let us mention for example the cases of strabismus surgery [30], gastro-intestinal surgery [31], plastic surgery [32] and more general papers dealing with comparative investigations of various sites in human surgery [33–36], in animal experimentations [37, 38] and for veterinary surgery as well [39].

In no case was a severe adverse reaction reported. The general features observed histologically are those of a mild inflammatory reaction with the presence of

fibroblast-rich granulation tissue, polymorphonuclear leucocytes and multinuclear giant cells of foreign-body type. However, the general fate is that after several months no residual suture fragments, nor foreign body granulomas, are still detectable, as pointed out by Bergman *et al.* [40], from investigations of intestinal anatomoses, urinary bladder and abdominal wall closures in rabbits, or in oesophageal end-to-end anastomoses in piglets [37], vascular anastomoses [41], or in the case of healing of colon and stomach wounds in dogs [38], or for single-layer intestinal sutures [36].

Later on, 90/10 poly(glycolic-co-*L*-lactic) (PLA 10 GA 90) copolymers known as poly glactin 910^{R} or as Vicryl^{R} sutures appeared [42]. Insofar as biocompatibility is concerned, polyglactin 910^{R} and Vicryl^{R} materials appeared to be well accepted by living tissues. Inflammatory reactions and fates similar to PGA and PLA compounds [43] were reported [44–46].

The family of aliphatic polyesters aimed at suturing applications has quickly grown in recent years, as discussed in a recent review by Devi and Vasudevan [42]. However, the development of similar compounds for other applications is a worthwhile source of information on biocompatibility as it provides data on behaviour with respect to various tissues.

Although PGA has been patented for applications in orthopaedic surgery [47], its rapid resorption precluded real use for bone fracture internal fixation. In contrast, more stable LA polymers, which have greater half-life times *in vivo*, had a potential for this type of application as suggested early in the literature [10]. Fast degrading GA-containing lactic acid copolymers (PLA *X* GA *Y*) were not appropriate to fracture fixation because of too-short lifetimes and mechanical property retention. However, PGA and fast degrading GA-containing lactic acid copolymers appeared of special interest for bone reconstruction. Indeed, artificial bone defects created in the mandible or in long bones were rapidly filled up with new bone after degradation of bioresorbable poly(α-hydroxy acids) loaded with calcium phosphate by Leray *et al.* in 1977 [48]. At the same time, Nelson *et al.* [49] reported on the evaluation of PLA/GA copolymers in solid spheroidal form as osteogenic agents in rats. Later on Sedel *et al.* [50] presented data collected from intraosseous and juxtaosseous implantation of massive PLA *X* and PLA *X* GA *Y* copolymers in sheep. Hollinger observed similar findings in rats for bone plates made of various LA/GA-containing polymers. The latter discussed his data in terms of osteogenicity [51]. More recently, a totally bioresorbable composite material made of reinforcing PGA fibres embedded in a semi-crystalline PLA matrix [52] was implanted as bone plates and no difference with non-reinforced PLA was detected insofar as biocompatibility was concerned [53]. In parallel, clinical experimentation in humans started in the maxillofacial sphere for bone fracture fixation [21, 54] and bone augmentation and reconstruction [55, 56]. On the one hand, 23 patients received orbital floors and a further 10 were osteosynthesized with PLA 100 and PLA 96 bone plates (some being PGA-reinforced) to treat mandibular, maxillo-malar or fronto-malar fractures after fixation by using metallic or bioresorbable screws [54]. On the other hand, bone defects due to maxilla and mandibular cysts were rapidly reconstructed after filling of the cavities by fast-degrading PLA 37.5 GA 25 or PLA 50 polymeric implants shaped for good spatial fitting of the holes [55]. In several cases, PLA 37.5 GA 25 was found to induce rather active inflammation during the first days, which was not observed for PLA 50 [55]. In all the other cases, excellent biocompatibility was reported, judging from the fate of implants, of the surrounding tissues and of the patients. For all the clinical experimentation where follow-ups were feasible, it has been found that a first stage with inflammatory reaction characterized by the presence of polymorphonuclear leucocytes, giant cells, a few macrophages and fibroblastic activity evolved later on in two directions, depending on the lifetime of the implants and thus on their chemical and configurational structures: encapsulation by bony tissue with interposition of a thin layer of fibrous tissue for slow-degrading bioresorbable compounds [54], or degradation and replacement of intraosseous implants by new bony tissue in the case of fast-degrading ones [55], the fibroblastic activity being progressively replaced by osteoplastic activity, with formation of growing bony tissue islets around immature and later mature osteocytes.

After three years implantation in sheep, long-lasting PLA 100 bone plates showed a thicker fibrous capsule with respect to data at one year and histological evidence of degradation became detectable at the periphery [57]. In terms of biocompatibility, late development of biological activity around embedded long-lasting implants is definitely related to a phase of dramatic degradation with release of low molecular mass materials which have to be eliminated and are thus handled by normal elimination and metabolization processes. Accordingly, behaviour of long-lasting and fast-degrading implants is quite similar but occurs on different timescales [57]. *In vivo* degradation of poly(lactic acid) of different molecular masses has shown that after 48 weeks implantation period lower molecular mass PLA 100 samples (0.89×10^6 Da) were degraded faster than the higher molecular mass samples (1.99×10^6 and 2.94×10^6 Da) [58]. Small differences due to structural and/or chemical compositions have never been carefully investigated and are difficult to appreciate. The final phase has always been the resolution of inflammation and fibroblastic activity, with return to normal as it has been conclusively established for the suture material. No particular implantation site effect has been reported. Poly(α-hydroxy acids) in contact with bone behaved like sutures in contact with soft or hard tissues and thus exhibited excellent biocompatibility.

A particular domain of applications of bioresorbable polyesters is that of drug delivery, for which they have been used either as implants, microparticles or nanoparticles [59]. The literature is far from being clear from the view point of biocompatibility in this area. Indeed, relatively little work has been done on the problems posed by fully operating systems, i.e. systems

operating *in vivo* in animals. If polymer matrices play an important role, it is obvious that other compounds such as the drug (which is voluntarily introduced in the polymer mass), or such as residual solvents, surfactants, etc., which are not desired and sometimes ignored, make these features difficult to use for generalization.

A detailed investigation of cisplatin microspheres, whose matrices were derived from various members of the poly(α-hydroxy acid) family, has been recently completed with our poly(α-hydroxy acids) [60]. It included the pathological appreciation of the fate of unloaded bioresorbable microspheres in rat liver after injection in the portal vein.

For all the polymers, a mild foreign-body reaction was detected from histological examination of embolized liver. Embolization was extended to the whole liver with microspheres present in portal veins. In the first weeks, mild foreign-body reactions with progressive appearance of giant cells were observed for all the polymers. At three weeks, PLA 50 microspheres, which degraded slowly, exhibited subcritical inflammatory response with macrophages and lymphocytes, whereas GA-containing copolymers (PLA 37.5 GA 25 and PLA 45 GA 10) showed, at the same time, a more intense inflammatory response with giant cells lying close to the particles. Inflammation increased with time with diffusion to the periportal area. Later on, giant cells invaded the particles. For PLA 37.5 GA 25, intense giant cell activity was observed in the presence of endocytosed particle fragments. The digestion of polymer fragments required several months with limited macrophagic activity. No scar tissue was observed after seven months for PLA 37.5 GA 25. Actually, two types of evolution were detected again. Either degradation was slow and a mild inflammatory reaction was observed (PLA 50 for example), or degradation was fast and a foreign-body reaction appeared with giant cells contributing to clean up the site (GA-containing copolymers).

Biocompatibility includes other biological phenomena such as immune response, carcinogenicity and thrombogenicity. The literature is rather poor regarding these points, which should be scientifically considered in the future for complete understanding of polyester behaviour *in vivo*. As far as immunogenicity and carcinogenicity are concerned, sutures have been used for almost 20 years now and no real problem has been reported so far. As for thrombogenicity, no detailed investigation has been reported as far as we know, even though attempts have been made to use PLA material in vascular grafts [61, 62].

Therefore, from the present combination of literature with our own experience, it is possible to state that poly(α-hydroxy acids) are polymers of generally good biocompatibility, regardless of shaping and site of implantation.

In spite of the presence of traces of residual polymerization initiators (including antimony trifluoride (few p.p.m.) which we used for some synthesis of GA/LA copolymers), of residual ethylene oxide (few tenths of p.p.m. in some cases) and sometimes of residual solvents (acetone, methanol, dioxane or methylene chloride), no significant adverse reaction has been detected after 12 years experimentation in animals and humans, for our homemade polymers and for compounds in the literature.

Finally, it appears that biocompatibility of polyesters depends primarily on other factors than the polymers themselves. The leaching of low molecular mass compounds either because of degradation or because of the presence of leachable impurities is the major source of triggering inflammation. Accordingly, problems of biocompatibility of bioresorbable polymers such as aliphatic polyesters is definitely related to biodegradability.

4. Biodegradability, bioresorbability

At the present time, one can consider that the ability of poly(α-hydroxy acids) to degrade is well established and most people agree that chain scission occurs through simple hydrolytic reactions with no contribution of enzymes, although the presence of enzyme molecules has been mentioned as affecting degradation to some extent in the cases of PGA [63] and PLA [64, 65] as in the case of another bioerodible aliphatic polyester, namely elastomeric poly(ε-caprolactone) [66].

From physical and physico-chemical view points, enzymes which are large molecules cannot penetrate massive synthetic polymers. There are at least three reasons for that: size exclusion, poor affinity of enzymes for non-aqueous media and, maybe, unfavourable thermodynamic characteristics which usually lead macromolecules of different types to segregate.

TABLE IV Mass changes for PLA 50 and PLA 100 tensile bars (25 mm long, 2 × 2 mm^2 cross-sectional area) with and without esterase in a pH 8 buffer medium (data collected in D. F. Williams' laboratory)

Polymer	Solution	Time (weeks)	Initial mass (g)	Final mass (g)	Mass change (g)
PLA 50/1	Buffer	16	0.393	0.137	− 0.256
PLA 50/2	Enzyme	2	0.395	0.519	+ 0.124
PLA 50/3	Enzyme	4	0.400	0.646	+ 0.246
PLA 50/4	Enzyme	8	0.402	0.745	+ 0.343
PLA 50/5	Enzyme	16	0.397	0.307	− 0.090
PLA 100/1	Buffer	16	0.399	0.482	+ 0.083
PLA 100/2	Enzyme	4	0.412	0.437	+ 0.025
PLA 100/3	Enzyme	8	0.405	0.442	+ 0.037
PLA 100/4	Enzyme	16	0.408	0.382	− 0.026

Actually, the identification of the mechanisms of chain cleavage *in vivo* is a difficult problem. Indeed, indications must be found *in vitro* by using model media before being confronted with *in vivo* data.

The analysis of the literature from the view point of the different factors which can affect both *in vitro* and *in vivo* behaviours of polyesters regardless of their chemical structure is almost impossible because only a very few authors report data on parameters like molecular mass (MM), molecular mass distribution or polydispersity (MMD), the presence of low molecular mass compounds (LMM) and their identification or the characterization of polymeric materials after sterilization. Here again, we prefer to comment in detail on several points which deserve further examination in the light of data made available to us recently.

The first comment concerns the involvement of enzymes in the hydrolytic scission of aliphatic polyester chains. The second deals with the fact that many polyesters show bimodal macromolecular mass distributions during chain degradation. The last one concerns the contribution to polymer instability of initially present impurities and additives or of compounds which are absorbed when polyesters are put in close contact with model media or complex body fluids.

5. Enzymes versus simple water in the degradation of aliphatic poly(α-hydroxy acids)

The suggestion has been made several times that enzymes may be involved in the degradation processes of polymers. This statement includes polymers one would suppose to be stable [67]. Authors generally based their discussion on *in vitro* loss of radioactivity of ^{14}C radio-labelled polymers and sometimes on the decrease of mechanical properties.

Holland *et al.* [16] have examined critically the literature dealing with the contribution of enzymes to aliphatic polyester degradation and came to the conclusion that, for glassy polymers, little enzyme involvement is expected in the early stages. The involvement can become more pronounced in the later stages, however, as erosion and physical fragmentation of the polymer occur. In contrast, for polymers in the rubbery state, enzymes can play a significant role in their degradation. The latter statement reflects recent data reported for poly(ε-caprolactone), which showed a rate of degradation at the surface 600 times larger with respect to the inner part of implants [66–68].

However, we believe that when *in vitro* and *in vivo* degradation are compared, or when enzyme-free and enzyme-containing buffer media are compared, as is generally done in literature, differences can be expected for many other reasons than enzymatic degradation of macromolecules. Nevertheless, it is accepted that in the later stages of degradation, enzymatic activity is involved [69]. Indeed, LMM ester by-products or hydroxy-acid metabolites which are released can be digested by enzymatic processes when fragments of polymer are being endocytosed by phagocytic cells according to histological evidence of engulfment before elimination [60]. At the very beginning of the degradation processes, when high MM macromolecules are present as a polymer mass, other phenomena have to be taken into account before considering experimental distinctions which can be observed between data collected in model media with and without enzymes as reflecting the contribution of enzymes.

Possible explanations can be suggested which should be investigated carefully in the future. Polyester chain degradation occurs through hydrolytic phenomena. As such, they must be regulated by kinetic laws, and hydrolysis of ester bonds is known to be an equilibrated process [7]. Therefore, phenomena which can remove degradation by-products may well affect the reaction rate. In this respect, elimination of degradation by-products either by enzymatic reactions (*in vitro* or *in vivo*), or by diffusion from the degradation site (*in vivo*) because of increased fluid transfers related to inflammatory responses and thus to the appearance of LMM by-products (as mentioned in the previous chapters), may well explain an increase of hydrolysis rate without direct involvement of enzymes.

Another remark must be made insofar as the use of model enzyme media are concerned. Although experimental conditions are not always well described, one can suspect [67] that large amounts of enzymes are used with respect to polymer concentration (1:1 mass ratio in the given reference). Under these conditions, the enzyme must be regarded as a chemical compound from both chemistry and physical chemistry view points. Let us tentatively mention possible effects such as solubility changes of hydrophobic compounds in lipophilic microdomains present in protein molecules, complexation of some ions or ionic compounds present in the buffer medium or in the polymer mass, or any other physico-chemical effects which can be expected from complex molecules like enzymes when they are not at their catalytic concentrations. Even if conclusive data are not available to bear out these remarks, the fact that modification of physico-chemical equilibria (solvent and ion uptakes, presence of surfactants at the surface) can affect degradation rates, and thus biodegradation of aliphatic poly(α-hydroxy acids), is now obvious [70]. This point is supported by data reported by Makino *et al.* [71] for plasma proteins, even if, in this particular paper, half lifetime assigned to PLA 100 microcapsules seems to be rather small ($t_{MM\frac{1}{2}} = 50$ days).

Further inconclusive information exists on the same line. Recently, we have collaborated with Williams in studying the effect of an enzyme on the properties of miniature tensile bars, whose behaviour *in vivo* has been reported previously [17]. Five samples of PLA 50 and four of PLA 100 were assessed for susceptibility to degradation by esterase. All bars were weighed accurately and their dimensions, in respect of width and breadth within the gauge length, were determined. Each bar was then exposed to either a buffer solution (0.1, M borate pH 8.0 at 37 °C) or enzyme solution (esterase, EC3 1.1.1, type 1, derived from porcine liver,

supplied by Sigma, in solution in 0.1 M borate buffer at pH 8.0). The activity of the enzyme was measured as 100 units per mg protein at 24 h. Enzyme solutions were prepared fresh each day. Experimental conditions and results are shown in Table IV.

At the end of the time period the samples were weighed. As expected from the literature and from our experiences [17], PLA 50 samples which were exposed to solutions (either buffer or enzyme) for 16 weeks had distorted and fragmented such that dimensions were not possible to record. For samples at 2, 4 and 8 weeks, the weight changes are shown in Table IV. Clearly, PLA 50 bars absorbed large amounts of fluid over the eight week period (over 80% of the initial weight), but then weight loss became rapid as degradation was taking place. It is likely that figures result from the sum of water-absorption weight gain and degradation weight loss. Anyhow, it would appear from the 16 week data that the degradation in buffer is faster than with the enzyme, although there were too few specimens to confirm this finding statistically. At this stage, it happened that the degrading polymeric mass was soft because of plasticization and degradation. Basically, this physical state should have improved the penetration of enzyme molecules and polymer chain mobility. Nevertheless, no significant difference was detected between the two media.

As for PLA 100, it absorbed fluid far less readily than PLA 50 as expected from its semi-crystalline structure. The weight increase at 8 weeks was less than 8%, i.e. an order of magnitude less than shown by PLA 50. Furthermore, no difference was found between the mechanical properties of PLA 100 at 16 weeks whether in buffer or enzyme. Therefore, both PLA 50 and PLA 100 were not affected by the presence of the selected esterase medium. PLA 50 degraded in both buffer and enzyme far more rapidly than PLA 100, in agreement with *in vivo* data [17]. In a previous work, Williams [64] has shown that lactate dehydrogenase gave ambiguous results with PLA under different experimental conditions. In contrast, Proteinase K, pronase and bromelain showed significant effects while the effects of esterase ficin and trypsin were found to be minor. Accordingly, the absence of activity of esterase observed in the cases of PLA 50 and PLA 100 does not preclude possible effects of other more efficient enzymes, even if we strongly believe, as many others do [15, 70, 72, 73], that PLA chain degradation is exclusively due to simple hydrolysis.

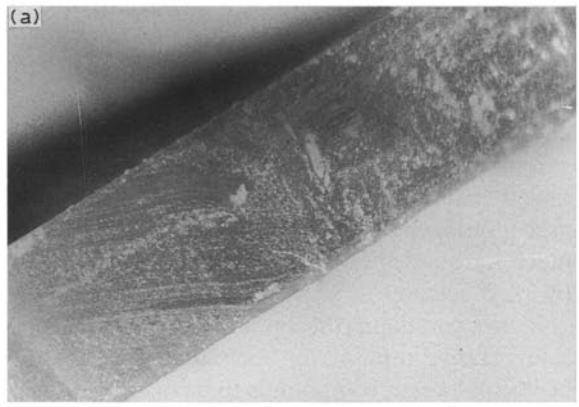
If data collected in Table IV are not quantitatively conclusive insofar as enzyme contribution to degradation is concerned, the fact that both weight change and area change are affected by the presence of esterase is of particular interest with respect to the previous remark on the possible effects of enzyme on physico-chemical characteristics of aqueous buffer media. A very small weight loss was seen with PLA 100 in enzyme while the specimen in buffer was still showing a weight gain (indeed, quite a considerable weight gain in comparison to PLA 100 in enzyme). Compared with the ability of PLA surfaces, as surfaces of all materials actually, to bind plasma proteins [71], it is likely that in one way or another, the presence of enzyme in the medium leads to surface modification and modification of other physico-chemical characteristics. This may well explain the fact that, if anything, the buffer has a greater effect on PLA 50 than the enzyme. Of itself, this finding is limited. However, it has to be compared with recent data reported by Tsakala [74] which show that PLA 50 implants degrade less rapidly in the presence of esterase than in a phosphate buffer medium. At this point let us mention the recent data by Tabata [75] on surface-dependent macrophage phagocytosis of polymer microspheres made of LMM LA and GA homo and copolymers precoated by various proteins. Apparently, phagocytosis was promoted by IgG, tuftsin and gelatin coatings, whereas bovine serum albumin reduced it significantly.

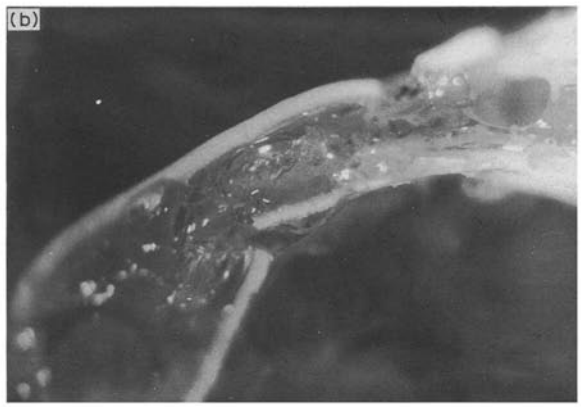
According to the previous comments, it is likely that the enzyme versus simple hydrolysis would benefit from new arguments if one better knew the consequences of the presence of enzymes, lipids, cations, amphilic compounds like surfactants, etc., on phenomena like absorption, diffusion, ion-exchange, ion selectivity in a degrading polyester mass full of alcohol, ester and acidic groups.

6. Bimodal and multimodal molecular mass distributions of degrading aliphatic polyesters

Among the quite numerous papers dealing with aliphatic polyester degradation, only a small number report data on changes in molecular mass distribution or polymolecularity. Most of the investigations of MM changes were carried out by viscometry, which only reflects average variations in MM.

Reed and Gilding have investigated the molecular mass loss profiles of PGA DEXON^{R} suture by GPC in hexafluoroacetone and of LA/GA copolymers either in hexafluoroacetone or in chloroform depending on the GA content of these copolymers [76]. GPC curves at pH 7 and 37 °C, which reflect *in vitro* MMD changes of PGA sutures versus degradation time at body temperature, showed monomodal GPC profiles at low degradation times and bimodal degradation profiles at large degradation times, after 56 days, for example. Unfortunately, no precise characterizations of the evaluated compounds were given. Later, we reported a series of GPC profiles for PLA *X* miniature tensile bars implanted in sheep, and we clearly showed that the profiles of fast-degrading specimens were bimodal [19]. These findings reflect a complex degradation mechanism of polyester specimens. At that time we suspected a correlation with the morphology of the implants and also that the presence of a LMM peak separate from the high molecular mass peak was due to faster degradation in the amorphous region, in agreement with similar interpretations found in literature [76, 77]. However, bimodal GPC curves were also observed for amorphous PLA *X* stereocopolymers ($10 < X < 90$) and especially for PLA 50, where the presence of crystalline microdomains has never been detected even during the degradation process,





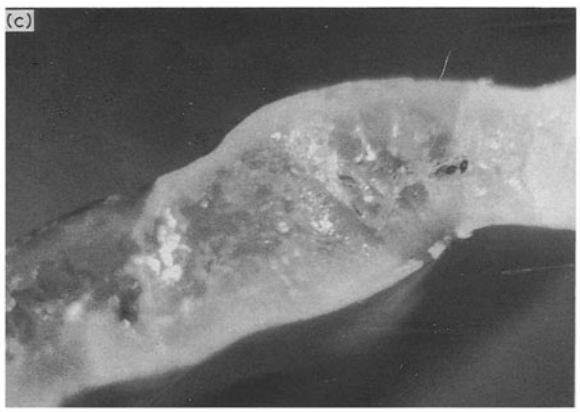


Figure 1 Optical microscope pictures of sections of PLA 50 parallel-sided plates: (a) initial aspect; (b) after 35 days *in vitro* in non-buffered water; and (c) after one month osseous implantation in sheep.

which is known to cause an increase of crystallinity for semi-crystalline PGA and PLAs [78].

To clear up this point, investigations have been undertaken based on the monitoring of the fate of 2 mm × 10 mm × 10 mm compression moulded parallel-sided plates allowed to age in various model media and *in vivo* [79]. For this, complementary techniques, including X-ray, GPC, dynamic mechanical testings, impact strength, etc., are being used. One of the first pieces of information which has been drawn from this programme is an interpretation of the bimodal MMD shown by degrading amorphous poly(α-hydroxy acids). Indeed, we have found that the plates become heterogeneous in terms of MM when they are ageing in aqueous media, regardless of pH and chemical structure. Optical examination after drying and breaking of the specimens clearly shows that colours of the uniformly honey-like solid become heterogeneous in colour after some time in water, namely whitish at the surface and light brown in the central zone (Fig. 1). These features had been previously observed on the miniature test bars implanted *in vivo* several years ago, but were not considered as important at that time [19]. Slicing of the plates and GPC measurements on the resulting slices has revealed that MMs are much lower in the central part than at the surface. As MM determinations are usually performed by taking out a large piece from the bulk, both HMM compounds from the surface and LMM ones from the centre are analysed and thus give rise to average bimodal GPC profiles (Fig. 2). The present understanding of these findings is that a membrane of polymer is formed at the surface which is at equilibrium with surrounding aqueous media and thus degrades at a given rate with relatively free diffusion of ions and water according to physico-chemical characteristics of the polymer-surface–aqueous-medium system. This slowly degrading polymer acts as a semi-permeable membrane with respect to the inner mass of degrading macromolecules in which the concentrations of carboxyl and alcohol groups generated by polymer chain cleavages increase with no possibility of the chain fragments escaping before their size fits the cut-off of the outer membrane or before this membrane breaks down. We do not know yet whether the pH decreases in the central part. This particular point depends on ion exchange processes between the polymer mass and the surrounding aqueous medium. Nevertheless, the inner medium must be different either because of Donnan effects, or increase of osmotic pressure, or cation selectivity, or any other factors or combination of factors which are known to contribute to ion-exchange systems with variable capacity and hydrophily [80].

These findings agree well with remarks which appeared in the literature of PLA and PLA GA microspheres [81, 82], which suggest that bulk degradation is rather a general mechanism for polyester hydrolysis. In these papers, it is stated that the inner part of the microspheres seems to degrade faster than the outer part. A difference of crystallinity between the outer

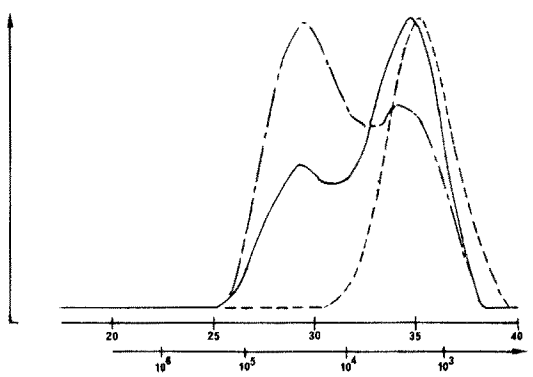


Figure 2 GPC chromatograms of PLA 50 parallel-sided plate allowed to age for 35 days in a model non-buffered aqueous medium: (——) massive sample, (– – –) outer whitish layer; (– – – – –) central honey-like part.

and inner zones was suggested to account for the difference in degradation rates [81]. One can reasonably presume that PLA 25 GA 50 which has been used by Vissher *et al.* [81] was not a semi-crystalline material. Therefore, it is likely that the differences in degradation rates observed for the microspheres are similar to those observed for our parallel-sided PLA *X* plates. A modification of surface properties by residual surfactants, in the case of microspheres, or by the contact of the walls of the mould, in the case of plates, cannot be excluded.

In their paper, Kenley *et al.* [82] point out that bulk erosion clearly occurred in the case of their PLA GA copolymers derived from DL-lactic acid and glycolic acid. Their data show the presence of an induction period of one week which was not observed for our PLA 25 GA 50 terpolymers. However, it must be noted that Kenley *et al.* used 1-dodecanol as chain terminator. Presumably, this hydrophobic aliphatic end-capping group should have some effects on degradation rates, as it has been mentioned for acetylated PLA polymers [83], and thus stabilize the inner material with respect to normal PLA. The result is the same, namely a difference of degradation rates between surface and bulk. It is likely that similar phenomena occur in the case of semi-crystalline poly(α-hydroxy acids). However, they probably overlap with the difference of degradation rates due to the presence of crystalline and amorphous domains and average profiles are then observed.

Therefore, we are forced to conclude that biodegradability of polyesters of the α-hydroxy type appears to be dependent not only on chemical structure, configurational structure, MM, MMD, presence of residual compounds (oligomers, monomers, solvents, initiators), presence of adsorbed and absorbed compounds such as lipids [84], but also on morphologies such as crystallinity [19, 85] and physico-chemical factors related to water absorption [86], ion-diffusion, ion-exchange, ion-selectivity or ionic strength and pH buffer concentration as shown by Makino *et al.* [87].

From this remark, it becomes obvious that biodegradation of aliphatic polyesters can be dramatically affected by the presence of additives such as plasticizers, or drugs in the case of polymers used for drug-delivery systems.

7. LMM-containing poly(α-hydroxy acids)

The fact that oligomers or even HMM chemicals can affect dramatically the degradation and thus the biodegradation of aliphatic polyesters of the poly(α-hydroxy acid)-type being now well recognized, one could consider that sufficient knowledge exists to obtain solutions and thus to remove the effects. Several years ago we showed that a careful extraction of LMM compounds present in the polymeric mass recovered after bulk polymerization of lactides is important for considerably improving the properties of ready-for-implantation sterilized poly(α-hydroxy acid) components [88]. Recently, Leenslag *et al.* [78] have confirmed that the removal of residual LMM compounds, such as the catalyst, oligomers or remnants of monomer, has a remarkable effect on the mechanical properties and degradation of PLLA (PLA 100) specimens in model aqueous medium. The authors pointed out the plasticizing effect of residual solvents without further comments. They also mentioned that elimination of oligomers by dissolution–precipitation by the acetone–methanol couple led to much less stable polymers than solid–liquid extraction by ethyl acetate.

If one compares the literature of poly(α-hydroxy acid) massive implants for bone surgery, which have to be free of foreign compounds to have high mechanical properties and long lifetimes, with that of drug-loaded implants and drug-loaded microparticles for drug delivery, it becomes obvious that the hydrophilic or hydrophobic character of the load (in terms of drug-delivery devices), or of impurities (in terms of biomaterials), are two of the major factors which determine the ability of the polymeric mass to absorb water and thus which affect the degradation kinetics of the whole mass. Releases of hydrophobic compounds have been reported for periods of time as long as six months to one year for (LA) stereocopolymers and LA–GA copolymers as in the case of PLA 50 combined with d-norgestrel which are normally totally resorbed within six months in the unloaded form [89]. In contrast, dramatic releases due to the collapse of polymer matrices have been observed after a few weeks for PLA 50 loaded with a hydrophilic drug [60]. The effects are similar if the load is not chemically inert. For instance, Maulding *et al.* [90] have reported that poly(α-hydroxy acids) degrade much faster when they are loaded with basic drugs. Although this should be confirmed, one can presume from the preceding remarks that the differences of degradation rates reported by Leenslag *et al.* [78] between ethylacetate- and acetone–ethanol-extracted PLA 100 are related to the effect of residual solvents present in the polymer mass, since ethylacetate is much less hydrophilic than acetone. Of course, the nature of the solvent and its behaviour with respect to water (or any other chemical present in the surrounding aqueous medium) is only part of the problem. Indeed, in the same paper, correlation between decrease of molecular masses and decrease of tensile strength seems to be very much dependent on the extraction method. Ethylacetate-extracted polymers surprisingly retained their tensile strength even if their MM is one tenth of its initial value, whereas no mechanical properties remained for the acetone–ethanol-extracted polymer at the same decrease of initial MM. The affinity of impurities for water is one factor, but the own affinity of the polymer for water also contributes. It has been claimed that GA-containing LA polymers degrade much faster because of the higher hydrophilicity of GA repeating units with respect to LA ones [16, 76]. However, Pitt and Gu [91] suggested recently that the origin of the more rapid rate of hydrolysis of PLGA (PLA 30 GA 70) relative to PCL and PLLA (PLA 100) appears to be the intrinsic reactivity of the glycolate linkage. This statement is based on the fact that the rate of erosion (degradation)

but not the rate of chain cleavage was enhanced by various neutral and basic reagents.

At this point, it is of interest to mention that mechanical stress can significantly affect the degradation as shown by Miller and Williams for PGA sutures. The degradation, monitored by changes in the tensile load at break, was considerably enhanced by pre-straining the material to one-half of the normal extension at break [92]. The influence of water, as of many other compounds which can act as plasticizers, on glass transition of poly(α-hydroxy acids) has dramatic effects on degradation. Sieman [86] has shown that the water absorption of poly(DL lactic acid) (PLA 50) and compositions thereof with salicylic acid, caused T_g reductions up to 12 °C and 28 °C respectively. The author concluded that unexpected changes in the thermal, mechanical and diffusive properties of polymer–drug combinations can occur. The influence on biological properties may be dramatic as well.

After these comments on chemical, physico-chemical and mechanical factors which can affect more or less the biodegradability of aliphatic polyesters in general, let us consider briefly the fact that everything can be reversed by other steps along the way to ready-for-implantation devices. Two of these steps are of particular interest, namely sterilization and storage.

Insofar as sterilization is concerned, it is now well established that heat and β- or γ-radiations lead to degradation of polyester chains during sterilization, whereas ethylene oxide respects the integrity of these chains [4, 17]. However, as it has been mentioned for other polymers, ethylene oxide, which appears as having a good affinity for polyesters, is rather difficult to remove from massive samples [93]. In this regard, ethylene oxide behaves quite similarly to dichloromethane whose ultimate remnant traces (below 10 p.p.m.) have been shown difficult to remove from PLA *X* and PLA *X* GA *Y* microspheres [60]. The degradation of polyester chains by β- or γ-sterilizing radiations is dramatic when high mechanical properties are required [17]. One might think that the slight decrease of molecular masses which results from the radiation cleavage is acceptable for applications which do not require high mechanical properties, as in drug-delivery devices for example. Actually, it has been shown recently that lifetimes of poly(α-hydroxy acid) microspheres are dramatically affected too by radiation sterilization, a point which is of considerable importance when well-defined drug-release profiles are desired [94]. Nevertheless, it seems that in the particular case of those cis-platin PLA 50 microspheres which release the drug through a matrix-controlled diffusion process, the release profiles are dramatically affected because of earlier catastrophic degradation and not because of changes in the diffusion process or characteristics of the matrix before collapsing. Indeed, collapsing of sterilized and non-sterilized microspheres occurred after 12 days and 60 days respectively, whereas before collapsing both types of microspheres showed similar release rates [60].

It is now well known that storage of LA and GA polymeric compounds is a problem because of slow degradation, unless the material is kept in a dry atmosphere. Recent results on unloaded PLA *X* and PLA *X* GA *Y* microspheres have shown that storage combined with sterilization can be the source of slow degradation during long-term storage even in a dry atmosphere [60]. It is likely that this type of ageing is due to slow evolution of chain fragments and radicals formed at the sterilization stage. The phenomenon seems to be larger for GA-containing copolymers. The larger the GA content, the larger the storage degradation. Much further work is required to bear out this finding, which could be a serious problem if it is confirmed.

Many other secondary factors can contribute to the hydrolytic degradation processes of aliphatic polyesters and thus can affect to some extent biodegradability, interaction with tissues, and the fate of polymeric devices in a living body. The effects of most of these factors are poorly understood and quantitative investigations have to be done. However, one must keep in mind, as already mentioned several years ago [19], that most of the factors which can affect aliphatic polymer chain degradation are interdependent. Therefore, only careful investigations on well-defined compounds will provide one with conclusive information on the behaviour of given aliphatic polyester implants.

8. Other aliphatic polyesters

As mentioned above, the literature is far less complete for the other aliphatic polyesters than for poly(α-hydroxy acids).

For compounds like poly(dioxanone) and poly(ε-caprolactone), etc., the reader is advised to consult the review by Holland *et al.* [16].

One compound, poly(hydroxy butyrate), or PHB, deserves more comment to clear up the present perception of the field of biodegradable and bioresorbable aliphatic polyesters. In their review, Holland *et al.* [16] recall the main characteristics of the behaviour of PHB as perceived from the literature insofar as biodegradation and enzymatic hydrolysis are concerned. The main point is that PHB has been proposed as a biodegradable material on the basis of its degradation characteristics in certain biological environments, namely in the presence of soil bacteria. This finding has led to claims that PHB and PHB–HV copolymers (HV, hydroxyvalerate) may be used to achieve degradable materials and devices [95], including drug-releasing systems [12, 83]. As early as 1971, Schmitt and Frazza mentioned that PHB sutures did not degrade significantly *in vivo* [12, 96]. Kronenthal mentioned briefly that PHB showed an onset of degradation *in vivo* after eight weeks but no more information was given [5]. PHB-drug systems have been regarded as degradable [12] on the basis of drug release profiles *in vitro* and *in vivo*. However, Williams in a recent paper clearly showed that PHB and PHB–HV copolymers, processed to form monofilament fibres, do not undergo any significant loss of mechanical properties even after six months [97]. If one considers in more detail the data reported on *in vivo* and *in vitro* behaviour, one can find a small

decrease of load at break *in vivo* with respect to *in vitro* right after implantation, but no more changes later on. They also show that PHB can support up to 5 Mrad (5×10^4 Gy) before significant loss of tensile strength can be detected *in vivo*. The stability of PHB has also been reported by Helevirta *et al.* for injection-moulded PHB rods [98]. A recent work by Holland *et al.* [96] on PHB–HV copolymers shows that the poly(α-hydroxy acid) story is back, as the authors underline very well the effects of several factors which affect the lifetimes and degradation rates, including molecular mass, copolymer ratio, physical form of the samples, temperature, pH, crystallinity, etc. Anyhow even if the authors report evidence of degradation for LMM compounds with poor mechanical properties, HMM copolymers with good mechanical properties exhibited 1% weight loss after 200 days at pH 7.4 and 37 °C for melt press discs. Here again, behaviour depends very much on the definition of the compounds in the series of HB–HV copolymers.

Another polymer, poly(β-malic acid), PMLA 100, was synthesized for the first time several years ago [13, 99] and is presently studied in our group for its potential application as a water-soluble bioresorbable carrier and as the basis of solid polymeric materials which can be achieved when pendant acidic groups present as side chains are turned hydrophobic by proper chemical modification. At the moment, PMLA 100 is known as a water-soluble polymer regardless of the pH. It degrades rather rapidly at neutral pH under physiological temperature and ionic strength [100]. The LD_{50} of PMLA given i.p. to mice is above 3 g kg^{-1} body weight. So far, no specific antibody has been detected even after repeated administration in rabbits. The degradation rates as well as physical characteristics depend on chemical modification of pendant acidic groups to neutral ester ones such as benzyl ester derivatives. The racemic homopoly-(benzyl β-malate), PMLABe, seems to be almost stable when implanted *in vivo* [101]. Recently, routes to optically active PMLA 100 have been found [102, 103]. However, no information on biodegradation is available yet.

9. Conclusions

There is no doubt that some aliphatic polyesters are biodegradable polymers of excellent biocompatibility. For those which appear as non-biodegradable, as referred to therapeutic applications, it seems possible to make them degradable in living media by different ways: mixture with low molecular mass chemicals or degradative radiations. Of course, none of these solutions is recommended to achieve systems totally controlled insofar as physical, physico-chemical, mechanical and biological properties are concerned. A careful examination of the literature of aliphatic polyesters shows that biodegradability as referred to therapeutic applications must be appreciated with respect to specification lists and that the factors which can affect their behaviour *in vivo* must be considered as interdependent and thus can hardly be studied separately. Nevertheless, aliphatic polyesters seem to degrade by random hydrolytic chain-scission probably with autocatalysis by generated acidic end groups. In spite of the various problems related to their biodegradability, they seem to be versatile enough to cover large ranges of properties and to allow the finding of original solutions to temporary therapeutic applications such as osteosynthesis, bone reconstruction, and drug delivery in complement of the successful suture materials which have been commercially available for almost two decades.

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