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PRESENT AND FUTURE OF PLA POLYMERS

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ABSTRACT

Lactic acid-based aliphatic polyesters (PLAs) are well known bio-compatible bioresorbable polymers which are being increasingly used as biomaterials for temporary therapeutic applications. Because of their sensitivity to water and the formation of degradation by-products which can be easily metabolized by microorganisms, this type of polymers also has potential to replace commodity polymers in packagings or as mulch films. From an overview of synthesis routes, structural characteristics, and performances, an attempt is made to evaluate the future of PLA polymers insofar as industrial development is concerned.

INTRODUCTION

High molecular weight aliphatic polyesters of the poly(2-hydroxy acid) type were synthesized for the first time more than 40 years ago when the ring-opening polymerization of 1,4-dioxane-2,6-dione (glycolide = GA) and 3,5-dimethyl-1,4-dioxane-2,6-dione (lactide = LA) was discovered [1, 2]. For many years these polymers, which form the PLA/GA family, were regarded as useless compounds because of their sensitivity to heat and water which precluded thermal processings based on extrusion or injection molding. This situation ended in the 1960s when advantage was taken of their sensitivity to water to make artificial degradable sutures of the poly(glycolic acid) type, PGA, aimed at replacing denatured collagen known as Catgut [3, 4]. In 1966, Kulkarni et al. [5] showed that high molecular weight poly(L-lactic acid) and poly(DL-lactic acid) were also degradable in vivo and

thus of interest for biomedical applications. Since then, poly(2-hydroxy acids) have been studied extensively with respect to potential applications as temporary therapeutic aids in surgery and in pharmacology [6]. PLA/GA devices for bone fracture internal fixation (Biofix from Finland, Phusilines from France) and antitumoral drug delivery systems (Zoladex from UK, Decapeptyl from France, Enanthone from Japan) are now commercially available. Because of their biocompatibility, their degradability, the mineralization or metabolization of their degradation by-products, and the fact that a large range of properties can be covered by taking advantage of copolymerization and stereocopolymerization, PLA/GA polymers are presently considered as the most attractive compounds for temporary therapeutic applications in the biomedical field [6].

During the last 5 years, people have realized that polymers were becoming a source of ecological problems because of the huge amounts of bioresistant wastes generated from the 70 millions tons of polymers produced each year in the world.

Beside more or less problematic solutions like incineration, reprocessing of wastes, pyrolysis, or other chemical degradations aimed at regenerating monomers, bioassimilation of polymers by environmental microorganisms after degradation or biodegradation is regarded with interest, at least from a basic viewpoint, because it could offer a solution by eliminating dispersed packaging wastes from the environment or mulch films from culture fields. They could also be used for pesticides, insecticides, or hormones in local delivery in plant therapy on the basis of the concept of sustained release drug delivery. Ideally, such applications should require polymers functional for the targeted application and also biocompatible, i.e., capable of respecting environmental life and allowing biological recycling if corresponding monomers are released from the biomass and degraded by-products can return to it.

In this paper we present an overview of the present knowledge on the origins, the structural characteristics, and the performance of lactic acid polymers in order to comment on their future with respect to industrial development. We will examine successively the situation insofar as synthesis, chirality, thermal properties, mechanical properties, and degradation mechanisms are concerned.

THE FAMILY OF LACTIC ACID-BASED POLYMERS

The literature is quite confusing about poly(lactic acid) polymers mostly because authors usually do not clearly define the type of PLA they are dealing with. This is primarily due to the fact that many authors belong to other disciplines and are thus not well informed about polymer science and the effects of chain composition and chain structure on the macroscopic properties of polymeric materials. In order to easily reflect the composition of LA-derived polymer chains, we have introduced simple acronyms, namely PLA_XGA_Y where X = percentage of L-LA units and Y = percentage of GA units [7]. Of course, these acronyms can be adjusted to include comonomeric units other than GA in the case of copolymers derived from other cyclic compounds such as caprolactone or ethylene oxide (Table 1). The use of these acronyms is not yet generalized in the literature.

TABLE 1. Chemical Structures and Acronyms of Poly(α -Hydroxy Acids) Derived from Lactic and Glycolic Acids

Chemical structure	Acronyms
$-\left[\text{O}-\underset{\text{CH}_3}{\overset{\text{H}}{\text{C}}^*}-\text{CO}- \right]_n$	PLA ₁₀₀ poly(L-lactic acid)
$-\left[\text{O}-\underset{\text{CH}_3}{\overset{\text{H}}{\text{C}}^*}-\text{CO}-\ddot{\vdots} \right]_n \text{comonomer B}- \left]_q$	PLA _{(100-Y)B_Y} ($Y = q/(n + q)$) (L-LA/GA copolymers)
$-\left[\text{O}-\underset{\text{CH}_3}{\overset{\text{H}}{\text{C}}^*}-\text{CO}-\ddot{\vdots} \right]_n \text{O}-\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}^*}-\text{CO}- \left]_p$	PLA _X ($X = 100n/(n + p)$) (LA stereocopolymers)
$-\left[\text{O}-\underset{\text{CH}_3}{\overset{\text{H}}{\text{C}}^*}-\text{CO}-\ddot{\vdots} \right]_n \text{O}-\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}^*}-\text{CO}-\ddot{\vdots} \right]_p \text{comonomer B}- \left]_q$	PLA _X B _Y ($X = 100n/(n + p + q)$) ($Y = 100q/(n + p + q)$) (terpolymers)

MONOMERIC SPECIES AND SYNTHESIS OF LACTIC ACID-BASED POLYMERS

Lactic acid-based polymers can be produced from various monomers and by different routes (Figs. 1 and 2). The poly(2-hydroxy acid)-type backbone can be formed by polycondensation or step-growth polymerization of lactic acid with other hydroxy acids (Fig. 2) [8–10]. It can also be obtained by chain-growth polymerization of lactide with other cyclic monomers such as caprolactone or ethylene oxide. Lactide presents the particularity of being composed of two lactic acid units linked by two ester bonds to form a dimeric cyclic monomer (Fig. 2). Both lactic acid and lactide are chiral, and thus one has to deal with two optical isomers or enantiomers in the case of lactic acid and four isomers, or diastereoisomers, in the case of lactide. This cyclic dimer bears two asymmetric carbon atoms which can be identical, as in the case of L-lactide, D-lactide, and DL-lactide, or different as in the case of *meso*-lactide (Fig. 2). The latter is rather difficult to prepare in a high optical purity form and is rarely mentioned in the literature. L-Lactic acid is a product of biotechnologies. Racemic lactic acid can be obtained either by racemization of L-lactic acid or by synthesis through oil chemistry. L- and DL-Lactide are obtained in two steps from L-lactic acid and DL-lactic acid, respectively [11]. *meso*-Lactide is extracted from the filtrates remaining after DL-lactide recrystallization.

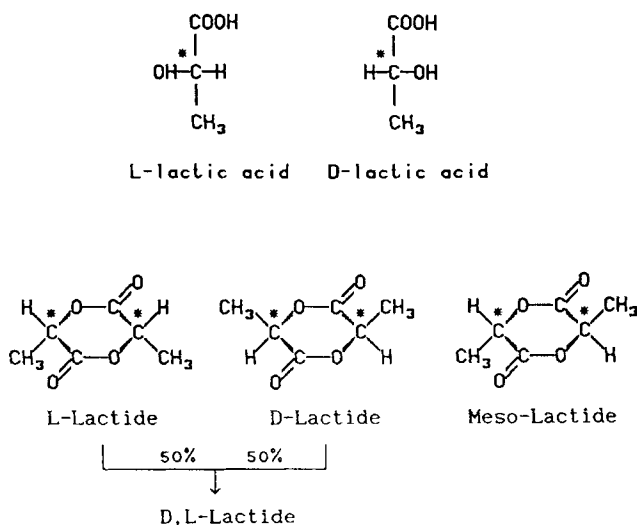
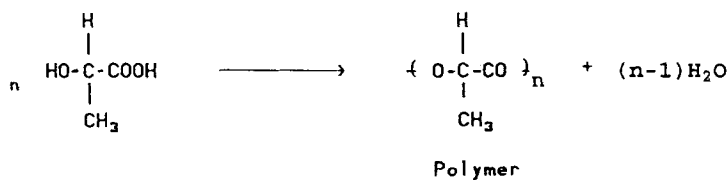


FIG. 1. Lactic acid and lactide monomers.

The polycondensation of hydroxy acids is generally performed by distillation of water, with or without catalyst, vacuum and temperature being progressively increased [8-10]. This is a rather simple step which leads to oligomers with low molecular weights (< 5000 daltons, $M_w/M_n \approx 2$). Temperatures above 180°C usually cause coloration. Higher molecular weights (50,000) have been obtained by postcondensation in organic solution using dicyclohexylcarbodiimide (DCC) [12]. However, this method has not been developed industrially.

Polycondensation or step-growth polymerization



Ring-opening polymerization

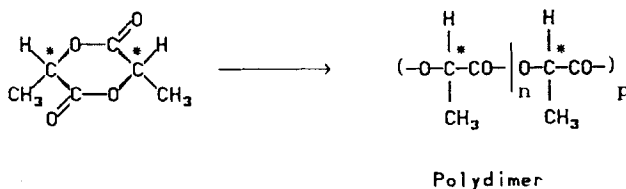


FIG. 2. Routes to make poly(2-hydroxy acid)-type backbones.

So far, high molecular weight polymers are obtained from the ring-opening polymerization of lactide-containing feeds, either in the bulk at different temperatures or in organic solution [11]. Many compounds can initiate the ring-opening polymerization of lactide-type cyclic dilactones. In the case of lactide, the literature shows that almost all the possible mechanisms (anionic [13, 14], cationic [15–17], or by insertion after complexation [18–23]) have been reported. Critical factors are the initiator concentration [21, 23–26]; the polymerization temperature [16, 21, 23, 26, 27]; the polymerization time [13, 16, 21, 23–27]; the presence of acids [11], of water [23], or of alcohols used as coinitiators [28]; and other impurities. On the other hand, secondary reactions such as depolymerization with monomer regeneration at equilibrium [23, 25, 29, 30] or transesterification [13, 20, 21, 31] are generally observed and must be controlled. With respect to industrialization, the use of an organic solvent is possible; however, bulk polymerization would be preferred if the problem of heat transfer in large batches could be solved [11]. In the biomedical and pharmacological fields, stannous octoate is generally recommended for initiation because it gives rather fast polymerization and has been approved by the US Food and Drug Administration. Many years ago [32] we selected powdered zinc metal as a convenient initiator for biomedical applications because zinc is biocompatible and a useful nutritional oligoelement. This initiator requires longer polymerization times than stannous octoate, especially for L-lactide-rich feeds. It is now used by our group as a standard in order to make the comparisons of the data collected over the years more consistent. Combined with purification by the solvent/nonsolvent technique, zinc leads to polymers which are extrudable or processible by compression or injection moldings. Heat processed devices like bone plates, screws, and rods are now currently made industrially in different countries, at least on a small scale. Sometimes people do not purified the crude polymer and process it as-polymerized [33]. In this case, molding is impossible and the devices have to be machined. In any case, the lactide monomers have to be carefully dried to yield high molecular weight compounds, and processing has to be carried out carefully with polymers of intermediate molecular weight in order to preserve the quality of the initial polymer and to obtain devices with good mechanical properties. Films, micro-, and nanoparticulates can be made from solutions in organic solvents. Slight degradation is generally observed, but the main problem is the removal of residual solvents. This can be achieved at high temperatures and under vacuum, an operation which is not always acceptable because of the risk of deformation and degradation.

STRUCTURAL CHARACTERISTICS OF LACTIC ACID-BASED POLYMERS

As recalled above, the PLA family includes copolymers with other monomers and thus can present all the classical structures generally found in polymer science, namely random, diblock or multiblock, star, etc., with all the consequences one can predict for such differences. Molecular weight is also an important parameter, as for all polymers. However, the most striking feature is chirality. The presence of asymmetric carbon atoms generates structural particularities which make lactic acid-derived polymers rather special as compared with other polymers. For the sake of clarity, comments will be limited to homo- and stereocopolymers of lactic acid

(PLA_X) (Table 1). However, the distribution of the chiral repeating units can be very different, depending of the synthesis route and on the chiral monomer(s) [30, 34, 35]. Polycondensation of optically pure L-lactic acid and ring-opening polymerization of optically pure L-lactide should lead to the same isotactic chain structure, provided no racemization occurs during chain growth. It is of interest to note that minor differences can be generated when a fragment of the initiator remains anchored at one or two chain ends as in the case of the ring-opening polymerization via the insertion mechanism. The same is true for D-lactic acid and D-lactide which are mirror images of L-lactic acid and L-lactide, respectively. In contrast, dramatic differences in main chain structures can be observed as soon as one deals with stereocopolymers composed of L- and D-lactic acid repeating units. Step-growth polymerization of mixtures of L- and D-lactic acids leads to a random distribution of the L- and D-units, whereas ring-opening polymerization of the lactide dimer leads to nonrandom distributions because the chain grows through a pair addition mechanism. These structural differences were identified many years ago [34]. However, only a few authors have taken the corresponding consequences into account [30, 34–36]. A similar comment can be made in the case of transesterification reactions and racemization which both tend to cause chain randomization although total racemization is extremely rare.

PHYSICAL AND MECHANICAL PROPERTIES

Basically, lactic acid polyesters (PLA_X) have the characteristics of a glassy material with T_g in the 55–60°C range. Because of the presence of one chiral center per repeating unit, the corresponding macromolecules are more or less stereoregular, and thus the macroscopic morphology depends very much on X , with variations being similar in the symmetrical ranges $50 < X < 100$ and $50 > X > 0$. D-Units in a poly-L chain behave like impurities. However, melting temperature and crystallinity decrease rather rapidly with increasing X because of the pair addition mechanism. PLA 92 is still slightly crystalline whereas PLA 87.5 is amorphous. Highly crystalline PLA_X can be obtained with high mechanical properties, especially Young's modulus and tensile strength. PLA 100 is a strong but brittle material. Less stereoregular PLA 98 and 96 have better mechanical characteristics due to their lower crystallinity but not to the plasticizing effect of D-units since T_g is almost the same for all PLA_X under dry conditions [7]. Interestingly enough, oligomers can be used to plasticize the polymers, a feature of great interest for adjusting mechanical characteristics [37]. As for all polymers, the physical and mechanical characteristics depend very much on processing history, on molecular weight, and on molecular weight distribution. Because of the difficulty to control all these parameters, compounds mentioned in literature are far from being comparable, even if they bear the same name. This remark was made for the first time 13 years ago [7] and it is still valuable today. Finally, PLA macromolecules appear very versatile because they can lead from waxy amorphous oligomeric compounds to very strong crystalline devices. Carefully processed stereoregular PLA polymers are rather resistant to atmospheric moisture and aqueous media at normal temperatures. Highly crystalline PLA 100 can last more than 10 years under normal conditions of moisture and temperature, provided it has been carefully processed, but this is not true when

impurities are present in the polymer matrix. Therefore, one must keep in mind that the degradability of lactic acid-based polymers depends on many more factors than was initially thought, as underlined a few years ago [38].

HYDROLYTIC DEGRADATION

The very first investigations revealed that PLA/GA polymers degrade hydrolytically and that the cleavage of ester bonds is catalyzed through carboxylic chain ends. The number of chain ends increases as degradation advances, the catalytic effect also increases, and hydrolytic degradation is said to be "autocatalytic" [39, 40]. A couple of years ago the phenomenon of heterogeneous degradation was discovered to be typical of the hydrolytic degradation of PLA/GA large-size, thick devices [41]. This phenomenon is characterized by a faster degradation inside than at the surface, leading, for some of the members of the PLA/GA family, to hollow structures (Fig. 3). This interpretation has been questioned regarding the possibility of a skin effect due to molding history [42]. Actually, autocatalysis can be the source of many other phenomena such as size-dependence of the degradation rate [43], nonrandom chain cleavages, and degradation-induced morphology changes [44]. For example, it has been recently shown that large size devices degrade much faster than submillimetric particles or very thin films [45]. In other words, the thinner the device, the slower the hydrolytic degradation. These features cannot be explained by molding heterogeneities. However, sooner or later (4 weeks up to several years, depending on many factors [38]), PLA/GA polymers will be returned to their constituting hydroxy acids and will be assimilated by living cells.

As for the ability of living cells or microorganisms to attack PLA/GA surfaces by an enzymatic process, no conclusive demonstration has been made available so far, although many authors have mentioned some modifications of degradation rates in enzyme-containing aqueous media on the basis of with/without experiments [45]. Presently it seems that only water-soluble oligomeric compounds released from partially degraded or oligomer-containing matrices can be degraded in the presence of cells as high molecular weight poly(hydroxybutyrate) does, for example [46]. Recently, a careful in-vitro investigation of the degradation of PLA stereoco-

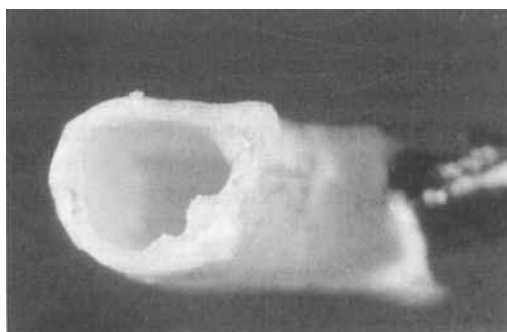


FIG. 3. Part of hydrolytically degraded specimen showing the faster internal degradation (2×2 mm initially).

polymers in the presence of proteinase K has shown that solid PLA does biodegrade [47]. However, this work did not demonstrate that PLA is biodegradable *in vivo* or under real outdoor conditions. In this respect, PLA/GA polymers are presently degradable compounds which can be referred to as "bioresorbable" with respect to assimilation or excretion by animal bodies, and as "bioassimilable" with respect to the giant living system formed by the planet [48].

FUTURE OF LA-BASED POLYMERS

For many reasons, namely rather complex structures, complex degradation mechanisms, ignorance of polymer science, etc., a great deal of confusion exists in PLA/GA literature, generally because investigations have been carried out on poorly defined compounds. Many people talk about PLA as if it is a single magic compound. Actually, as for polystyrene, polyethylene, poly(vinyl chloride), and other commodity polymers, PLA reflects a large family of compounds whose future will depend very much on structure-property relationships. In this respect, degradable LA-based polymers offer a large range of characteristics which have to be confronted in the lists of specifications of various time-limited applications one can find in human activities. The field of biomedical and pharmacological applications is now opened, and markets are becoming available which can absorb rather high added values. Plant therapy and related problems might be potential markets, but research is only starting in this field. So far, LA-based polymers are still expensive materials if one refers to packaging applications. However, chemical engineers have not yet exhausted all the possible solutions to the problem of cheap monomer and polymer productions. A United States company, Cargil, recently claimed a continuous process to make high molecular weight PLAs cheaply. Insofar as cost-effectiveness is concerned, one can predict that production costs will certainly never be as low as are those of present biostable polymers. Processing LA-based polymers is always a delicate operation. However, it seems that special machines with careful control of humidity and temperature might permit processing of large amounts of polymers. Therefore, the future seems to be mostly dependent on first defining what a life-respecting polymer has to be. We are still totally ignorant about the possible impacts of degradation by-products on living and nonliving environmental systems. A great deal of research will be necessary in order to fill the void. If there are finally practical niches, the question will be the creation of new markets, and the future will depend primarily on the attitude of society and consumers with respect to extra costs. From a technical viewpoint, LA-based polymers appear as good candidates for further industrial applications if bioassimilation becomes a strict prerequisite in the field of life-respecting materials. There is no doubt that the intensity of current research efforts on PLA/GA polymers will bring further insights on the perspectives and thus more accurate and consistent predictions.

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