Lactide polymerization faced with therapeutic application requirements

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SUMMARY : The ring opening polymerization of cyclic dilactones of the 1,4-dioxane-2,5-dione-type derived from α-hydroxy acids such as lactic and glycolic acids leads to hydrolytically degradable and bioresorbable aliphatic polyesters of the poly(α-hydroxy acid)-type (PLAGA). Nowadays, taking advantage of the PLAGA family for therapeutic applications is one of the attractive area in polymer science. With such rationale, any advantages expected from advances from the viewpoint of the science of polymeric materials have to be confronted to the chemical, physico-chemical, physical and biological phenomena imposed by living systems and media. The result is generally a compromise necessarily issued from a multidisciplinary approach. This contribution discusses the problem in general on the basis of the present understanding of the synthesis, the architecture and the hydrolytic degradation of PLAGA macromolecules confronted to biocompatibility and biofunctionality requirements.

Introduction

Nowadays, polymers of the poly(α-hydroxy acid)-type derived from lactic and glycolic acids (PLAGA) are the most attractive and prospected compounds with regard to surgical and pharmacological therapeutic applications. Although such polymers can basically be made by different routes, namely step-growth polymerization of the lactic and glycolic acids themselves or post-condensation of conveniently functionalized polycondensates or ring opening polymerization of lactide and glycolide cyclic dimer of lactic and glycolic acids. The latter is by far the most prospected and the most efficient route to make high molecular weight polymers and copolymers composed of lactyl and glycolyl repeating units (1-3). It has been known for many years that the corresponding aliphatic polyester backbone is intrinsically sensitive to water and to heath and is thus degradable in water-based media including living ones (4-5). Threads to suture soft tissues were developed industrially as early as 1970 (6-7). As early as the late 70's, it was found that almost any property of the poly(α-hydroxy acid) polymers can be modulated through copolymerization and stereocopolymerization of the various cyclic dimers which can be formed from lactic and glycolic acids (8-10). It was also

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found early (10) that long lasting poly(L-lactic acid) showing less than 10% decrease of molecular weight over the first year of contact with aqueous water can be made provided both the polymerization and the purification of the polymer are well conducted (11). Even totally bioresorbable composite devices made of a PLA matrix reinforced by PGA fibers were introduced with some success as early as 1978 to fix bone fractures (12). On the other hand, it has been known for many years that glycolide and lactide can be polymerized by a number of catalysts and initiating systems (13) and almost any possible basic mechanism, namely anionic, cationic, or involving coordination to metal ions, has been invoked to account for the particularities observed depending on the polymerization conditions (13-14). During the last 10 years, several initiator or catalyst systems have been proposed to improve the properties of PLAGA polymers, namely decrease the molecular weight distribution, minimize the content in residual monomers, and/or control the repeating unit distribution in copolymers (15-17). Last but not least, the degradation of these polymers has been extensively investigated under various conditions. Despite the fact that a few enzymes can attack a poly(α-hydroxy acid) backbone under special model conditions (14-16), the absence of enzymatic biodegradation due to contact with living human tissues or cells or even with outdoor micro-organisms is now well accepted (17). So far only water soluble oligomers have been found biodegradable and capable of being bioassimilated by the human organism or by outdoor microorganisms under natural conditions (18-19). The general mechanism by which PLAGA polymeric devices degrade in contact with aqueous media was identified several years ago. Absorbed water molecules cleave the main chain ester bonds at random according to an auto-accelerated process involving catalysis by carboxylic acid end groups, the so-called autocatalysis (20). However, other phenomena contribute to the general mechanism because the reaction occurs in a solid matrix. The whole degradation process actually depends on a combination of diffusion, chemical reaction and solubilization phenomena which normally leads to heterogeneous and not homogeneous degradation of the polymeric mass(21). This complex mechanism accounted for many rather unusual phenomena such as i) formation of hollow structure and observation of bimodal molecular weight distributions for partially degraded large size devices depending on the initial morphology (22-23), ii) faster degradation of large size devices as compared with small ones such as thin films or microparticles (24), iii) formation of crystalline residues from initially intrinsic copolymer or stereocopolymer chains (25-26), iv) catalytic or inhibiting effects of basic loads depending on the amount introduced (27). With this regard, the latest major finding was the difference in behavior shown by some PLAGA polymers synthesized from stannous octoate and from zinc-based compounds. It was found that polymers derived from stannous octoate initiation are generally more hydrophobic than those initiated with zinc metal or zinc lactate, mostly because both esterification of some chain ends by 2-ethyl hexanoic acid and presence of water insoluble hydrophobic side products or impurities issued from the stannous octoate (28-30).

As compared with classical biostable polymers, PLAGA polymers do not lead to competitive materials unless degradability and bioassimilation are required. On the other hand, degradability and biocompatibility are not sufficient to promote the use of PLAGA polymers as sources of biomaterials. Indeed the actual devices made of these polymers must also be biofunctional, i.e. they must perform correctly before being degraded and bioassimilated. Of course, the balance depends very much on the required specifications and on whether the macromolecules can allow one to fulfil them. Properties required from bone fracture fixation devices are dramatically different from properties required from sutures, microspheres, nanospheres or micelles. Fortunately, PLAGA macromolecules are outstandingly versatile because of the well-documented possibility to make a great number of tailor made copolymers according to a LEGO®-type strategy based on the copolymerization and the stereocopolymerization of glycolide and lactide stereomers, the latter being a tool never used in the field of artificial polymeric materials, mostly because of unaffordable cost.

The number of papers dealing with PLAGA polymers and copolymers which appear in literature every year is increasing very rapidly. Although the interest of PLAGA polymers was extended recently to temporary outdoor applications after the outstanding chemical engineering work performed by Cargill in USA, the rationales for most of these papers is still biomedical and pharmacological applications primarily. Among all of them, a significant proportion is aimed at searching for new initiator systems in order to achieve faster polymerization, and best mechanical properties. However the relevance of the corresponding strategies with respect to biomedical applications is not straightforward. The aim of this contribution is to revisit the whole problem at the light of recent findings which were ignored or just suspected twenty years ago when people started to enlarge the prospecting of the potential of PLAGA polymers as bioresorbable polymers. For this, we will consider the general criteria related to the specifications of a few typical applications. Then we will recall some of the structural and hydrolytic characteristics of the PLAGA polymers. Last but not least, comparison will be made in order to evaluate the pertinence of some choices.

Prerequisites for biomedical applications

As we stated many years ago, the choice of a bioresorbable polymer must be based on a specification list (31). Before being degradable, a polymeric device aimed at serving for temporary therapeutic applications must be firstly a biomaterial and as such must fulfil two types of requirements, namely those related to biocompatibility and those related to biofunctionality. The latter type includes sterilizability, storability related to the period of limitation and ease to manipulate by the clinician. These general requirements are to be adapted according to actual targeted applications. Examples of the main criteria are tentatively given in Table 1 for three typical applications, namely osteosynthesis of bone fractures, scaffolding for bone reconstruction and drug delivery from microparticles.

Table 1 : Importance of characteristics and/or effects of the typical properties required from bioresorbable therapeutic devices

Requisites	Bone fracture fixation	Bone cavity filling	Microparticles
Duration	3-4 months	3-4 weeks	Healing time or release characterics
Mechanical strength	Critical	Not important	Not important
Morphology	Critical (crystallinity vs. Amorphousness)		
Thermal properties	Critical (Tg and Tm)	Important (Tg)	Critical (morphology)
Surface characteristics	Minor	Minor	Critical
Biocompatibility	Avoid crystalline particles Avoid rapid release of leachables Avoid sharp edges		

In many instances the final choice will result from compromises including biocompatibility criteria. Indeed one must keep in mind that living tissues and organisms react always according to the surrounding environment and related stresses. Body fluids can act as a solvent for impurities entrapped within a polymer matrix. On the other hand, released compounds issued from polymerization and processing stages, namely monomer, oligomers, initiator, solvent, etc., can generate particular morphological characteristics such as crystallinity or porosity, and cause toxicity or undesired physical aging due to slow release or slow uptakes of low molecular weight compounds according to phase partition. Last but not least any tiny particulate or sharp hedge can generate an inflammatory response involving natural defenses with the risk of dramatic effects on adjacent living tissues.

Confrontation between polymer and application criteria

Improving properties like molecular weight, molecular weight distribution, block formation, etc. by working on polymerization conditions and initiators, that are important for the final properties of a classical polymeric device, are not necessarily good in the case of PLAGA bioresorbable polymers. Let us take a few examples to show how much this remark can be critical.

PLA polymers are known to lead to plastic devices with rather good mechanical properties comparable to those of poly(methyl methacrylate), PMMA. However, there are specific shortcomings. Firstly, these polymers are sensitive to water and to heath. Some people have tried to minimize the processing-related degradation by starting from ultra high molecular weight compounds. This a poor solution because the enormous viscosity actually increases degradation through shear phenomena and related overheating, thus precluding extrusion or injection molding. Secondly, these polymers have a much lower glass transition temperature (Tg) than PMMA, Tg ranging close to 60°C instead of 100°C. Improving some properties can be achieved by copolymerization. However, copolymerization generally causes a decrease of the Tg temperature. Having Tg close to 37°C, the body temperature, can be good or bad, depending on the targeted applications. It can be good to fill up bone cavities or to control the release of drug from implants or microparticles. It can be awfully bad in the case of bone fracture fixation, i.e. when rigidity is required. So far, only a very few comonomers can lead to higher Tg values (32). Another trend that is found in literature of bone fracture fixation consists in looking for the highest initial mechanical properties. To reach this goal, people considered materials resulting from careful polymerization in end up with ultra high molecular weights and highly stereoregular crystalline materials as in the so-called as polymerized, self-reinforced, and die-drawn compounds investigated in The Netherlands, Finland and Japan respectively. The counterpart is that more or less porous materials containing more or less residual monomer (as-polymerized compounds) or oriented fiber-like domains (die-drawn compounds) are obtained that will lead to degradation-resistant residual and inflammatory particulates upon degradation. Furthermore, these choices compel devices to be machined instead of being injection molded. Corresponding materials have generally high initial mechanical properties but they loose their resistance faster than less crystalline ones on aging in aqueous media.

According to polymer science, fighting the initial crystallinity of a stereoregular polymer can be made by different means, namely quenching, copolymerization or, in the case of PLA polymers, stereocopolymerization. Quenching, especially when it results from injection-molding, is positive. However, it turns out that amorphous stereoregular PLA polymers can crystallize at body temperature upon hydrolytic degradation, a feature that was related to the decrease of Tg caused by water, and maybe lipid absorption, and to the decrease of molecular weight. The higher the isotacticity the greater the trend. Copolymerization and stereocopolymerization usually lead to undesired decrease of Tg. Last but not least, appealing to block copolymers or stereocopolymers is a possibility but it increases the risk of residual crystallite formation. Formation of low molecular weight crystalline residues either of the isotactic PLA-type or of the stereocomplex-type, have even been shown from reputed intrinsically amorphous PLAGA copolymers with high contents in D-LA units and in GA units. The formation of such residues was related to the presence of rather short stereoregular segment of polymer chains that can lead to crystallite formation when they are liberated upon hydrolytic degradation (25-26). So far, the best compromise to minimize the effects of these problems consisted in a decrease of the stereoregularity of a poly(L-lactic acid), PLA100, by introducing 2% of D-units in the poly(L) chain to yield a PLA 98 polymer, at least in our hands. This polymer keeps a high melting temperature, can be processed to amorphous devices by injection molding, generate less and smaller crystalline residues, has enough strength to fix short bone fractures, of resorb in a time compatible with bony tissue reconstruction.

As for improving the polymer chain formation, efforts have been made recently to take advantage of initiators and catalysts leading to fast polymerization, such as lanthanide-based ones that are also sources of more or less transesterification side reactions. However no information are available on their degradation and biocompatibility behavior, sofar. Actually, therapeutic applications can afford rather large costs and added values and thus fast polymerization is not a critical factor. On the other hand, transesterification reactions can be of interest for decreasing the partial stereoregularity of polymer or copolymer chains due to chain growing according to a chiral center respecting pair addition mechanism. Many years ago, we selected zinc metal as a suitable initator for lactide polymerization and copolymerization instead of tin octanote. This choice seems to be profitable because it is now known tin octoate initiated ring opening polymerization of lactide and glycolide in the bulk, as usually done in industry nowadays, leads to more hydrophobic, more stereoregular, more crystalline, more degradation resistant and less transesterified compounds than zinc. The resulting polymers also retain more initiator residues than the zinc-intiated one. More recently we showed that zinc lactate was the actual iniating species in the bulk zinc metal-initiated polymerization. Zinc lactate is now used as initiator in the industrial production of PLAGA polymers aimed at making bioresorbable devices, especially interference screws. From a more general viewpoint, the choices retained for this kind of application are completely different from those made by most of the industrial groups or companies (33).

The above comments were mostly related to constraints related to polymer synthesis, macromolecule architecture and biocompatibility. However, biomedical and therapeutic applications imposed other operation such as sterilization that is polymer aggresive regardless of the method use. Unless shape preservation and mechanical properties and molecular structure modifications, such as chain cleavage or crosslinking, are not critical factors for the targeted application, sterilization has to be performed according to mild process, thus excluding dry or humid hot atmospheres and γ or β irradiations. Today, gas sterilization with ethylene oxide is used but will be banned sooner or later because of the high toxicity of this gas. Sterilization by cold plasma in hydrogen peroxide atmosphere was recently approved by FDA for injection molded devices and provides an interesting alternative, surface characteristics being not critical in the case of hydrolytically degradable polymers for bone surgery.

In the case of drug delivery, it has been shown that stereoregular PLAGA polymers leading to crystalline matrices usually exhibit much faster release rates of matrix insoluble drugs, as compared with amorphous PLAGA polymers. This was related to the fact that crystalline domains do not accommodate drug molecules as do amorphous domains (34). The trend can be minimized if plasticizing and crystallinity-depressing compounds such as residual solvant, monomers or oligomers are present in the formulation. Dramatically different behaviors can be observed if one deals with basic or acidic drugs or additives due to their effect on the mechanistic characteristics of the hydrolytic degradation and the critical role played by carboxylic chain ends (27). In the field of drug release, the choice is generally oriented towards intrinsically amorphous PLAGA copolymers to make implants, or tiny spherical particles with smoother surfaces than grounded particles. Whether degradation has to be rapid to contribute to control the release of the drug or to be slow in order to promote diffusion control only followed by post-release elimination of the matrix waste is still a matter of discussion. We usually preferred the second choice because controlling the release of a drug through diffusion-degradation phenomena seems to be a greater challenge than through simple diffusion. Sterilization of drug delivery devices is sometimes problematic but processing under sterile conditions is generally a good alternative. Surface characteristics can be a source of concerns in the case of diffusion controlled phenomena involving tiny devices with rather large surface to volume ratios because such tiny devices are generally processed in the presence of surfactants which remain adsorbed. At this stage, polymerization conditions might seem rather far from contributing. However, one must keep in mind that 2-ethyl hexanoic acid residues issued from stannous octoate initiation look like surfactants of the fatty acid type and might concentrate at the surface of particles. This problem has not been addressed specifically in literature so far.

Conclusion

In this contribution, attempts have been made to show that polymerists can try to improve very much the material properties of PLAGA polymers on the basis of the remarkable potential of these polymers for biomedical and therapeutic applications. However, they must keep in mind that material properties are only a minor part of the problems that have to be solved if one wants to really apply therapeutic devices based on these polymers at the clinical level in human with commercial polymers. I hope that, with this contribution, people will convinced that, any scientific contribution to the field of PLAGA polymers aimed at therapeutic applications should include a careful description of the polymer synthesis, structural and processing characteristics. This is critical if one wants to be able to compare between polymers obtained by the very original ring opening polymerization of lactic and glycolic acid cyclic dimers.

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