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Feature Article

After soft tissues, bone, drug delivery and packaging, PLA aims at blood ☆

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ABSTRACT

Natural polymeric materials have been used for thousands of years by humans, including in medicine. However, such materials lacked reproducibility and presented risks of immunogenicity in the case of therapeutic applications. Polyesters derived from lactic acid enantiomers have been extensively investigated in medicine to make various devices like bone plates and screws, pins, staples, etc., or to serve as matrices of implants, micro- and nanoparticles in pharmacology, and more recently to replace biostable plastics in some of their environmental applications. Prior to extend this large spectrum to blood and stenting, structural and degradation particularities that make lactic acid-based polymers suitable for blood and stenting are recalled. The clues to select a stereocopolymer instead of the homopoly(L-lactic acid) to make a bioresorbable stent are discussed in comparison with stenting requirements. Occasionally, the contact of a stent with blood generates the formation of thrombi. The first event is always protein deposition with possible activation of the coagulation cascade and of defence proteins of the complement. In a recent work, the adhesion of model proteins (albumin, fibrinogen and γ-globulins) at physiological concentration was investigated using Optical Waveguide Lightmode Spectroscopy (OWLS). Under the selected model conditions, it was shown that pegylation minimized albumin deposition but did not exclude proteins totally. In contrast, albumin deposited first on any surface, including a pegylated one, precluded any further deposition of the other proteins. This unexpected finding may be of great interest to improve the hemocompatibility of surfaces in contact with blood like those of stent struts.

Contents

1. Introduction . . . 517
2. Precursors of lactic acid-based polymers . . . 517
   2.1. Lactic acid . . . 517
   2.2. Cyclic dimer . . . 517
3. A multitude of PLA . . . 518
   3.1. Lactic acid polycondensation . . . 518

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3.2. Lactide ring opening polymerizations . . . 518
4. Morphologies of lactic acid-based polymers . . . 519
5. Hydrolytic degradation of lactic acid-based polyesters . . . 519
6. Lactic acid-based polyesters as sources of degradable stents in contact with blood . . . 520
7. Interactions of lactic acid-based polymers with proteins . . . 522
8. Conclusions . . . 524
Acknowledgements . . . 524
References . . . 524

1. Introduction

During the last seventy years, artificial polymers have progressively invaded all the human activities. Poly(methyl methacrylate), silicones, polyethylene, polyamides, polyurethanes and many others derived from fossil oil were industrially developed as materials partly because of their outstanding resistance to biodegradation compared with biopolymers. With the perspective of oil shortage in the future and also for economical reasons, the trend is now to find routes to make such polymers from renewable resources. On the other hand, to avoid the use of biostable polymers when their material function is desired for a limited period of time after which it is desirable to eliminate them, developing degradable polymers is an issue today for polymer chemists and for biologists. In medicine, many diseases or trauma are relevant to the use of time-limited therapeutic aids like drug delivery, tissue engineering, regenerative medicine, etc. Degradable polymers are also of interest in ecology as one of the solutions to solve the problem of municipal waste management. They also have a potential in agriculture as mulching films, for pesticide and insecticide administrations, for seed protection, etc.

In the literature, there are many biostable polymers and degradable polymers derived from natural resources. In the late 1960's, hydrolytically degradable sutures made of artificial poly(glycolic acid) appeared on the US market [1]. In parallel, increasing attention was paid to lactic acid as source of degradable polyesters, according to the huge number of publications, reviews and patents issued since the 1970's. Among the artificial degradable polymers for medicine, lactic acid-based ones dominate because: (i) they are degradable in the human body; (ii) degradation by-products can be eliminated from the human body by kidney filtration and bioassimilation [2] and even from the environment by bacteria and fungi [3]; (iii) the L-lactic acid precursor is issued from renewable resources [4]. In many contributions to literature, the abbreviation PLA is considered as corresponding to a defined polymer like PS corresponds to polystyrene or PMMA to poly(methyl methacrylate). Actually it is far from being the case because chirality and multiple synthesis routes are sources of many lactic acid-based polymers with very different chain structures, morphologies and material properties including degradation. Therefore, there is not one PLA but a number of PLAs, thus justifying the use of the plural in the title of this article.

The main goal of this lecture was to discuss the extension of the range of applications in medicine to a particular human "tissue", namely blood. In the field of biomedical materials known as biomaterials, any targeted application is confronted with specific requirements [5]. Although attempts to take advantage of the degradability of PLA-type polyesters to develop more or less degradable prosthetic blood vessels have been reported [6], research is presently oriented toward the development of bioresorbable stents [7]. Prior to introduce the corresponding problems and requirements and some prospected solutions, particularities of lactic acid-based polymers have to be recalled to help understanding why this family is exceptional when the goal is tuning device behavior and tissue machinery. To approach a new application, it is important to have a clear vision of what lactic acid-based polyesters are.

It is well known that lactic acid-based polymers can be made by polycondensation of lactic acid and by ring opening polymerization (ROP) of lactide cyclic diesters composed of two chiral lactyl moieties [8,9]. However the literature is sometimes confusing when properties and degradation are concerned. Let us start by a few remarks concerning the monomer precursors.

2. Precursors of lactic acid-based polymers

2.1. Lactic acid

It has been known for more than a century that lactic acid is chiral [4]. Its enantiomers have similar chemical properties. They have also similar physical properties except opposite rotatory actions on a plan polarized light. The two configurational isomers are traditionally known as L- and D-lactic acids. According to IUPAC, they are (*S*)- and (*R*)-2-hydroxypropanoic acids, respectively [10]. Both isomers are issued from renewable resources. In contrast, racemic lactic acid composed of equivalent amounts of L- and D-isomers can be obtained by mixing bacterial stereoisomers or by racemization of one of them. However, in practice, racemic lactic acid composed of 50/50 L/D enantiomers is presently synthesized from fossil oil and as such cannot be considered as biobased (Fig. 1).

2.2. Cyclic dimer

The second route to lactic acid-derived polyesters is based on the ring opening polymerization of cyclic dimers or lactides composed of two enantiomers (diastereoisomers) combined by esterification. There are several diastereoisomers that are presented in Fig. 2, namely L-lactide composed of two L-lactyl units, D-lactide composed of two D-lactyl units, *meso*-lactide composed of one

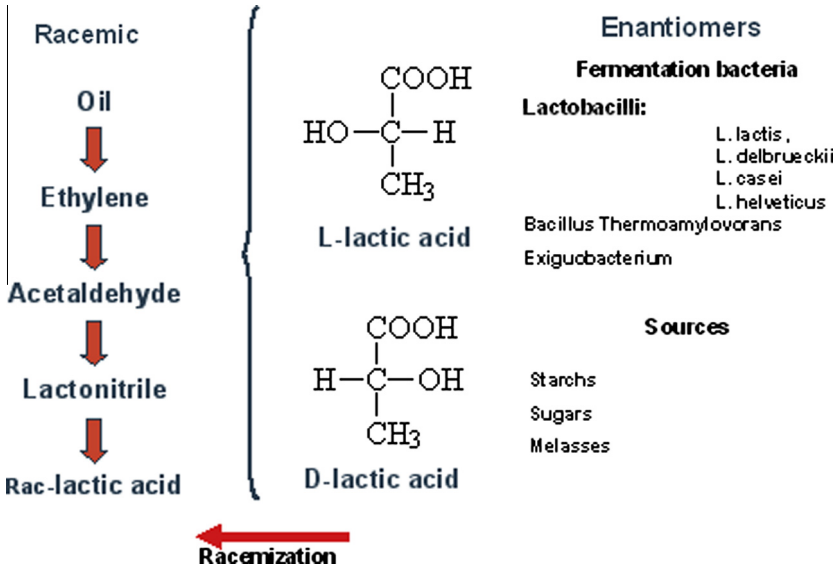

Fig. 1. Origins of lactic acids.

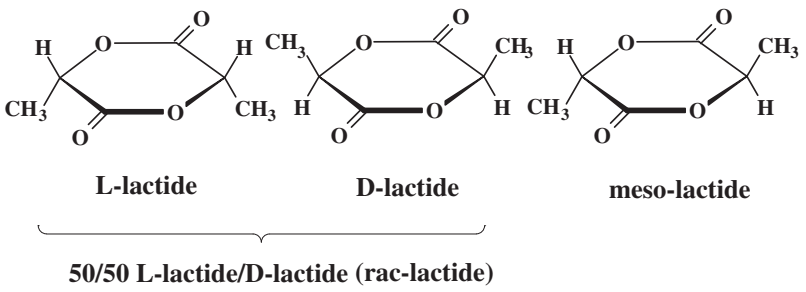

Fig. 2. Formulae of the various lactide monomers of lactic acid-based polyesters.

L and one D-lactyl units and the racemic lactide that is an equimolecular mixture of L- and D-lactides.

3. A multitude of PLA

3.1. Lactic acid polycondensation

When polycondensation is used to make aliphatic polyesters by dehydration between lactic acid molecules, the process leads to various poly(lactic acid) polymer chains depending on the composition of the feed. In the case of feeds composed of L or D enantiomer, homopolymers are obtained, meaning that all the lactyl repeating units have the same (L) or (D) configuration in the absence of racemization. In the case of mixtures of the two enantiomers, stereocopolymer chains composed of L- and D-lactyl units are obtained in proportion corresponding to that of the feed since the two lactic acid isomers have the same reactivity. L- and D-lactyl units are distributed at random, i.e. according to a Bernoullian statistic [11,12]. For many years, it was believed that only low molecular mass lactic acid polycondensates could be obtained by this route. Nowadays, high molecular mass PLAs are accessible by dehydration at high temperature in high boiling temperature solvents [13] or by solid-state post condensation [14]. Beside the Bernoullian unit distribution, polycondensates are characterized by OH and COOH chain ends.

3.2. Lactide ring opening polymerizations

The ROP of lactides can be initiated by a number of chemical compounds [15]. However the so-called tin octoate and zinc lactate are predominant in the literature of biomedical applications. Regardless of the initiator, macromolecules grow by addition of pairs of lactyl units. In the case of the ROP of lactides in the melt using tin octoate, hydrophobic C8 residues are present at one end or as pollutants that makes the resulting polyester hydrophobic [16]. In the case of zinc lactate, and of zinc metal as well, it is a lactyl residue analogous to main chain units which is added. Chain ends are thus similar to those of polycondensates, and polymers are more hydrophilic than in the case of tin octoate [17,18]. In polymer applications, chain ends are generally ignored. It is not the case when degradation in aqueous media is concerned, as we will discuss in the next section.

The ROP of L- and D-lactides yields stereoregular homopolymers that are comparable to those obtained by polycondensation of L- and D-lactic acids, except occasionally at chain ends. In the case of racemic lactide, *meso*-lactide and unbalanced mixtures of racemic lactide with one of the diastereoisomers, the pair addition leads to configurational structures different from those of polycondensates for similar gross compositions. Macromolecules derived from racemic lactides are enriched in pairs of similar configurations and thus are more stereoregular that chains derived from *meso*-lactide enriched in pairs of opposite configurations. The effects of these configurational enrichments are also found in the case of lactide mixtures [19]. ROP mechanisms can complicate the configurational structures due to pair additions. Anionic polymerization causes some racemization [20,21] whereas cationic [22] and mainly coordination–insertion polymerization preserve the initial chirality [9]. Above 100 °C transesterification side-reactions tend to randomize the chiral units but not completely because of the stereodependence of ester rearrangements [23]. Stereoselective polymerization of a mixture of L- and D-lactides in which a growing chain attaches a monomer of the same configuration preferentially is a means to promote stereoregularity with respect to normal the ROP of a given feed [24]. In stereoelective polymerization, the same trend is observed but because one diastereoisomer is polymerized preferentially, leaving the other as residual monomer [25]. There are also means to synthesize block stereocopolymers with particular unit distributions. Last but not least, stereocomplex can be formed between poly(L) and poly(D) chains [26,27] or between poly(L) and poly(D) segments in block copolymers [27]. Stereosequence-dependent hydrolytic degradation can also change the unit distribution in stereocopolymers [28]. Combined with the general effects of molecular mass and mass polydispersity, the various macromolecular structures lead to very different macroscopic properties like solid state morphology.

4. Morphologies of lactic acid-based polymers

Although there are some lactic acid-based dendritic systems under investigation in the literature [29], lactic acid-based polymers and stereocopolymers are primarily linear polymers that are more or less stereoregular as indicated previously. To exemplify the complexity of chain structure–morphology dependence, let us consider some lactic acid-based stereocopolymers with similar gross composition, namely 50/50 L/D. Such stereocopolymers can be made from racemic lactide and from *meso*-lactide, by stereoselective polymerization of racemic lactide, and also by stereocomplexation of poly(L) and poly(D) homopolymers. Basically, the first two are amorphous; the third one will be likely semi-crystalline depending on the length of stereoblocks, whereas the last one is highly crystalline with a high melting temperature (~240 °C). Table 1 shows the composition-dependence of morphology and of melting temperature in the case of stereocopolymers synthesized by ROP in the presence of zinc metal [30]. Similar trends are observed for stereocopolymers synthesized by other routes. In the case of stereocopolymers of the polycondensate-type which are less stereoregular, the ranges are different for the same gross composition. As for any semi-crystalline polymers, morphology depends on quenching and annealing and thus on processing conditions. It also depends on aging in aqueous media like blood.

Table 1
Gross composition-dependence of the morphology of lactic acid-based homo and stereocopolymers polyesters synthesized by ring opening polymerization of mixtures of L- and D-lactides in absence of stereoselection and stereoelection.

Content in L-units %	Abbreviation	Morphology	Melting temperature
100–92	PLA100–PLA92	Decreasing crystallinity	~175 to ~124°
92–8	PLA92–PLA8	Amorphous	–
8–0	PLA8–PLA0	Increasing crystallinity	~124 to ~175°

From this brief recall of the main structural particularities of lactic acid-based polyesters, one can already conclude that there is an almost unlimited number of PLAs with different composition in chiral units. The commonly used PLLA, PDLA and PDLLA abbreviations are not indicative enough and we introduced many years ago the PLAX abbreviations with X being the percentage in L-units. PLAX informs on the composition in chiral lactyl units but not on unit distributions and thus on morphology [30].

The glass transition temperatures (Tg) of lactic acid-based homopolymers and stereocopolyesters in the solid state are all in the range of 55–60 °C, the values depending on how data are collected. Mechanical characteristics of dry solid lactic acid-based homo and stereocopolymers do not differ very much either. In contrast, significant differences are observed when the same polymers are in contact with water which is a plasticizer.

5. Hydrolytic degradation of lactic acid-based polyesters

The hydrolysis of a carboxylic ester function is well known in organic chemistry. Basically it depends on the concentrations of ester groups and of water. It also depends on the presence of catalysts such as bases or acids. Since ester bonds generate acid functions, the rate of ester cleavage increases generally as the reaction advances according to a phenomenon named "autocatalysis". Applied to polyesters in an aqueous medium, ester hydrolysis leads to important particularities [31]. Once a device made of a PLA matrix is placed in contact with an aqueous medium, water penetrates more or less rapidly according to hydrophilicity, and the hydrolytic cleavage of ester bonds starts [32]. Each cleaved ester bond generates new carboxyl and hydroxyl hydrophilic end groups. The local acidity increases and hydrolysis speeds up [31]. For a time, the partially degraded macromolecules remain insoluble in the outer medium and thus stay entrapped in the matrix. There is no weight loss. However, as soon as the partially degraded macromolecules become soluble, diffusion starts from the surface to the outer aqueous phase. Weight loss is observed and a gradient of acidity is formed in the bulk

because soluble fragments entrapped well inside continue to generate acidity and cause a faster degradation inside and the increased concentration in soluble products compared with the surface can go up to creating a internal void in some cases [33]. To summarize, the whole process depends on four main factors: – the amount of absorbed water molecules initially absorbed that depends on the hydrophilicity of the matrix, the rate of water absorption being rather rapid with respect to the rate of ester cleavage; – the rate of ester cleavage that depends on the structure of macromolecules; – the rate of diffusion of macromolecular degradation products through the hydrated matrix provided a gradient of concentration is established by the products soluble in the outer medium, and – the solubility of these degradation products in the receiving medium that depends on their affinity for that medium. Therefore, any phenomenon that can affect one or several of these main factors will affect also degradation characteristics. A number of such factors have been identified. Let us mention molecular mass, polydispersity, morphology, presence of acid or based or pollutants, outer medium, chirality, etc., including chain ends. Crystalline domains do not offer space to water molecules. In contrast, the free volume present in amorphous domains allows water to penetrate and thus hydrolytic degradation is faster that in crystalline ones, regardless whether they existed initially or appeared during degradation [34]. The shape and the size of an object made of lactic acid-based aliphatic polyester are also important factors. The smaller the size, the slower the degradation rate, provided the polymer is pure and in the absence of other influencing factors like hydrophobic chain ends. The greater stability of small devices come from the fact that soluble oligomeric formed in the bulk can easily escape through the close surface, thus precluding the formation of acidity gradient [35]. On the other hand, hydrolysis occurs preferentially in amorphous domains [33] or at the level of steric irregularity [28]. Therefore, stereoregularity tends to increase during hydrolytic degradation, a phenomenon that can generate semi-crystalline zones in an initially amorphous matrix or increase the crystallinity of a semi-crystalline one [33]. In biomedical applications, the hydrolysis-resistant crystalline particles that are left at the end can be dramatically inflammatory.

6. Lactic acid-based polyesters as sources of degradable stents in contact with blood

To make a biomedical device exploitable for a particular application, it is essential to consider the list of requirements specific of this application, including biological ones [36,37]. *In vivo* the physico-chemical properties (temperature, pH, ionic strength, presence of proteins and other chemicals) of the local fluids (blood, lymph, vitreous, bile, extracellular liquids, etc.) are imposed. Furthermore, tissue healing is based on a series of events, namely inflammation that promotes activation of necessary biological elements, consolidation and later on remodeling necessary to restore the normal tissue as much as possible [38]. The duration of the whole process depends on the tissue. More time to heal is necessary for a bone fracture than for a soft tissue injury.

For several thousands of years, natural materials have been used for therapeutic purposes. Threads derived from collagen were known since the beginning of the 19th century and used as Catgut sutures [39]. However, such compounds lacked reproducibility and versatility. They also presented risk of immunogenicity. In the late 1960's, the first artificial "bioabsorbable" sutures made of poly(glycolic acid) or of a copolymer of glycolic and small amounts of L-lactic acid appeared on the US market [40]. These polymers were well adapted to the requirements of temporary suturing because they are good fiber-forming, rather hydrophilic and able to degrade within two weeks and to bioresorb in less than two months. Presently the word "bioabsorbable" is less and less considered as pertinent because absorption does not mean only degradation. It just reflects disappearance from the initial location. In literature, terms like degradable, biodegradable, bioresorbable are also used. Recently, IUPAC made recommendations to link these terms to specific phenomena [41]. Briefly, degradable and degradation correspond to chemical cleavage of macromolecules. Biodegradable is specific of cell-mediated phenomena and not applicable to *in vitro* enzymatic degradation because enzymes active *in vitro* can be absent *in vivo*. Bioresorbable is restricted to degradable polymers whose degradation by-products are proved eliminated via natural pathways (lungs and kidneys). Following these recommendations is important to avoid misuse of terms that leads to misleading and misunderstanding.

Lactic acid-based polyesters are intrinsically more hydrophobic than glycolic acid-based analogues because of the presence of pendent methyl groups. Accordingly, they are more resistant to hydrolytic degradation and require much more time to bioresorb [33]. The outstanding ranges of chain structures, morphologies, degradation mechanisms and degradation rates in aqueous media as well as the fact that oligomeric by-products and lactic acids are biodegradable and bioresorbable have been largely exploited in medicine, pharmacology, agriculture and in environmental protection for time-limited applications, even if there are limits [36]. In medicine, stereocopolymers were not frequently considered and only a few were tested up to the human level and found to be better candidates than PLA100 because of faster and adaptable lifetime. Let us mention some biomedical examples to which I participated: – PLA96 to replace silicone-based orbital floor prostheses [42], – PLA50 plasticized with oligoPLA50 to replace biostable periodontal membranes [43], – PLA50 to fill up bone cavities in maxillo-facial surgery [44], – PLA98 as source of bioresorbable interference screws [45]. This PLA98 interference screw was compared with a (PLLA) PLA100 one. It was reported that the PLA100 one degraded very slowly and was not replaced by bony tissue in contrast to screws made of PLA98 after a couple of years [46,47]. Unfortunately, the small PHUSIS Company which commercialized the PLA98 interference screws and intervertebral cages went in compulsory liquidation two years ago. In pharmacology, members of the PLA family have been considered to make implants, microspheres and nanosystems [9]. In agriculture pesticide and insecticide sustained delivery are applications as well as

seed protection. As for environmental applications, many compostable objects are now on the market like cutlery, plates, cups and packaging often referred to as made of PLA whereas they are made of stereocopolymers combined with additives [9].

In the 1990's, people started looking for vascular applications of degradable materials that implied contact with a particular liquid tissue, namely blood, and corresponding constraints. If bony tissues require more time to heal than soft tissues, among soft tissues artery wall requires more time (~2–3 months) than skin (2 weeks). PLLA (PLA100) fibers were tested to make or reinforce tubular prostheses and help regeneration of a blood vessel without success [48].

A stent is a little device that is implanted in a more or less obstructed artery by interventional cardiologists in order to improve or restore blood flow. Basically, a stent is a deformable meshed tube crimped on a balloon attached to a catheter. The cardiologist inserts the catheter in an artery and drives the balloon up to the obstructed zone where the stent is expanded by inflating the balloon (Fig. 3).

The first stent implanted in 1986 was metallic [49]. Since then, metallic stents have been extensively used by interventional cardiologists to treat coronarian arteries and avoid myocardial infarction and patient death. If metallic stenting saved many lives, it presents some shortcomings: – the presence of metal generates flashes in X-rays and Magnetic Nuclear Resonance imaging and thus does not permit to take advantage of these techniques; – the persistent rigidity causes local stress shielding and penalize the remodeling of the injured artery wall; – the scaffolding function is required for a couple of months, i.e. for the time necessary for artery wall healing while the metallic device stays in place for the rest of patient's life. Basically, a polymeric bioresorbable stent, also referred to as scaffold, is a better solution [50]. Indeed organic matter does not cause flashes and the duration of the scaffolding function can be adjusted to secure the consolidation period and to restore the local stresses and dynamic favorable to remodeling. Among the few compounds that have potential for this, lactic acid-based polyesters are by far the most attractive candidate because of the outstanding number of possibilities offered by synthesis routes, macromolecular structures and solid state morphologies. Many companies are trying to take advantage of such versatility that no other polymer possesses, except biopolymers. Rather different strategies, compounds and designs are prospected (Table 2). However, it is rather difficult to comment the nature of the used polymers further because of a lack of available information. Anyhow, to be successful, bioresorbable stenting has to meet several requirements tentatively listed in Table 3 together with issues (see Fig. 4).

Several companies have disclosed first-in-man test. However, only the Abbott BVS bioresorbable stent is now at the commercial level with struts composed of PLLA (PLA100) coated by a thin layer of PDLLA (PLA50) loaded with Everolimus, an antiproliferative drug [51]. The company found solutions to most of the issues. However, the c.a. 2 year scaffolding time is considered as too long. The possibility to take advantage of configuration-dependent degradation of PLA50, PLA75 and PLA92 stereocopolymers

Table 2
Some PLA-type polymers under current pre-clinical and clinical investigation as bioresorbable stents.

Company	Polymer(s)[a]
Abbott	PLLA+(PDLLA coating)
Kyoto medical	PLLA
Arterial remodeling technologies	PLA98 or P(D + L)LA
Orbus-Neich medical	PLLA + PCL + PDLLA
Elixir medical	PLLA
Huaan biotechnology	PLLA + PLAGA + PLACL
Amaranth medical	PLLA

[a] GA = abbreviation for glycolic acid; CL = abbreviation for ε-caprolactone.

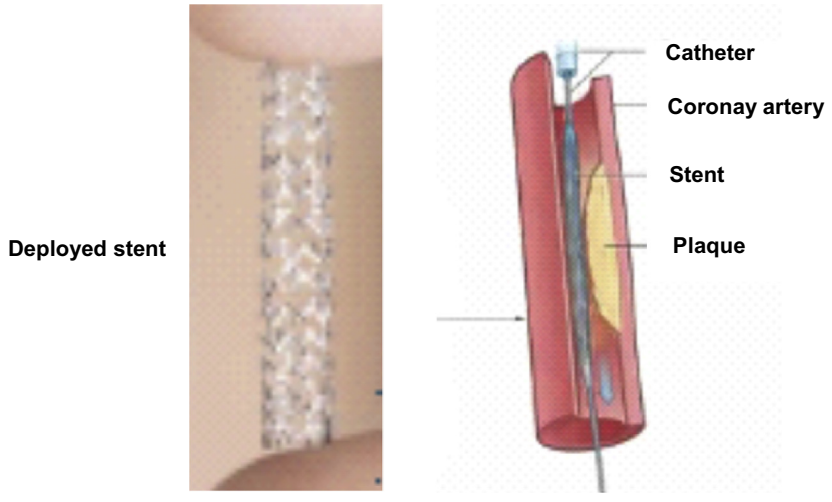

Fig. 3. Example of a tiny coronarian stent between fingers (left) and its position prior to balloon inflation (right).

Table 3
Requirements and issues specific to bioresorbable stenting.

Requirements	Issues
Suitable polymer	Hydrolytically degradable
Biocompatibility	With arterial tissues and blood
Design	Strut thinness
Processing	Molding vs. Laser cutting
Sterilization	Molecule and size-respecting
Crimping on a balloon	No relaxation, no creeping
Crimping stability	High Tg or sheath
Circulation up to the heart	Flexibility
Deployment	Shape memory or ballooning
Absence of recoil (size stability)	High Tg
Radial strength	Maintaining arterial lumen open
Absence of hyperplasia (restenosis)	Antiproliferative drug or not
Fast endothelialization	Absence of cell toxicity
In situ monitoring	Gold markers or radio-opacifying additive
Degradability	Labile junction between repeating units
Scaffolding duration	Match restoration cell machinery
Bioresorbability	Mineralization to H_2O and CO_2 or kidney filtration
Biocompatible by-products	Absence of cell toxicity and hemocompatibility
Stability on storage	Packaging under dry atmosphere
Cost	Social security limits

was previously demonstrated in the rabbit model [52]. More recently, it was shown that an experimental drug-free stent based on PLA98 was able to dismantle after c.a. 2 months in the pig animal model [53,54]. For arterial tissue, the required scaffolding time is assumed to be 2–3 months. Beyond, the stent must break down to suppress the scaffolding function and disappear later on to leave a functional artery.

7. Interactions of lactic acid-based polymers with proteins

One of the problems faced occasionally in animals is the presence of thrombi [52]. Briefly, in the case of an implanted polymeric stent in contact with blood, a thrombus can have different origins more or less interdependent. One is the unavoidable and immediate deposition of blood proteins, in particular albumin and opsonins, that may trigger complement and coagulation cascades. This mechanism depends on surface chemistry (functionality) and physic (roughness) characteristics (Fig. 5 left). The other one is the perturbation of the blood flow due to the presence of struts that generate stases (Fig. 5 right). The thinner the struts, the lesser the risk of turbulence and stases is.

As indicated before, the first event that occurs when blood is in contact with a foreign surface is protein deposition generally with denaturation (conformational changes) as schematically represented by the first layer deposited onto the surface in Fig. 5 Top. Other layers adhere with less and less denaturation up to reaching equilibrium with unperturbed proteins present in flowing blood. Among these proteins are complement ones. Once activated these defence proteins can aggress local tissue if they cannot eliminate the foreign matrix. To avoid protein deposition, one of the most recommended means is "pegylation". This term reflects the presence of a poly(ethylene oxide) (PEO) layer physically or chemically attached [55]. In literature, pegylation is generally considered as precluding

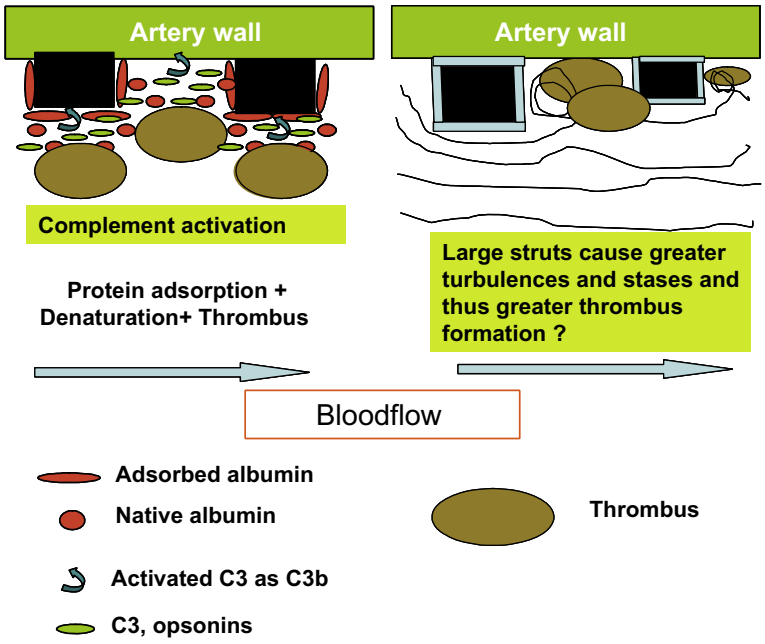

Fig. 4. Schematic representations of thrombus formation related to surface interactions with proteins and coagulation and complement activations (left) and to turbulences and stasis formation (right).

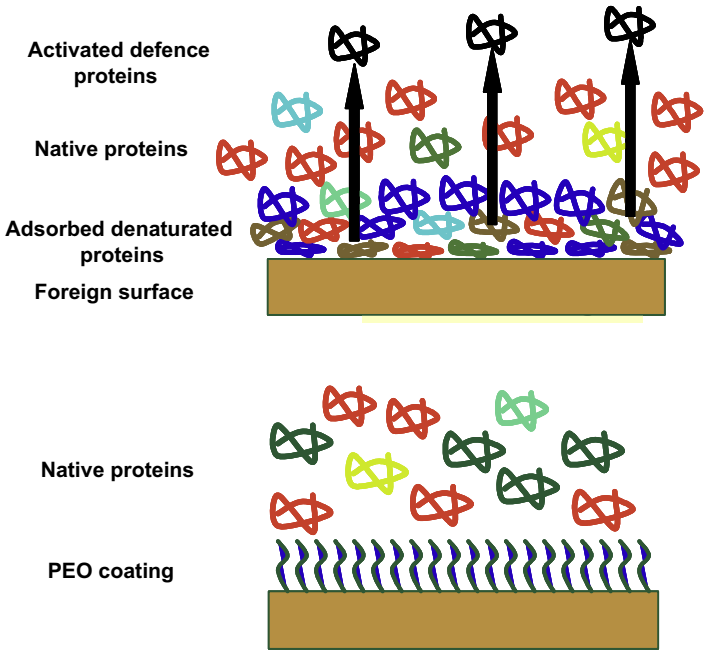

Fig. 5. Schematic representation of the denaturing action of surfaces on adsorbed proteins (Top) and the excluded volume-based repulsion of proteins when surfaces are pegylated (Bottom).

interactions with blood proteins because of excluded volume-related repulsions (Fig. 5 bottom) although adsorption and compatibility have been reported for some of these proteins occasionally [56,57].

Pegylation could thus be a solution to minimize thrombus formation in the case of lactic acid-based bioresorbable stents and thus to improve hemocompatibility. The major problem to investigate the behavior of blood in contact with pegylated surfaces is the complexity of the medium and especially the presence of albumin in large excess (40 g/dm^3). Surface Plasmon Resonance (SPR) is well-established but proteins are generally tested individually at concentrations far lower than physiological ones, c.a. 1 g/dm^3 instead of 40 g/l for albumin, below blood osmolarity, and occasionally in the presence of surfactant [58,59].

Although it is less used than Surface Plasmon Resonance (SPR), Optical Waveguide Lightmode Spectroscopy (OWLS) is emerging as a powerful tool to investigate interactions of molecules and macromolecules on surfaces. The fundamentals of OWLS have been described in details in literature [60]. The sensor chip is based on a fine optical grating prepared on a thin waveguide layer carried by a glass substrate. A linearly polarized light (He–Ne laser) is coupled with the evanescent light by the diffraction grating into the waveguide layer, provided that the in-coupling condition is fulfilled. The light is guided by total internal reflection to the edges of the waveguide where it is detected by a photodiode. The sensor chip is coated to create a particular surface and a solution of the interacting species is allowed to flow on this surface up to signals leveling off, then a flow of solvent eliminate the non-adhering molecules to leave a rinsing-resistant layer of affine molecules. Mass and thickness of this layer are finally computed.

In a model approach, we recently tried to take advantage of OWLS to monitor the fate of albumin, fibrinogen and γ-globulins at their physiological concentrations in HEPES buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid at pH = 7.4) after contact with sensor chips coated with diblock poly(D L-lactic acid)-*block*-poly(ethylene oxide)s and triblock poly(DL-lactic acid)-*block*-poly(ethylene oxide)-*block*-poly(DL-lactic acid) copolymers. Corresponding homopolymers were used as controls. The three protein systems were investigated separately, as a mixture and when added successively according to different orders of addition [61].

Protein deposition was detected on all surfaces, including those bearing PEO segments on their surface. Adsorption depended on the protein, on the surface and also on the presence of the other proteins. The presence of PEO did minimize the amount and the thickness of adsorbed albumin but exclusion was not observed in agreement with previous suggestion [56]. The adsorbed layer of γ-globulins and fibrinogen were 2 times and 8 times thicker, respectively, than the layer of albumin in the case of the diblock copolymer and 3 and 12 times thicker in the case of the triblock. When a mixture of the three proteins was applied to pegylated surfaces, the thicknesses of the adsorbed layers were much smaller. When the proteins were tested successively, it was found that anytime albumin was adsorbed first, there was no other adsorption of any of the two other proteins. It was not the case when one of the other proteins was added first. Therefore, it was concluded that the adsorbed albumin was able to prevent the adsorption of the other proteins, even in the case of PLA50 in the absence of pegylation as shown in Fig. 6. The absence of difference between initial and final levels shows the absence of deposition.

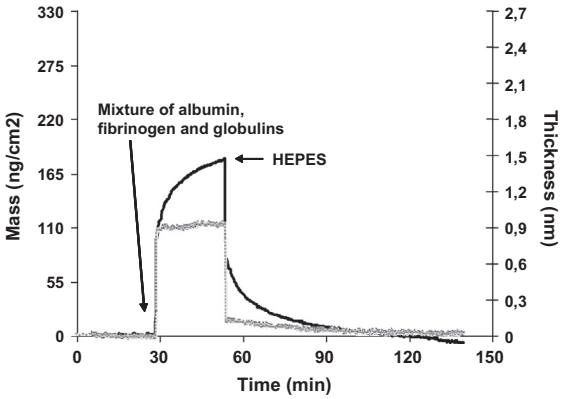

Fig. 6. Absence of difference between initial and final levels of OWLS mass (solid) and thickness (dotted) profiles in the case of a solution of mixed albumin ($40\ g/dm^3$) + fibrinogen ($4\ g/dm^3$) + γ-globulins ($10\ g/dm^3$) in HEPES buffer allowed to flow between ~30 and ~60 min on a PLA_{50} layer bearing a layer of rinsing-resistant albumin (0–30 min), and finally rinsed with the buffer up to levelling off [56].

This outstanding finding suggests that it was the presence of albumin adsorbed on a surface, pegylated or not, that made that surface compatible with other proteins. As a consequence, dipping a device to be in contact with the blood of a patient in a solution of albumin could be a very simple means to avoid further protein deposition and maybe platelets adhesion after *in vivo* implantation.

8. Conclusions

The exceptional chirality-dependent macromolecular structures, morphologies and degradation characteristics of lactic acid-based polymers briefly recalled herein offer a mine of matrices among which biomaterialists together with other specialists have already found members suitable to help bone and soft tissue self-healing and developed commercially. Blood is now an attractive target. However the complexity of the medium and the adversity of many of his components (defense proteins against foreign substances, coagulation proteins, platelets, restenosis related to smooth muscle cells proliferation, etc.) are obstacles. Solutions are under investigation in interventional cardiology to replace metallic stents by bioresorbable ones on the basis of many compromises. Drug-free and drug-eluting semi-crystalline lactic acid-based polymers appear as good candidates with regard to the specific requirements. Nevertheless the interactions between surface and proteins, surface and cells and surface and blood elements are still far from being under control.

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