J Mater Sci: Mater Med (2009) 20:437–446
DOI 10.1007/s10856-008-3581-4

Degradable and bioresorbable polymers in surgery and in pharmacology: beliefs and facts

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Received: 26 June 2008 / Accepted: 29 August 2008 / Published online: 25 September 2008

Abstract The number of articles dealing with degradable polymers and macromolecules is increasing rapidly and the number of proposed compounds as well. However, not all have a high potential for effective applications. This contribution examines first the criteria to be taken into account when commercialisation of polymeric compounds and devices aimed at helping the body for a limited period of time, i.e. the healing time, is the main goal. What is really known is tentatively analysed by considering some of the candidates present in literature confronted to the targeted potential applications. Tentative comments are made on what should be done to qualify a candidate. Last but not least, trends in the search for polymers to be exploited in presently attracting areas such as bioresorbable stents, hydrogels to deliver bioactive macromolecules like proteins and polynucleotides or polyelectrolytes to temporarily complex charged biomacromolecules like proteins or genes are considered.

1 Introduction

Instead of presenting one more example of potentially biodegradable polymeric system based on the work we are currently doing in the field of Biomaterials, I would like to share with the audience of the latino-american meeting COLAOB 2008 an attempt to confront the present knowledge to the criteria to be satisfied for developing commercially degradable systems adapted to time-limited therapeutic applications.

For thousands of years, humans have attempted to use naturally available compounds to make tools and devices of practical interest, thus turning substances to materials. Rather recently, they discovered how to create novel compounds unknown in Nature that were also rapidly turned to materials. The latest type is artificial, i.e. non-natural, polymers that have been known as such for less than 90 years [1]. Many familiar polymeric compounds are presently used with great success in surgery (prostheses, tissue regeneration,…) and in pharmacology (controlled drug delivery, gene transfection, medicated prostheses, etc…). However, their exploitation results, in most cases, from adaptations of industrial brands to biocompatibility and regulatory requirements. Although advances are still necessary for medical devices based on classical polymers, innovations in the field of therapeutic polymers rely on more sophisticated strategies, nowadays. This is the main reason for scientists to look for novel compounds adapted to applications that require a therapeutic aid to help the normal healing process.

For the last forty years, increasing attention has been paid to the so-called "biodegradable" or "absorbable" therapeutic systems in order to replace currently used biostable (or long lasting) metals, alloys and ceramics or to provide novel therapeutic solutions, anytime a therapeutic function is required for a limited period of time [2] (Table 1).

In surgery, degradable sutures, bone fracture fixation devices, stents, dental reconstruction, tissue engineering, etc.… are attractive targets, some having already received

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Table 1 Examples of typical time-limited applications relevant to macromolecules or polymers with beneficial short life-times

Surgery Time-limited devices	Pharmacology Controlled drug delivery	Tissue engineering Scaffolding
Sutures, staples	Implants	Porous matrices
Osteosynthesis devices	Microparticles	Cell-matrix constructs
Stents	Nanoparticles	Tissue substituts
Wound dressings	Self assembled micelles and aggregates	
Membranes for guided tissue regeneration (GTR)	Polyelectrolyte complexes	
Tissue fillers	Hydrogels	
Tissue constructs	Polycations for gene transfection	

commercial applications. In pharmacology, sustained release from degradable polymeric matrices is exploited in human, especially in birth control and cancer therapy. However, other applications that require degradation are still at the research level. It is the case of polymer-based functions like targeting of receptors, cells or organs, promoting intracellular penetration of recalcitrant drugs, transfecting genes and releasing drugs at the right place and the right dose. Tissue engineering is largely based on cell cultures onto polymer surfaces or into porous polymer scaffolds that should be eliminated also at the end. Until now, attention has been primarily paid to cell behaviors (adhesion and proliferation, less frequently phenotype) and much less to the fate of the scaffolds designed to support correct tissue formation.

Like any biomaterial, a polymeric system (macromolecule, assembly of macromolecules, device) aimed at serving for a limited period of time before degradation and elimination from the body, must first fulfill severe criteria related to biocompatibility and biofunctionality. Most contributions reported in literature conclude generally at the potentiality level, sometime in the absence of any biological test. Evaluating the biological behavior is more and more recommended from in vitro tests involving cells instead of animals. However, in vitro tests can be only indicative because there are no experimental conditions that can mimic the reality of a human or an animal body when it faces a foreign material or compound. Therefore, in vivo tests have to be included in the research strategy, despite their cost, species dependence and ethic—related limits if one wants to pave the route to real applications. This is seldom performed although thousands of literature contributions claimed in vivo biodegradability, sometimes adopting wrong, only partially demonstrated or even undemonstrated statements. One of the major difficulties in working in the field of non-permanent polymeric materials for time-limited applications is muldisciplinarity. In other words, there is no real expert. Knowledge and advances can result only from partnerships of specialists of different and complementary disciplines working together closely and fairly. Polymer science is a mature science that plays an important role. Itself is based on various disciplines, namely chemistry, physics, physical chemistry with rather specific and complex fundamental laws completely different from those governing small molecules and inorganic compounds. Therefore, polymer scientists have to be involved in the search for degradable polymeric devices and systems of therapeutic interest.

Let us first examine some of the problems related to the field of the so-called "biodegradable polymers of therapeutic interest" in attempts to update literature and make it more useful for new comers. The history of the so-called "absorbable" or "biodegradable" polymers started more than 40 years ago soon after the appearance of the concept of "biomaterials" [3, 4]. A fast literature search is enough to show that many people are now entering the field, stimulated by the interest of the society and of the clinicians for novel therapeutic solutions, in particular for solutions avoiding the storage of foreign compounds in the human body and, more and more, in the animal one too. Figure 1 shows the number of papers issued from a search when the following terms are combined: "polymers or drug or scaffold" and "degradable or biodegradable or

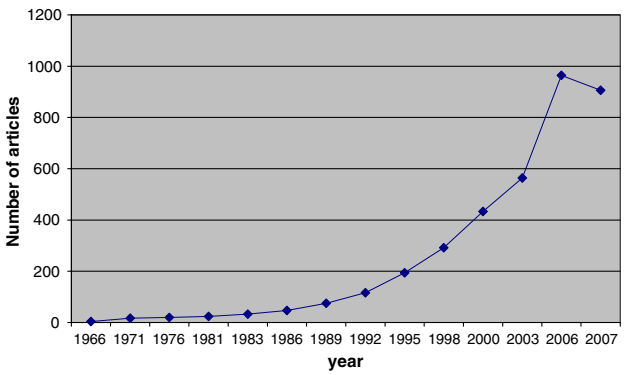


Fig. 1 Insight into the number of publications per year when combining "polymers or drug or scaffold" and "degradable or biodegradable or bioresorbable or resorbable or absorbable or erodible" in a search using ERLWebspirs

resorbable or bioresorbable or absorbable or erodible" are combined. A closer look can show that if the number of authors increased fast, the number of proposed polymeric systems also increases.

However, not all the proposed macromolecules, polymers and polymeric systems can be considered as relevant to effective temporary functions in surgery, pharmacology and/or scaffolding in tissue engineering, by far. The question is how to show the qualification of a novel potential candidate?

2 What makes a degradable macromolecule or polymer of interest for biological applications?

It is largely admitted that the loss of properties of a degradable therapeutic system must be adapted to the cell growth and tissue reconstruction machinery. To this, one of the critical criteria is lifetime since, in most reported cases, cells adhere and grow acceptably unless aggressive functions or compounds are present at the surface of released. Of course, the compatibility with soluble foreign macromolecules can be more problematic in pharmacology. Any macromolecule or polymer undergoes physical and chemical aging or, in other words, there is no polymeric system that can last for ever. Therefore, all the known polymers can be considered as degradable, meaning that macromolecular structures loose progressively their chemical integrity as reflected by a decrease of molecular weight, for instance. The effects are deleterious. In the case of polymeric compounds functioning in contact with an animal or human body, degradation becomes a profitable property and thus one more line in the list of required criteria typical of the considered application. In the field of biomaterials, the general criteria are rather well defined although it is generally difficult to quantify them. The list includes criteria related to biocompatibility and biofunctionality. In the case of degradable systems, this list must be complemented by "elimination from the body" or "bioassimilation" (Table 2).

Because these criteria are interrelated, it is necessary to include them in the research strategy from the very beginning, at least ideally. For instance, sterilization that is seldom taken into account in scientific papers can have dramatic effects on a system optimized independently. If they are discovered late in the development, these effects can ruin the whole work. In a close future, showing degradation or biodegradation will not be enough. The fate of degradation by-products will have to be demonstrated to regulatory agencies. Unless their in vivo storage is proved harmless, degradation by-products will have to be shown as eliminated from the body, a criteria that is reflected by the term "bioresorption" nowadays. From this viewpoint, the terms "absorbable" and "erodible" that are often used, are not scientifically sound, absorption meaning neither degradation nor elimination for sure, and erosion meaning "surface degradation" only. Normalization bodies like ASTM, CEN, IUPAC, or ISO have not issued a universal terminology but they are working to it. Regulatory agencies of many different countries are also keen to find means to handle the particular case of degradable polymeric devices or systems that are initially relevant to the biomaterials regulations but end up as small molecules and thus should become relevant to pharmaceutical regulations, even if these blood-circulating small molecules are not drugs. Chemical degradation can occur at the surface or on the bulk, depending on whether the reaction rate is greater or smaller than the diffusion of the chain cleaving reagent within the matrix. In the case of chain cleavage caused by water, the initial hydrophoby of the polymer and the solubility of polymer chains or degradation-by products in body fluids are critical factors for the degradation and the elimination via the kidneys. Enzymatic degradation is normally limited to the surface of solid polymeric devices because protein molecules can hardly penetrate solid polymer matrices. In the case of soluble macromolecules, enzymatic cleavage can occur either at chain ends or at random inside main chains or both. At this point, it is worth noting that the terms degradation and biodegradation reflect mechanisms of chemical breakdown of macromolecular structures but do not say anything regarding the fate of the degradation by-products. Therefore, one needed a term to reflect the fate of these by-products and "bioresorption" is now considered as pertinent and should be used specifically only when foreign material and residues have been shown assimilated or eliminated from the living host, regardless of the followed route, namely lungs or kidneys or insertion in biochemical processes.

Table 2 Typical criteria to be respected by potential polymer candidate for time-limited applications in vivo

Biocompatibility	Biofunctionality
Non toxic	Adequate properties
Non immunogenic	Mechanical
Non carcinogenic	Physical
Non thrombogenic	Chemical
	Thermal
	Biological
	Easy to handle
	Sterilizable
	Storable
	Resorbable[a]
	Approved

[a] Degradation by-products, drug and any other product involved in the formulation of a degradable system has to be taken into account

3 What is the present situation?

It is difficult to identify the number of different polymeric systems relevant to time-limited applications in the field of biomaterials that appear in literature. According to Scholar One Scifinder, the number of scientific articles claiming work based on biodegradable polymers is c.a. 26,778 between 1999 and 2008, a number that include compounds of biomedical or environmental interests. Table 3 lists some of the major polymers of therapeutic interest, together with degradation products when they are identified.

3.1 Aliphatic polyesters

The family of aliphatic polyesters is, by far, the richest in terms of members as shown in Table 4. Many reviews are available in literature [5–7].

Among these members, lactic acid and glycolic acid-based polymers, stereocopolymers and glycolic acid copolymers (PLAGA) have been studied extensively for the last 30 years [5]. It is now admitted that their degradation in vivo is hydrolytic. However, this hydrolytic degradation is very complex because it depends on many interconnected factors [6]. This complexity is now well documented in literature although the subtleties of the hydrolytic degradation of poly(α-hydroxy acid) are still not always taken into account, even in the recent literature. In vivo, these polymers are definitely degradable and bioresorbable as they end up to lactic acid enantiomers and glycolic acid that are inserted in biochemical pathways. During degradation, aliphatic polyesters form smaller and smaller main chain fragments up to small oligomers (DP < 9 at neutral) that are then soluble in aqueous media and thus can be eliminated via the kidney route. The in vivo fate of lactic acid polymers was identified many years ago using radio-labeling [3], including in earthworms [8]. Besides the difficulty to optimize biofunctional criteria, degradation characteristics, and tissue reconstruction machinery, a major problem is raised by particles of crystalline residues that can be formed under various circumstances [9]. With this regard, one of the more cited paper is that published by Bergsma et al. [10] who reported dramatic late edema after up to ~ 6 years implantation of osteosynthesis devices to treat zygomatic bone fractures in humans. These devices were machined from masses of as-polymerized, ultra high molecular weights, highly stereoregular and crystalline PLLA (or PLA100) homopolymer synthesized using stannous octoate as polymerization initiator. The strategy was selected to reach the best initial mechanical properties in the dry state. Nowadays, one can say that this was the worse choice to do because: (i) monomer and initiator residues remained entrapped, (ii) the high initial crystallinity form large amounts of tiny and rough highly resistant particles when the amorphous phase was degraded, (iii) machining yielded rather rough surfaces, and (iv) stannous octoate increased the natural hydrophoby of PLLA polymers [11]. Such particles are now known as very inflammatory and thus well explain the late dramatic inflammatory response. Since then, many devices based on PLA100, PLAX stereocopolymers and PLAGA copolymers have been optimized and commercialized successfully for more than 20 years [12–14]. It is the case of the interference screw for instance [15]. However, it is also now well identified that the behavior of such screws is dependent on the type and on the history of the member of the PLAGA family [16]. Similar comments could be made in the case of sutures derived from other members of the aliphatic polyester family, namely poly(glycolic acid), PGA, poly(glycolic acid-co-lactic acid), and polydioxanone, for instances.

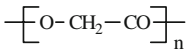
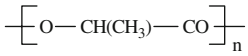
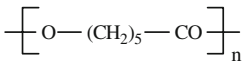
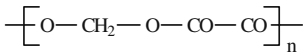
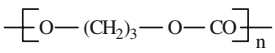
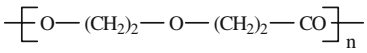
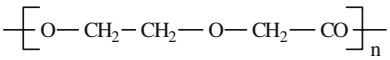
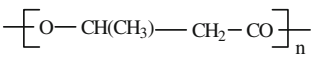
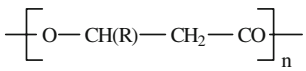
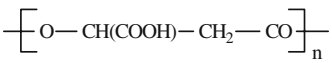
Table 3 Major polymers qualified usually as "biodegradable" with respect to or in relation to in vivo potential applications

Polymer family	Origin	Leading compounds	Degradation end-products
Aliphatic polyesters	Chemicals and/or natural small molecules	Poly(lactic acid)s and co-polymers[a]	Lactic acid and glycolic acid (metabolites)
Chitosan	Chemistry on chitin	Undefined	Unknown
Alginates	Chemistry on algae	Undefined	Unknown
Poly(β-hydroxy acid)s or PHA's	Bacteria and/or chemicals	Poly(β-hydroxy butyrate) and hydroxyvalerate copolymers	Hydroxy acids (metabolites)
Poly(tyrosine carbonate)s	Chemicals and natural small molecules	Undefined	Chemicals, metabolites and oligomers
Polyanhydrides[b]	Chemicals		Chemicals
Poly(orthoesters)[b]	Chemicals		Chemicals

[a] Some members are exploited in marketed devices in surgery and pharmacology

[b] Some members are exploited in pharmacology

Table 4 Some members of the aliphatic polyesters family

Polymers	Acronyms	Formula
Poly(glycolic acid)	PGA	
Poly(lactic acid)s	PLA	
Poly(ε-caprolactone)	PCL	
Poly(1,4-dioxane-2,3-dione)		
Poly(1,3-dioxane-2-one)		
Poly(1,5-dioxepan-2-one)	PDXO	
Poly(para-dioxanone)	PDS	
Poly(hydroxy butyrate)	PHB	
Poly(hydroxy alkanoates)	PHA's	
Poly(β-malic acid)	PMLA	

3.2 Other aliphatic polyesters

Poly(ε-caprolactone) and poly(β-hydroxy alkanoate)s are very often introduced as biodegradable in papers dealing with biomaterials, drug delivery and tissue engineering. These polymers can be biodegraded by outdoor living organisms (bacteria and fungi). In contrast, they are not biodegradable in animal and human bodies because of the lack of suitable enzymes. Of course, these polymers are degradable hydrolytically in these bodies but their lifetimes are usually too long with respect to the criteria of typical time-limited therapeutic applications, and too short for long term uses as biostable biomaterial. This is exemplified in the case of PHB [17], of the so-called poly(β-hydroxy octanoate), PHO [18], or of poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate)-based polymers [19]. Of course, copolymerization and chemical modification are means to increase the rate of cleavage of these macromolecules as in the cases of complex multiblock copolymer chains made of PHBHV segments combined with poly[glycolide-*co*-poly(ε-caprolactone)] [20] and carboxylated poly(ε-caprolactone) [21]. However the degradation of stereocopolymers and copolymers macromolecules can be the source of complications in terms of respect of living systems. To make a long story short, it is enough to mention that in such heterogeneous macromolecules, chain cleavage occurs at the

weaker main chain bonds and the intrachain selectivity among the various cleavable bonds affects the more degradable chain segments to leave the most biostable ones, a feature that can be problematic if the residues are toxic or can crystallize and/or form inflammatory particles. The problem has been examined in details [22] and is applicable to most of the degradable polymers with multiple constitutive repeating units and main chain breakable bonds with different reactivity. This is one more reason to monitor carefully the fate of degradation by-products and their effects one cells, tissues and organs. Recently, it was shown that glycolic acid can dramatically affect the growth of keratinocytes although it has no effect on fibroblasts [23].

To my knowledge, the complete resorption of devices made of aliphatic polyesters other than lactic and glycolic acid-derived ones, has not been demonstrated, except, maybe, in the case of poly(β-malic acid) [24].

3.3 Chitosan

Chitosan is generally introduced as biodegradable [25, 26]. However, literature search did not revealed any conclusive proof of total degradation in vivo, regardless of the mechanism [25]. Considering recent publications, the practical interest of chitosan in the field of bioresorbable materials or soluble macromolecules is still a matter of potential if one takes into account all the criteria to be satisfied. It is not because the lysozyme enzyme can attack the poly(glucosamine-*co*-acetyl glucosamine) chains in vitro [27] and because lysozyme is a human enzyme, that any chitosan is going to be fully degraded in vivo. Enzymatic degradation by lysozyme in vitro leads to the sugar but it is still to show complete degradation. Partially deacetylated beta-chitins were prepared under mild conditions and subjected to lysozyme treatment. The degradation rate proved to be affected markedly by the extent of deacetylation and showed a maximum at about 50% deacetylation. The rate then decreased, and the derived chitosan with a degree of deacetylation of 0.97 was not degraded at all [28]. If chitosan derives from the chitin biopolymer, it is again a family and the in vivo degradation depends also very much on the degree of deacetylation, the higher this degree the slower the degradation rate [29]. Similar trends have been observed in the case of acetylated chitosan fibers prepared by acetylating chitosan filaments to various extents [30]. The absence of in vivo toxicity of chitosan-type polycations is not demonstrated for sure. If insoluble chitosans or those complexed with other polymers like DNA are not strongly interacting with living systems, soluble low molecular weight ones have been found slightly toxic despite their polycation structure [31].

3.4 Alginates

Alginate is also the generic name of a large family of copolymers of the polysaccharide-type issued from algae. Thanks to they natural origin, alginates are sometimes considered as degradable in animal and human bodies. However, their in vivo degradation behavior is only beginning to be understood [32]. Polysaccharidic alginates that combine different proportions of glucuronic and mannuronic acid-based units repeated alternatively are of interest as hydrogels. Gelation is due to physical cross-linking thanks to complexation with calcium ions. The disappearance of the gel made of unmodified alginates result from the slow exchange of divalent ions by monovalent ones. For this reason, physically cross-linked gels exhibit poor stability in vivo and thus chemical cross-linking is recommended to make more stable gels [33]. Although chemical modifications do not preclude in vivo degradation, they introduce novel constitutive units whose fate has to be demonstrated if bioresorption is claimed. In literature, one can hardly find a demonstration of the bioresorption of high molecular weight alginates at the top of their disappearance from the site of implantation. For instance, various swabs of calcium alginates were implanted subcutaneously in rats to evaluate their biodegradability and ability to evoke local tissue reactions. Implant sites were evaluated after 24 h and after 7 days, 28 days and 12 weeks. Histological sections showed no noticeable degradation of the swabs within the 3 month observation period, contrary to some published reports. Following subsidence of a modest foreign body reaction, implants became embedded in thin fibrous sheaths which were infiltrated with vascular channels and fibroblasts [34].

3.5 Polyorthoesters

Polyorthoesters were among the very first artificial polymers degradable under conditions mimicking physiological conditions and also in contact with mucosa for drug delivery. Several generations have been issued. Only the latest that includes lactyl-lactic acid segments to generate the acid necessary to cleave the main chains has been shown to have all the necessary attributes to allow commercialization [35]. Apparently, no attention was paid to the demonstration of their bioresorbability when proposing them as matrices for controlled drug release.

3.6 Polyanhydrides

Polyanhydrides degrade more or less rapidly in aqueous media [36]. In contrast, aromatic ones are more resistant and have been considered positively for drug delivery, especially to treat brain tumors. Their behavior in vivo was

investigated in animal prior to clinical investigations in human [37]. Basically, such macromolecules can be degraded up to the hydrolytic derivatives of their molecule forming their constitutive repeating units [38].

3.7 Tyrosine-PEG-derived poly(ether carbonate)s

These polymers combine the ethyl ester of deaminotyrosyl-tyrosine—based diphenol and PEG in the presence of phosgene. The resulting polymer chain degrade thanks to the presence of PEG that increases the hydrophilicity. The higher the content in PEG, the faster the degradation was [39]. Interestingly, copolymers of this series where iodine is fixed on aromatic rings was recently shown as degradable with degradation rates depending on the composition. HPLC, NMR and mass spectrometry were used to show the formation of the constitutive low molecular weight compounds and oligomers. Whether complete resorption was achieved was not mentioned [40].

4 What to do to qualify candidates?

Weight loss, molecular weight decrease, viscometry, visual, optical and electronic microscopies, holes or etching under cell growing on surfaces or within scaffolds are common means that are generally used to show chain degradation of a polymeric system. Infrared, ultraviolet, nuclear magnetic resonance and mass spectrometry are also excellent tools to show changes in repeating unit composition or distribution. However, these techniques cannot provide information to show whether the observed degradation is due to sole chemistry (degradation) or to cell biological activity (biodegradation). In vitro investigation can help showing whether degradation is purely chemical. However, the experimental conditions must try to mimic the physiological ones, especially body fluids. This is usually achieved in a pH = 7.4 buffered aqueous medium at 37°C and 0.15 ionic strength corresponding to the osmolality of blood. The pH is generally controlled using phosphate buffer. However, people ought to be careful checking that the buffering capacity of the buffer is sufficient to maintain the pH if acidic or basic degradation products are formed. Commercial buffered saline is generally a poor buffer. This is the reason why we always use 0.13 molar pH = 7.4 phosphate buffer. This solution is not perfect because multivalent ions like calcium or phosphate can interact with the charged macromolecules and affect the degradability. Protein-free cell culture media can also be used, however one must keep in mind that no model conditions can take into account the composition of body fluids, especially in ions and proteins that a foreign material faces in vivo. Enzymes under abiotic conditions, i.e. in the absence of their generating cells or organs, are sometime used in comparison with enzyme-free medium to show biodegradability. Such a strategy must be handled carefully. Indeed, degradation by enzymes under abiotic conditions does not prove these enzymes will be present where the polymer to be degraded is located in an animal or a human body. Good examples to support this remark are poly(ε-caprolactone) and poly(β-hydroxy alkanoate)s that both degrade in the presence of lipase for the first and bacterial depolymerases for the second. However none of these enzymes is present or available in an animal or human body, as shown by the long lifetime of these polymers in vivo. Last but not least, even if one can distinguish between chemical degradation and biodegradation, it is important to underline that only the mechanism of chain cleavage is reflected. These terms and the corresponding data do not provide any information about the fate of the degradation by-products. As mentioned above, to show bioresorption, the late stages of degradation have to be monitored like small molecules of pharmaceutical interest, i.e. by monitoring by-products tissue and blood concentrations, body distribution, urine analysis, exhaled gas. The methods of choice are fluorescence and radiolabeling. However, one must keep in mind that any labeling raises the risk of property modification. This is the reason why ^{14}C and ^{3}H β-emitting radioactive isotope of ^{12}C and ^{1}H are preferable to radio-nuclei like ^{137}I, especially in the case of non-proteinic compounds that do not implicate stable label in the absence of tyrosine residues. In the past, we have tritiated lactic acid and malic acid-derived degradable polymers, sometime with relatively high specific radioactivity to monitor their fate in animals where degradation by-products are highly diluted [41, 42]. The French Nuclear Regulatory Agency in charge of nuclear protection has not renewed the permission to run the

Fig. 2 Equipment for tritiation of artificial polymers at high Specific Radioactivity at the University Montpellier 1 (France)

special equipment installed in our university, so far, thus precluding the use of this powerful and conclusive method to show bioresorption (Fig. 2). If radio-labeling is still rare, the technique should attract companies working for the pharmaceutical industry. However, they will have to learn how to handle polymers consistently and rule out the risk of post-labeling isotopic exchange or improper cleavage of a segment of macromolecule bearing this isotope.

5 Hits on some hot domains of applications

For many years, degradable, biodegradable and bioresorbable polymeric systems have been studied academically. Because of the number of criteria to be satisfied, only a few of them have been developed commercially. This is the case of sutures, staples and meshes to help soft tissue repairing, of bone plates, screws, vertebral cages, orbital floors, anterior cruxiate ligaments reconstruction in bone surgery, of guided tissue regeneration in dentistry to treat periodontal diseases, of wrinkle fillers in plastic surgery, of implants and microparticles in pharmacology, and of scaffolds for skin substitutes. Today, some other devices and systems are attracting researchers and companies. Let us consider the cases of bioresorbable stenting, hydrogels for the delivery of water soluble macromolecules and scaffolds for tissue cultures.

5.1 Bioresorbable stents

Today, people are looking to replacing bare metallic stents and drug eluting stents by bioresorbable ones assuming that they will promote endothelialisation and will render the healing artery its flexibility that is likely to be important in the wall restructuration machinery. Stenting is a typical application relevant to the concept of bioresorption. Indeed, its main role is maintaining the artery opened for the healing time and then disappear after a time which is not well identify yet [43]. Academics and several large or start up companies are active in this area. PLA100 (PLLA) stents have already been implanted in humans [44, 45], but this highly stereoregular polymer degrades very slowly as expected for stent composed of thin struts [46]. PLAX stereocopolymers are regarded as a better choice to match the degradation characteristics and the artery reconstruction machinery [47]. Poly(tyrosine carbonate) [48] are also engaged in the race but rather little is known presently on the exact performances of these polymers.

5.2 Protein, peptide and other hydrophilic macromolecule delivery

As mentioned above, drug delivery is one of the major domains of therapeutic applications relevant to the concept of bioresorption. Various polymer systems (implants, micro-and nano-particles, self-assembled aggregates and micelles of amphiphilic comb-like and block copolymers, respectively, and macromolecular prodrugs) have been proposed to temporarily entrap drug molecules or particles for the sake of controlled delivery [49]. Such applications that introduce foreign material or macromolecules in parenteral compartments known as closed to high molecular weight compounds, also requires bioresorption at the end, at least ideally. If releasing a drug from a sustained delivery device and obtaining a release profile is easy, matching degradation characteristics to the required dose, rate and duration of delivery under conditions where diffusion contributes in parallel is much more difficult. This is certainly the reason why only a very few systems have reached the market, so far. The difficulty is particularly important in the case of hydrophilic drugs and of bioactive macromolecules that diffuse too fast or are retained in solid matrices. Hydrogels are being considered as better adapted to find solutions to excessive affinity for body aqueous fluids [50]. Again, literature is rich in degradable hydrogels chemically or physically cross-linked. Several types of physically cross-linked lactic acid-based triblock copolymers combining hydrophilic and hydrophobic segments are presently investigated. The more common copolymers combine PLAGA segments with short chain PEG to allow elimination of biostable PEG residues through the kidneys [51–53]. Others combine degradable, eventually bioresorbable, segments (artificial like PLA or natural like collagen) cross-linked by polymerization after introduction of suitable function like double bonds, or by difunctional reagents like glutaraldehyde. In terms of bioresorption, cross-linking raises some problems because it generates structures that are no longer fully composed of resorbable entities. In this case, showing bioresorbability is critical.

5.3 Gene transfection

Another hot and fashioned area is gene transfection. In order to avoid the risk generated by the efficient retroviruses, people look for alternatives and polyelectrolyte complexes are among the systems that are investigated the most. Biostable and toxic polybases like polyethylenimine or poly(L-lysine) and many other polycations are being tested for gene transfection mostly in cell cultures. Polyelectrolyte complexes raised many fundamental problems. First, they are stable or unstable in salted media, depending on the pH, the nature of the ions and their concentration, and also the competition with other polyelectrolyte if they are present as it is the case in living media where many charged systems (proteins, micelles, cell membranes) bear ionized acid or basic functions). Body fluids are rather well defined in terms of ionic strength and thus condensed (complexed)

DNA-polycation particles have to remain stable in body fluids and avoid the phagocyting cells to reach their intracellular targets. In attempts to solve the problem of stability during their trip and instability once in the cell, we are examining the potential of artificial bioresorbable polyelectrolytes to transport charged peptides, proteins, antisense oligonucleotides and deliver them intracellularly. So far, only model systems have been studies where biostable polyanions and polycations mimic bioactive macromolecules. For positively charged macromolecule of interest, poly(β-malic acid) and poly(L-lysine citramide) are being tested. For negatively charged ones, poly(β-amino serinate), a polymer of the aliphatic polyester-type derived from serine is being tested in terms of stability in salted media and at various pH [54]. Whether this approach can be adapted to peptides, proteins, etc. is still unknown.

6 Conclusion

In conclusion, if making a degradable polymer backbone is quite easy for polymer scientists, finding the right behavior in body fluids or tissues, the right surface property, the right design, the right degradation rate (the right lifetime) and/or the right pore size is much more difficult, especially if one adds seldom investigated criteria like resistance to sterilization and to aging on storage, and respect of regulations. Therefore, including all criteria to be fulfilled in the initial strategy is an essential condition if one really wants to bring a novel therapeutic system based on the concept of bioresorbability up to clinical and commercial stages. There is no universal bioresorbable polymer although poly(lactic acid)s can fulfill criteria of many different applications, thanks to their outstanding chiral structures and to copolymerization. Nature itself has faced the problem since the number of macromolecular backbones she used to make the various biopolymers we are made of is very limited, briefly poly(α-amino acid), polysaccharide and polynucleotide.

Acknowledgements I wish to thank very much the organizing committee of COLAOB 2008 for inviting me to give this lecture.

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