Biodegradable polymers and composites in biomedical applications: from catgut to tissue engineering

Part 1 Available systems and their properties

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Biodegradable polymers form a unique class of materials that created an entirely new concept when originally proposed as biomaterials. That is, for the first time, a material performing a structural application was designed to be completely resorbed and to become weaker over time. This concept was first applied successfully with catgut sutures and later, with more arguable results, on bone fixation plates and pins. Current research on new and improved biodegradable polymers is focused on more sophisticated biomedical applications to solve patients' problems with higher efficacy and the least possible pain. One example is tissue engineering, in which a biodegradable scaffold seeded with an appropriate cell type provides a substitute for damaged human tissue while the natural process of regeneration is completed. An overview is given of the degradation properties and mechanisms of biodegradable polymers, their processability and biocompatibility, focusing on the aspects most relevant to biomedical applications. The main families of biodegradable polymeric systems are described and the systems that are commercially available or that are currently being studied and proposed for specific medical applications are reviewed.

Keywords: Biodegradable polymers, Natural polymers, Synthetic polymers, Biomedical applications, Biocompatibility, Degradation

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Introduction

A medical implant is often required to perform a function for a specific period of time, while the body heals itself or regains the ability to heal itself. When the implant no longer serves its useful function, two options are generally available: surgically remove the device or leave it in place in a non-functional capacity. There are obvious disadvantages to either choice. However, with the appropriate manipulation of polymer chemistry, mechanical properties and medical design, another option can be exercised. The implant material can be designed using a polymer that will, after fulfilling its function, completely and safely degrade and be resorbed by the body.¹⁻⁴

Therefore, the major and at the same time most basic reason for using a degradable polymer as an implant begins with a simple desire: to have a device that can be used as an implant yet will not necessitate a second surgical event for its removal¹⁻⁶ once it is no longer

needed. In addition to not requiring a second operation, the biodegradation may offer other advantages. For example, a fractured bone, fixed with a rigid, non-biodegradable stainless steel implant, may not heal properly and can eventually re-fracture upon removal of the implant. This happens because the bone does not carry sufficient load during the healing process, since the load is carried by the rigid stainless steel. This phenomenon is known as 'stress shielding'. However, an implant prepared from a biodegradable polymer can be engineered to degrade at a rate that will slowly transfer the load to the healing bone.^{5,6}

Degradation mechanisms and kinetics

Biodegradable polymers used in clinical applications should have resorption rates which are compatible with the healing rates of biotissues or with the performance of a specific function, depending on its final application in the human body.⁵⁻⁹ It is well known that the healing rate is different for each biotissue depending on its location in the human body, and can vary from days (in the case of dermal tissues, for example) up to several months (in the case of hard tissues such as bone).⁵⁻⁹ While a certain tissue is healing, the biodegradable polymers should maintain proper mechanical properties and assure their function. Finally, when the healing of the tissue is

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top, bulk erosion; bottom, surface erosion

1 Schematic representation of two modes of degradation

completed, the implanted biodegradable polymers must be normally completely degraded and should be resorbed as rapidly and safely as possible in order to minimise any unwanted side effects.⁵⁻⁹ Nevertheless, many biodegradable polymers, especially those of synthetic origin, are decomposed very slowly and remain as residues long after their practical functions are lost.

The rate of degradation of biodegradable polymers is dependent on their hydrophilicity, and on the accessibility of their hydrolytic unstable bonds to water (i.e. body fluids), and to specific enzymes or other molecules that can break these chemical bonds. Consequently, the water uptake capability of the material, its morphology, crystallinity, and molecular weight are key parameters that determine the degradation kinetics of the polymer^{7,10-13} and its loss of mechanical properties and weight as function of implantation time.

Biodegradability and bioresorbability

Those interested in the study of degradation and degradation mechanisms of biodegradable polymers will soon realise that the complexity starts from the most basic definitions and terminology that can be found in the literature. This serves to alert the reader that the definitions and terminology used herein do not result from a total consensus obtained among all the researchers working in the field.

For clinical applications, some authors think it important to distinguish between 'biodegradable' and 'bioresorbable' polymers. Biodegradable polymers are polymers that decompose in the living body, but whose degradation products remain in tissue long-term. On the other hand, bioresorbable polymers can be defined as polymers that degrade after implantation into non-toxic products, which are eliminated from the body or metabolised therein.⁷

Bioresorption can be divided in two phases. The first, designated decomposition, involves bond breaking in the main chain, a decrease in molecular weight and the production of oligomers and monomers. The main reaction for this process is hydrolysis. In the second stage of bioresorption, the decomposition products are involved in the metabolic cycles of living organisms. In spite of the differences, biodegradability and bioresorbability are generally used interchangeably.

Bioerosion and degradation

There are two distinct modes of degradation (see Fig. 1). In the first, known as bulk erosion,^{2,5,6,14} the rate at which water penetrates exceeds that at which the polymer is converted into water soluble materials, resulting in erosion throughout the device. All the

commercially available synthetic devices and sutures degrade by bulk erosion. The second type of biodegradation, known as surface erosion,^{2,5,6,14-16} occurs when the rate at which the polymer penetrates the device is slower than the rate of conversion of the polymer into water soluble materials. Surface erosion results in the device thinning over time while maintaining its bulk integrity. In general, this process is referred to in the literature as bioerosion rather than biodegradation.

Although bioerosion can be caused by the solubilisation of an intact polymer, chemical degradation of the polymer is usually the underlying cause for the bioerosion of a polymeric device. Several different types of chemical degradation mechanisms have been identified and these can be mediated by water – hydrolytic degradation/hydrolysis – or by biological agents such as enzymes – enzymatic degradation.^{6,7,16} For some authors, only degradation mediated by biological agents can be correctly termed biodegradation.

Polymers of natural origin are generally degraded in biological systems by hydrolysis and by the action of enzymes.^{7,9} Synthetic polymers are hydrolysed into low molecular weight oligomers and then to monomers by water or serum, but they are not susceptible to enzymatic degradation. It is generally accepted that the availability of water is almost constant in all soft tissues and varies little from patient to patient. On the other hand, the levels of enzymatic activity may vary widely not only from patient to patient, but also among different tissue sites in the same patient. Therefore, the polymers that undergo hydrolysis have more predictable *in vivo* degradation than those whose degradation is mainly dictated by enzymes. Furthermore, the degradation rate of polymers that are mainly degraded by hydrolysis can be more easily assessed by means of *in vitro* experiments.^{6,7,9}

Nevertheless, for most biodegradable polymers, hydrolysis is the most important mode of degradation. Several factors can influence the rate of this reaction,^{7,10,12,13,17,18} the type of chemical bond, pH, co-polymer composition and water uptake being the most important. Chemical and physical changes happening during the degradation of biodegradable polymers, such as the crystallisation of oligomers and monomers or pH changes, may have a substantial feedback effect on the degradation rate. Molecular weight is usually accepted as the most important parameter to evaluate degradation. However, other parameters may be used for monitoring degradation, such as the loss of mechanical properties and complete degradation into monomer, or monomer release kinetics. Although these parameters are related, they do not necessarily obey the same kinetics.

Tailoring of polymer degradation and erosion

In the cases where polymers tend to degrade too slowly or too rapidly for a specific application, it is possible, to a certain extent, to try to regulate the chemical degradation rate.^{14,16} This can be achieved, in many cases, by adding excipients that regulate pH, which affects reaction rates through catalysis. Degradation rate can also be controlled by changing the polymeric matrix structure by means of co-polymerisation or polymer blending. It has been shown, for example, that the introduction of acidic and hydrophilic monomers

increases water uptake of polymers, enhancing degradation. The introduction of a second monomer into the polymer chain may also affect the crystallinity or glass transition temperature and thus modify the degradation rate.

As mentioned before, polymer erosion is preceded by chemical degradation and these two mechanisms are determinant for the performance of biodegradable polymers. Polymer erosion is a far more complex process, because it depends not only on the degradation mechanism, but also on swelling, dissolution and diffusion of oligomers and monomers and morphological changes.^{7,10,12,13,17,18} Erosion may be evaluated by assessment of molecular weight loss, sample weight loss and changing geometry. These parameters do not usually change at the same rate. In order to tailor the polymer erosion, it is first necessary to understand how this parameter is affected by different factors.

During erosion, the morphology changes observed are first confined to the surface. Increasing roughness or porosity is commonly observed and may lead to autocatalytic degradation processes.¹⁴ The preferential erosion of amorphous parts of the polymer compared to crystalline parts is also typically observed. During degradation of polymeric chains, oligomers and monomers are created which are not necessarily released immediately and that can influence pH in degradation media, as well as inside the pores eventually formed. In addition, these monomers may crystallise during erosion. Changes in the crystallinity may also arise from the behaviour of partially crystalline polymers during erosion. Due to the faster degradation of the amorphous regions, the overall crystallinity of the samples increases. Crystallinity also increases during the erosion of intrinsically amorphous polymers. When immersing these samples in degradation media, their glass transition temperature is lowered due to the uptake of water, which leads to the recrystallisation of the polymer. The modelling of erosion is even more complex than the modelling of degradation due to the multitude of the processes involved. Therefore, there is only a very small number of approaches, relying on differential equations,¹⁴ for tailoring the erosion of biodegradable polymers and none of them covers all the aspects of this process.

Degradation during processing of biodegradable polymers

Most biodegradable polymers, particularly those that are commercially available, may be processed in a similar way to any engineering thermoplastic. In fact, most can be melted and formed into fibres, rods and moulded parts. Final parts can be extruded, injection moulded, compression moulded, or solvent spun or cast.^{5,8}

One of the main problems arising from processing of biodegradable polymers is the potential for molecular weight decrease due to the hydrolytic sensitivity of the polymer bonds. The presence of moisture during processing can reduce the molecular weight and produce significant changes in the final properties of the polymer. Therefore, it is essential to take extra care to dry the polymer before thermal based processing preventing moisture from contacting the polymer during processing.^{5,8} The drying procedure can be complemented with

vacuum drying or it can be performed in a resorption circulating air dryer. However, some precaution must be taken when drying polymers above room temperature. Amorphous polymers, for example, should only be dried at room temperature, since they may fuse when the drying temperature exceeds the glass transition temperature. Alternatively, other techniques may be used to avoid the presence of moisture in the manufacturing process.^{5,8} For example, packaging the polymers in small quantities so that the material is used up quickly during processing just after opening the package, avoids moisture absorption over time. Another method to prevent moisture from entering the system consists of blanketing the material hopper or material inlet with nitrogen or dried air.

The other main problem in the processing of biodegradable polymers is their susceptibility to thermal degradation. Most synthetic biodegradable polymers are synthesised by ring-opening polymerisation and there exists a thermodynamic equilibrium between the polymerisation temperature and the reverse reaction that will result in monomer formation. Excessively high processing temperatures can push the equilibrium to depolymerisation resulting in monomer formation during the moulding or extrusion process.^{5,8} The presence of excess monomer may act as a plasticiser, changing the mechanical properties and may catalyse the hydrolysis of the device resulting in altered degradation kinetics. Furthermore, there are strong interactions among temperature, moisture content, shear rate and residence time in the machine, and thus it is highly recommended to use the mildest possible processing conditions and perform a rigorous exclusion of moisture from the system. However, it is sometimes necessary to increase processing temperatures to reduce the melt viscosity or use higher pressures to enable the polymer to flow through small orifices to create fibres or fill a mould of a particular design. This happens, for example, when processing high molecular weight polymers and/or when using a ceramic filler to reinforce the polymeric matrix.

Biocompatibility testing of biodegradable polymers

Apart from favourable physico-chemical and mechanical properties, the most important requirement for a biodegradable polymer to be used in medical applications is its biocompatibility in a specific environment, together with the non-cytotoxicity of its degradation products.^{19–21} In fact, one of the major problems in the use of polymers as biomaterials is to make sure that they are biocompatible by themselves, and that the use of particular additives and/or processing technologies required to obtain different properties and or configurations will not interfere with the biocompatible behaviour.^{19,20}

In terms of biocompatibility, the requirements that degradable materials must fulfil are much more demanding than those for non-degradable materials.⁶ In addition to the potential problem of toxic contaminants leaching out from the implant, such as residual monomers, stabilisers, emulsifiers and many other types of additive, it is also necessary to consider the potential toxicity of the degradation products and subsequent metabolites.⁶ The practical consequence of

this consideration is that only a very limited number of degradable polymers have been shown to be non-toxic.

***In vitro* biocompatibility screening: types of test and interpretation of results**

Cytotoxicity testing represents the initial phase in testing the biocompatibility of potential biomaterials and medical devices. Its purpose is to act as a reliable, convenient, and reproducible screening method to detect, at an early stage in the testing process, cell death or other serious negative effects on cellular functions.^{22–29}

Cytotoxicity deals mainly with the substances that leach out of biomaterials.^{30,31} For example, polymers often have low molecular weight 'leachables' (additives, low molecular weight components, initiator fragments, etc.) that exhibit varying levels of physiological activity and cell toxicity.^{24,30,32} Therefore, knowledge of the degradation processes of biodegradable polymeric biomaterials and of the effects that their degradation products might have on the body is crucial for the long term success of a biomaterial.³³

The assessment of cytotoxicity forms the basis of *in vitro* test methods in existing national and international standards.^{34,35} Such methods can be applied to both direct and indirect testing assays. These assays differ mainly in the manner in which the test material is exposed to the cells. The choice of the method varies with the characteristics of the test material, the rationale for doing the test and the application of the data for evaluating biocompatibility.^{23,34–36} Direct contact techniques involve assays in which the material to be tested is brought into direct contact with the cells, usually by seeding a cell suspension onto the material.^{34,35} Indirect methods are of two types.^{34,35} The first consists of the separation of the material from the cells by a diffusion barrier, such as an agar layer, placed between the material and a cell monolayer. The second consists of the addition of an extract of the material to a cell monolayer. Indirect testing techniques are important for the detection of leachable substances, which could exert toxic effects on cells.³⁴

Beyond biocompatibility, i.e. absence of a cytotoxic effect, the overall functionality of a biomaterial also benefits from its bioactivity,^{37–39} i.e. promotion of biological processes furthering the intended application. Therefore, to assess the biofunctionality of a particular material, it is necessary to undertake a range of tests.^{22,23,25,26} After a preliminary study and a toxicological investigation of the material, its function and often its changes during use must be monitored.^{22,23,25,26} To evaluate the biocompatibility of materials or devices, quantitative tests are necessary to progress beyond simple morphological examination of biomaterial–cell interactions.

Assessment of *in vitro* biocompatibility

Cytotoxicity tests essentially consist of morphological evaluations to highlight and quantify the cells that have died or have undergone regressive phenomena after contact with the material.^{22,23,25,26,36}

If *in vitro* toxicity is defined as a negative or deteriorative effect of an agent on normal cellular biochemical functions, it is clear from a cell biologist point of view that these negative effects can manifest

themselves in different ways.³⁴ This offers a variety of possibilities for assessing cytotoxicity. Therefore, cytotoxicity is assessed after an appropriate exposure period (usually 24–72 h) by qualitative morphological evaluations or quantitative measures of cell death, inhibition of cell growth, cell proliferation, accumulation of protein, release of enzyme(s), release of vital dye or other measurable entity.³⁶

The essential philosophy for studying biofunctionality *in vitro* is to establish reproducible and quantifiable assays focusing on cells involved in biological parameters relevant to the biomaterial application. Therefore, in the assessment of biofunctionality *in vitro*, it is very important to use cells that are relevant for the final application of the material, in order to study the more specific aspects of biocompatibility.^{34,40} This means, for example, that for vascular prostheses, endothelial cells are appropriate, whereas for studying cell interactions with orthopaedic implants, chondrocytes or osteoblasts, should be chosen.

It is clear that the relevant parameters in these cases will include some of the functions studied under the heading of cytotoxicity, for example, cell proliferation. However, other cell biological parameters, not yet mentioned, are also of prime importance,^{34,40} such as cell adhesion, cell spreading and cell biosynthetic function.

Cell adhesion is probably the single most important aspect of cell interaction with a biomaterial, if the possibility that components of the material are cytotoxic is excluded.^{34,37,40–46} It is the prerequisite for further cellular functions, such as spreading, proliferation, migration and biosynthetic activity.^{34,37,40–42} Therefore, it is a field of obvious interest not just to biologists, but also to material chemists and surface engineers. Surface characteristics of materials, whether their topography, chemistry, surface energy or wettability, play an essential role in cell adhesion on biomaterials.^{43,47,48} It must be stressed that cell adhesion is desirable for biomaterials which are to be integrated into host tissues, such as orthopaedic implants in bone or in vascular prostheses which are to be pre-seeded with the patient's own endothelial cells.^{34,37,43,46,49} On the other hand, adhesion is a serious problem for blood-contacting surfaces that are not to be pre-seeded, such as catheters or sensors.^{34,37,40} Quantification can be carried out using image analysis systems at both light and scanning electron microscopy level and thus used to compare the efficacy of various substrata.

The major advantage of using *in vitro* methods for cytotoxicity/biocompatibility testing is their cost effectiveness and speed, which make them particularly suitable for screening large numbers of potential biomaterials and their modifications.^{22,24,31} This is all the more relevant against the background of current public (and expert) opinion on reduction of animal experimentation.^{22,32,36} Coupled with this is the high sensitivity of the methods, which enables potentially cytotoxic materials to be identified at an early stage in the testing procedure.^{26,29}

The fundamental problem of *in vitro* methods is the need to extrapolate to the *in vivo* situation.^{26,31,36} This problem cannot be solved by any amount of philosophical discussion, and thus it should be stressed that *in vitro* testing represents only one phase in assessing biocompatibility.^{26,36,40} Specimens classified as *in vitro*

biocompatible must enter a further phase of testing, which requires *in vivo* observation.

Main families of biodegradable polymeric system

Biodegradable polymers can be natural or synthetic, both presenting advantages and disadvantages. Some authors^{3,5,6} claim that synthetic polymers offer advantages over natural polymers and that the former can be tailored to give a wider range of properties and hence more predictable and reproducible materials. However, natural polymers are, in many cases, closer in structure to the natural tissues to be replaced/regenerated and, for this reason, might be more likely to induce the appropriate cell interactions with surrounding tissues that are fundamental in biomedical applications.¹⁹ Since both natural and synthetic polymers present important characteristics, it is believed that the best degradable polymers for biomedical applications, may be found by developing new biomaterials that combine the most favourable properties of synthetic and natural polymers.^{50–52} Another approach considered below consists of the reinforcement of polymeric matrixes with bioactive ceramic materials such as hydroxyapatite and other calcium phosphates. These fillers have the ability, in most cases, of improving the mechanical properties and the biological behaviour simultaneously.

Natural origin polymers

Natural polymers often have a highly organised structure, at both molecular and macroscopic levels, which – if it can be retained – will confer favourable performance characteristics on biomaterials, such as strength, or the ability to induce tissue ingrowth.⁵³ However, while natural polymers usually contain domains that can send important signals to guide cells at various stages of their development,^{50,53,54} this bioactivity can cause problems with antigenicity.^{53,54} When the material is implanted in a host, this stimulates an immune response, potentially leading to immune rejection. In addition, because the degradation of natural polymers often relies on enzymatic processes, there will inevitably be patient to patient variation in the degradation rate, depending on the activity of the individual's specific degradation enzyme.^{53,54}

Nevertheless, natural polymers were the first to be used as scaffold materials for tissue regeneration. For example, collagen fibres, bonded by glycosaminoglycans (GAGs) to form a matrix, have been used as a scaffold material for the regeneration of damaged skin^{53,54} to prevent fibrous scar formation during the healing process.

Synthetic polymers

Since synthetic biodegradable polymers are chemically synthesised, it is possible to control (with varying degrees of accuracy, depending on the polymerisation reaction, among other factors), their molecular weight and molecular weight distribution.^{53,54} These characteristics have a profound effect on the physical characteristics of the polymer, such as its strength and degradation rate. The degradation of synthetic polymers is, in general, brought about by simple hydrolysis,

although in some cases enzymatic processes assist in the degradation mechanism. Simple hydrolysis is desirable because the degradation rate does not vary from person to person (unless there are local pH variations due to inflammations, implant degradation, etc.). An additional advantage of synthetic polymers is that generally they tend to be more easily processable into a finished product.^{53,54}

Biodegradable composites

In recent years, several biodegradable polymers have been reinforced with hydroxyapatite and other calcium phosphates. Examples are the composites based on matrixes of poly(lactic acid) (PLA),^{55–57} polyethylene oxide/polybutylene terephthalate (PEO/PBT),⁵⁸ poly(hydroxybutyrate) (PHB)⁵⁹ and collagen.^{60–62} Also, reinforcement with Ca–P fibres, instead of the more widely used particles, has been tried.⁶³ The idea was to simultaneously enhance the mechanical performance of the material, trying to develop bone analogue composites, and improve the biological behaviour of the unfilled polymers. Generally, the biocompatibility of the materials proved to be better and, in some cases, a bone bonding behaviour could be observed.^{55,56,58} However, in most cases it was not possible to achieve mechanical properties in the range of human cortical bone.^{55,58,60–63}

Types of filler: hydroxyapatite, bioactive glasses, bioactive glass ceramics

Bioactive materials are developed to elicit or modulate a specific biological activity.⁶⁴ For bone implants, this activity is bone bonding.^{64,65} This may be defined as the establishment, by physico-chemical processes, of continuity between the implant and the bone matrix.⁶⁴ For such materials, bone formation may start both at the surface of the material and at the surrounding bone tissue. Bioactive ceramics are either very similar to bone apatite or they have the capability of forming a calcium phosphate (Ca–P) layer on its surface when implanted, that will promote bone bonding.^{66–72} Besides the hydroxyapatite (the major inorganic constituent of human bone), other types of calcium phosphate, such as fluorapatite or tricalcium phosphate (TCP) and biphasic HA/TCP ceramics,^{65,73–77} represent just some examples of materials that also present a bone bonding behaviour and that can be used as filler in biodegradable polymeric matrixes.

Bioactive glasses (of which Bioglass is the most widely used) are also capable of bonding to bone. In fact, this type of glass can promote,^{66,67,78,79} when implanted, the formation on its surface of a bone-like apatite layer that will avoid the traditional fibrous encapsulation allowing the creation of a continuous bone/glass interface. The most typical bioactive glasses are based on Na₂O–CaO–P₂O₅–SiO₂ systems, but alternatives incorporating, for example, B₂O₃, CaF₂, MgO, Al₂O₃, have been proposed.^{66–68,70–72,78–89} All these bioactive glasses exhibit bone bonding behaviour. However, the kinetics of calcium phosphate formation is strongly dependent on the composition of the glass. The formation of a titania or silica gel at the surface can also be responsible for conferring bioactive behaviour to an implant of another material.^{90–92} In particular, the role of hydrated SiO₂ appears to be essential.

Bioactivity: composites and biomimetic coatings

As stated above, it is becoming well established that the essential requirement for an artificial material to exhibit bone bonding behaviour is the formation on its surface of a calcium phosphate (Ca-P) similar to bone apatite.^{67,70,94-98} The presence of an apatite-like layer on the surface of an orthopaedic biomaterial is considered as a positive biological response from the host tissues, which will assure effective bone-to-implant fixation of bone replacement materials. Furthermore, it is known that clinical success requires the simultaneous achievement of a stable interface with connective tissue and matching of the mechanical behaviour of the implant with the tissue to be replaced.

Metals and ceramics are too stiff compared with cortical bone, and induce stress shielding. Polymers, especially polymer matrix composites, may be engineered to produce mechanical properties matching those of bone. However, to date, only PEO/PBT block copolymers (Polyactive) have been claimed to show bone bonding.^{58,94,98,99} Unfortunately, these materials cannot be used in load bearing applications due to their lack of mechanical strength.^{58,99}

Other work^{50,68,93,100-106} has adopted a different approach, aiming to mimic natural mineralisation processes to develop synthetic *in vitro* methodologies, whereby a mineral phase is deposited in a particular polymer matrix or on the surface of a polymeric substrate. In all these studies, it is important to generate chemical conditions at the interface that induce precipitation of the mineral phase. The term biomimetic (related to the formation of a Ca-P layer on the surface of an implant material) was introduced into the biomaterials community by the work of Kokubo *et al.*

and other workers.^{50,68,100-106} This type of coating has been produced on a wide variety of materials ranging from metals, non-biodegradable polymers and bioinert ceramics to natural materials such as bamboo.⁹³⁻¹⁰² However, biodegradable polymers have generally not been successful as substrates for nucleating these biomimetic Ca-P films, since their degradation increases the complexity of phenomena occurring at the polymer/solution interface. Among the few successful examples are starch based polymers; several studies have developed biomimetic routes to obtain bioactive Ca-P coatings on the surface of these biodegradable polymers.¹⁰⁷⁻¹⁰⁹

Polymeric systems for medical applications

The biodegradable polymeric systems widely used in medicine at present are mainly based on poly(lactic acid) (PLA)^{10,55,110-121} and poly(glycolic acid) (PGA)^{10,11,121-124} and their co-polymers.^{10,11,121,125-127} Other systems claimed to be biodegradable, e.g. collagen,¹²⁸⁻¹³⁴ poly(hydroxybutyrate) (PHB),^{59,135,136} polycaprolactone,¹³⁷⁻¹⁴² tyrosine derived polycarbonates (poly-DTE, poly-DTB, poly-DTO),¹⁴³⁻¹⁴⁵ polyphosphazanes,¹⁴⁶ polydioxanone (PDS),¹⁴⁷⁻¹⁴⁹ cellulose derivatives, chitin and chitosan,¹⁵⁰⁻¹⁵⁵ polyethylene glycol (PEG),^{149,156-159} polyvinyl alcohol (PVA),^{131,160,161} polyethylene oxide-polybutylene terephthalate (PEO/PBT) co-polymers,^{58,98,162} polypropylene fumarate (PPF),¹⁶³⁻¹⁶⁶ have been proposed, but none has really established itself in the market.

Table 1 presents typical mechanical properties and degradation data for selected biodegradable polymers for orthopaedic applications commonly used by the

Table 1 Typical mechanical properties (MP) and degradation data for several biodegradable polymers that might be used in orthopaedics: note that biodegradable polymers are hydrophilic and consequently their properties depend strongly on testing conditions (literature data compiled herein is usually based on tests carried out at 23°C and 55-60%RH)

Polymeric system*	Tensile modulus, GPa	Tensile strength, MPa	Bending strength, MPa	Degradation data (weight loss (WL) or mechanical properties loss (MPL))	Ref.
PGA	6.5-7.0	57-100	120-218	Complete WL in 60-80 days	1, 7, 11, 110, 123, 124
PLA or PLLA	2.0-5.1	10-75	45-145	Complete WL in 2-5 years; 50% MPL in 1 month for semi-crystalline and in 5 months for amorphous	10, 11, 113-115, 121, 168
PDLLA	3.5	60	130	Complete WL in 0.5-1 year	10, 121
Sintered self-reinforced PGA†	7-10	NA	200-260	67% MPL in 3 weeks; <i>in vivo</i> MP below cancellous bone in 4-7 weeks	11, 121, 123, 169
Hot drawn self-reinforced PGA†	13	NA	360	67% MPL in 3 weeks; <i>in vivo</i> MP below cancellous bone in 4-7 weeks	11, 121, 123, 169
Self-reinforced PLLA	7-8	120	245-275	60% MPL in 12 weeks	110, 11, 119, 121, 169, 175
Hot drawn PLLA				70% MPL in 24 weeks	
PHB	4	40	NA	NA	59, 110, 136, 167
Polycarbonates (DTE)	1.4-1.8	40-60	NA	40% WL in 16 weeks; 50% WL in 1 year	170-172
CA	1.6	26.5	NA	Only 6% WL after 180 days	150
PDS	2	30	NA	Complete WL in 180 days	110, 174, 175
Ti-6Al-4V‡	115	550-1000	980	Bioinert	173
Stainless steel‡	210	500-1500	400-800	Bioinert	173
Human cortical bone‡	7-25	50-160	195-235	NA	176-181

*PGA: poly(glycolic acid); PLA: poly(lactic acid); PLLA: poly(L-lactic acid); PDLLA: poly(D,L-lactic acid); PHB: poly(hydroxybutyrate); CA: cellulose acetate; PDS: polydioxanone.

†2-4.5 mm dia.

‡Bone, steel, and titanium are included as reference materials.^{173,176-181}

medical device industry. Polymers based on PLA and PGA represent the gold standard and consequently the data in Table 1 tend to give more importance to polylactide and polyglycolide based systems. These, and other natural origin and synthetic polymers that have received attention in the biomedical field, are described below.

Natural origin polymers

Type I collagen

Collagen is the major component of all mammalian tissues, accounting for approximately 30% of all protein in the human body. It is found in every tissue that requires strength and flexibility, such as skin or bone, for example, which are consequently convenient and abundant sources of this natural polymer. At least 15 types of collagen have been identified, type I being the most abundant.^{7,19} Because of its abundance and its unique physical and biological properties, type I collagen has been widely investigated for biomedical applications.^{7,19}

Collagen proteins are by definition characterised by a unique triple-helix formation extending over a large portion of the molecule. The individual molecules spontaneously polymerise *in vitro* into strong fibres that can be subsequently formed into larger organised structures. The collagen may be further modified to form intra- and intermolecular crosslinks, which aid in the formation of collagen fibres, fibrils and then macroscopic bundles that are used to form tissue.^{7,19}

Collagen crosslinking can be enhanced after isolation through a number of well described^{7,19} chemical techniques. The major drawbacks of solid crosslinked collagen still include a lack of deformability and flexibility and low tensile strength.¹⁹ It should also be stressed herein that, due to its structure, collagen is only mildly immunoreactive. Furthermore, collagen and its integrin binding domains assist in the maintenance of attachment-dependent cell types in culture.^{7,19} For example, fibroblasts grown on collagen matrixes appear to differentiate in ways that mimic *in vivo* cellular activity and to exhibit nearly identical morphology and metabolism.

Hyaluronic acid

Glycosaminoglycans (GAGs), which consist of repeating disaccharide units in linear arrangements, usually include a uronic acid component (such as glucuronic acid) and a hexosamine component (such as N-acetyl-D-glucosamine).^{7,19}

Hyaluronic acid (hyaluronan) is an anionic polysaccharide with repeating disaccharide units of N-acetylglucosamine and glucuronic acid.^{7,19} Hyaluronic acid is present in connective tissue, in the synovial fluid or articular joints and in the vitreous humour of the eye and it can be obtained from natural sources or via microbial fermentation. In dilute solutions, under physiological conditions, hyaluronate molecules exist as random coils with their own solvent shells.⁷ An increase in their concentration causes interpenetration of the chains and an entangled network.

Like collagen, hyaluronic acid can be easily chemically modified.^{182–185} The fact that it is not antigenic, eliciting no inflammatory or foreign body reaction, makes it desirable as a biomaterial. Its main drawback

in this respect is the limited range of its mechanical properties.¹⁸⁴ In addition, the role of hyaluronic acid as a key component in a tissue repair product is controversial. Some investigators have suggested that hyaluronic acid alone does not seem to have any effect, and hyaluronate–collagen composites may not be any better than collagen alone. However, other studies have indicated that hyaluronate–protein complexes play a significant role in the *in vivo* organisation of scar tissue.¹⁹

Several sponge formulations of derivatives of hyaluronic acid (produced by Fidia Advanced Biopolymers, Italy) are being used in tissue engineering experiments for the regeneration of bone and cartilage, for example, HYAFF 11 and ACP.^{186,187} HYAFF 11 sponges have 10–400 μm pores, 80% porosity and a surface area of 10.00 $\text{m}^2 \text{cm}^{-3}$. ACP sponges have 10–300 μm pores, 85% porosity and a surface area of 7.34 $\text{m}^2 \text{cm}^{-3}$ (Refs. 186, 187).

Alginate

Alginate is a polysaccharide isolated from seaweed, which has been used as an injectable cell-delivery vehicle and a cell-immobilisation matrix owing to its gentle gelling properties.^{188–196} Alginate is a family of copolymers of D-mannuronate and L-guluronate. It forms gels in the presence of divalent ions such as Ca^{2+} . The physical and mechanical properties of alginate gels are strongly correlated with the proportion and length of the polyguluronate block in the alginate chains. The advantages of alginate include its wide availability, low diffusional barriers for nutrients and relative biocompatibility.¹⁸⁸ However, alginate is claimed¹⁸⁸ not to be biodegradable in the human body and exhibits variations of composition and purity from batch to batch. Furthermore, gel formation is dependent on calcium ions, which can be lost following implantation.¹⁸⁸

Chitosan

Chitosan is a biosynthetic polysaccharide that is the deacetylated derivative of chitin. Chitin is a naturally abundant occurring polysaccharide that can be extracted from crustacean exoskeletons (crabs, shrimps, etc.) or generated via a fungal fermentation process.^{7,19} The biodegradation rate of this polymer is determined by the amount of residual acetyl content, a parameter that can be easily varied.¹⁹

Although chitosan is water soluble in diluted acid, it precipitates at a pH above 6.^{1,197} Chitosan forms a gel in the presence of anions such as phosphate. Due to its cationic nature, the polymer forms polyelectrolyte complexes with anionic proteins and polysaccharides. Chitosan–polyelectrolyte complexes can be used for controlled drug delivery.¹ Furthermore, chitosan gels, powders, films and fibres have been formed and tested for such applications as encapsulation, membrane barriers, contact lens materials and inhibitors of blood coagulations.¹

Chemical modification of chitosan products produces materials with a variety of physical and mechanical properties. Like hyaluronic acid, chitosan is not antigenic and is a well tolerated implant material. In fact, chitosan shows biostimulating activities in the healing process of various tissues.¹ Chitosan has been applied to conduct the extracellular matrix (ECM) formation in

tissue regenerative therapy.¹⁹⁸ The superior tissue compatibility of chitosan may be primarily attributed to its structural similarity to glycosaminoglycan in extracellular matrix.¹⁹⁸

Chitosan has also been formed into membranes, microspheres and matrixes suitable for several tissue engineering applications.^{1,19,197–201}

Poly(hydroxybutyrate) (PHB)

Polyhydroxyalkanoate (PHA) polyesters are degradable, biocompatible, thermoplastic materials made by several microorganisms.^{6,19} They are intracellular storage polymers whose function is to provide a reserve of carbon and energy. Although the structures of PHA can contain a variety of *n*-alkyl side chain substitutes, the most extensively studied is the simplest: poly(3-hydroxybutyrate) (PHB). PHB homopolymer, like all other PHA homopolymers, is highly crystalline, extremely brittle, and relatively hydrophobic.^{6,19} In addition, these polymers undergo hydrolytic and enzymatic degradation.^{7,10,59,135,167,202} However, the PHA homopolymers have degradation times *in vivo* in the order of years. In contrast, the co-polymers of PHB with hydroxyvaleric acid are less crystalline, more flexible, and more readily processable.^{6,19}

PHB has been found to have low toxicity, in part due to the fact that it degrades *in vivo* to D-3-hydroxybutyric acid, a normal constituent of human blood. Applications of these polymers include controlled drug release, sutures, and artificial skin as well as many industrial applications as paramedical disposables.^{6,19}

Synthetic polymers

Poly(glycolic acid), poly(lactic acid) and their co-polymers

As already mentioned at the beginning of this section, poly(α -hydroxyl acids), such as poly(glycolic acid) and poly(lactic acid), are currently the most widely investigated, and most commonly used, synthetic biodegradable polymers.^{1,5,19,53,126,203} They are currently the gold standard of the market that any new candidate must beat. These polymers are in fact the current benchmark in the biomedical industry.

Poly(glycolic acid) (PGA) is the simplest linear aliphatic polyester. Since PGA is highly crystalline, it has a high melting point and low solubility in organic solvents. PGA was used in the development of the first totally synthetic, absorbable suture, which has been commercially available since 1970 under the trade name Dexon.

In order to adapt the properties of PGA to a wider range of possible applications, co-polymers of PGA with the more hydrophobic poly(lactic acid) (PLA) were intensively studied. The hydrophobicity of PLA limits the water uptake of thin films to about 2% and reduces the rate of backbone hydrolysis compared with PGA. Co-polymers of glycolic acid and lactic acid have been developed as alternative sutures (trade names Vicryl and Polyglactin 910).^{1,5,19,53,126,203}

It is noteworthy that there is no linear relationship between the ratio of glycolic acid to lactic acid and the physico-mechanical properties of the corresponding co-polymers. Whereas PGA is highly crystalline, crystallinity is rapidly lost in co-polymers of PGA and PLA.^{1,5,19,53,126,203} These morphological changes lead to an increase in the rates of hydration and hydrolysis.

Thus typically 50 : 50 co-polymers degrade more rapidly than either PLA or PGA.

Lactic acid exists in two stereoisomeric forms which gives rise to four morphologically distinct polymers:^{1,5,19,53,126,203} the two stereoregular polymers, D-PLA and L-PLA, and the racemic form D,L-PLA. The fourth morphological form meso-PLA, is obtained from D,L-PLA but in practice is rarely used.

One of the disadvantages of these materials is that their degradation products reduce the local pH value, which, in turn, may accelerate the polyester degradation rate and induce an inflammatory reaction,^{19,53,203} although this problem has now largely been overcome by optimising processing methodologies to produce graduated breakdown. Another disadvantage is that the mechanical properties of highly porous scaffolds made from poly(α -hydroxyl acids) are relatively weak, which limits their use for hard tissue regeneration.^{19,53,203} On the other hand, PGA exhibits very interesting mechanical properties, but it degrades too rapidly for most applications and is very difficult to process (Refs. 7, 10, 11, 121–123, 168, 169). Consequently, the industry that manufactures bone plates and screws has been focusing more on PLA based systems or PLA/PGA co-polymers (Refs. 10, 11, 110, 111, 121, 123, 168, 169).

The PLA/PGA based polymers can be processed by standard injection or compression moulding,^{110,121,168,169} but the mechanical properties obtained do not allow for their use on any type of load bearing application. This is due to the melt crystallisation into a partially crystalline spherulitic structure without any preferred orientation of the crystalline and the amorphous domains. In order to move these materials into clinical application (other than surgical sutures) two self-reinforcing (SR) techniques have been developed:^{119,121–123,169,204} sintering and fibrillation. In the first method, highly oriented PLA fibres are joined together by a matrix of the same material by sintering at 5–25 K below the respective melting temperature at pressures around 50–80 MPa.^{11,121,169,205} In the fibrillation method, the polymer is oriented in the solid state by a drawing process. A melt moulded polymer billet is passed through a die in the solid state, after being slightly heated, transforming the partially crystalline structure into a highly oriented fibrillar structure by means of mechanical deformation.^{11,121,169} This method is capable of inducing a highly oriented polymer morphology with greatly enhanced mechanical properties (in the drawing/extrusion direction). However, both methods present a very low throughput as compared to standard melt based processes. Nevertheless, the application of these patented methods^{205,206} allowed the commercialisation and clinical application of SR-PLA and PLA/PGA based, bone fixation plates and screws, under the trade name Biofix.^{1,5,19,53,126,203,206} Further data on both types of self-reinforced material are presented in Table 1.

Poly(ϵ -caprolactone)

Poly(ϵ -caprolactone) (PCL) exhibits several unusual properties, not found among the other aliphatic polyesters.^{5–6,19} PCL is a semicrystalline polymer with a low melting point (57°C) and a low glass transition temperature. Thus, PCL is always in a rubbery state at

room temperature, which contributes to the very high permeability of PCL for many therapeutic drugs.^{5-6,19} Other unusual properties of PCL are its high thermal stability and its propensity to form compatible blends with a wide range of other polymers.^{5-6,19} Polycaprolactone degrades at a slower rate than PLA and can therefore be used in drug delivery devices that remain active for over a year. Based on a large number of tests, PCL is currently regarded as a non-toxic and tissue compatible material.^{1,5,6} Consequently, the Capronor system,⁶⁹ a one-year implantable contraceptive device, has undergone Phase I and Phase II clinical trials in the USA. It is interesting to note that in spite of its versatility, PCL has so far been predominantly considered for controlled release applications. However, in the past few years, PCL has also been widely proposed¹⁴⁰⁻¹⁴² for use in tissue engineering scaffolding.

Poly(dioxanone)

The ring-opening polymerisation of P-dioxanone resulted in the first clinically tested monofilament synthetic suture, known as PDS.^{5,147-149} However, PDS cannot be used for the manufacturing of implants due to its very poor mechanical strength.^{160,177,207-209} This material has approximately 55% crystallinity, with a glass transition temperature of -10 to 0°C. The polymer should be processed at the lowest possible temperature to prevent depolymerisation back to monomer. Poly(dioxanone) has demonstrated no acute or toxic effects on implantation. The monofilament loses 50% of its initial breaking strength after 3 weeks and it is absorbed within 6 months,⁵ providing an advantage over Dexon or other products for slow-healing wounds.

In the 1970s and 1980s, PDS was successful as a suture material, but has since lost its market¹⁴⁷⁻¹⁴⁹ to several new biodegradable polymers developed in the past 20 years that exhibit enhanced properties for this type of application.²¹⁰

PEO/PBT block co-polymers

Polyethylene oxide (PEO)/polybutylene terephthalate (PBT) co-polymers (PolyActive)^{58,98,162,207} have been investigated for bone replacement applications. PEO/PBT co-polymer possesses hydrogel properties and its bone bonding behaviour has been described under different experimental conditions. Another advantage of the use of PolyActive is that a range of PEO/PBT compounds can be synthesised by variation of the contribution in weight of the two individual components. This enables the controlled determination of the mechanical properties and degradation characteristics. Experiments with such a range of PEO/PBT co-polymers in a bony implantation bed established a direct relation between PEO content, calcification rate and bone bonding.¹⁶² However some authors^{208,209} contest these results.

As a scaffold, PolyActive 55/45 has been claimed to show suitable mechanical properties and good biocompatibility both *in vitro* and *in vivo*,²⁰⁷ but only for very small load bearing applications (typically for soft tissues like skin).

Poly(propylene fumarate)

Poly(propylene fumarate) (PPF) is an unsaturated linear polyester and is viscous at room temperature.¹⁶³ It can

be crosslinked at the time of surgery to form a solid degradable bone cement via an addition polymerisation with N-vinyl pyrrolidone (N-VP). As the crosslinking reaction proceeds, the PPF is transformed from a viscous liquid to a putty-like state before finally solidifying. During its liquid and putty state, the polymer can be injected or moulded into the bone defect. It is therefore well suited for several applications, since many bone injuries, for example, result in defects, which are relatively inaccessible and geometrically complex. Most addition polymerisation reactions are exothermic and generate large quantities of heat, but the crosslinking reaction between PPF and N-VP generates much less heat than, for example, the *in situ* polymerisation of PMMA (polymethylmethacrylate) and no local tissue necrosis has been noted in *in vivo* studies. At the time of crosslinking, PPF may incorporate particles of NaCl or other materials such as sugar, providing pores for the ingrowth of new bone and/or bioactive and osteoconductive fillers such as tricalcium phosphate to stimulate bone growth and improve mechanical performance.¹⁶³⁻¹⁶⁶

Poly(amino acids) and 'pseudo'-poly(amino acids)

Since proteins are composed of amino acids, it was an obvious idea to explore the possible use of poly(amino acids) in biomedical applications. Poly(amino acids) were regarded as promising biomaterials, since the amino acid side chains offer sites for attachment of drugs, crosslinking agents, or pendent groups that can be used to modify the physical-mechanical properties of the polymer. In addition, poly(amino acids) show a low level of systemic toxicity, owing to their degradation to naturally occurring amino acids.^{6,19}

Despite their apparent potential to be used as biomaterials, poly(amino acids) have actually found few practical applications.^{6,19} Most of them are highly insoluble and non-processable materials. The starting materials (N-carboxy anhydrides) are expensive and difficult to handle because of their reactivity and moisture sensitivity. Furthermore, the antigenicity of polymers containing three or more amino acids limits, to a very large extent, their use in biomedical applications. Owing to these difficulties, only a few poly(amino acids), usually derivatives of poly(glutamic acid) carrying various pendent chains at the γ -carboxylic acid group, are being investigated as implant materials.^{6,19}

In an attempt to circumvent the problems associated with conventional poly(amino acids), backbone modified 'pseudo'-poly(amino acids), were introduced in 1984.^{5,6,19,188} Recent studies indicate that the backbone modification of poly(amino acids) may be a generally applicable approach for improving the properties of conventional poly(amino acids).^{6,19,188}

Starch based polymers

As stated above, it is believed that improved biodegradable polymers for biomedical applications, including tissue engineering, will be achieved by developing synthetic biomaterials combining the most favourable properties of synthetic and natural polymers. These will, at the same time, allow precise control over material properties and the opportunity to attach functional groups that promote favourable cell-polymer interactions.⁵⁰⁻⁵²

Biodegradable blends of corn starch with several synthetic polymers have been proposed by University of Minho researchers as novel alternatives to commonly used biodegradable polymers for a variety of biomedical applications.^{211–233} These polymers are blends of a corn starch with various synthetic components: cellulose acetate, ethylene vinyl alcohol, polycaprolactone or polylactic acid. Their non-cytotoxicity and biocompatibility *in vitro* and *in vivo* has been confirmed by several studies.^{230–233}

Starch based polymers can be processed using non-conventional processing technologies and reinforced with bioactive fillers to obtain mechanical properties that allow their application as temporary substitutes for bone and/or as fixation plates/screws in the orthopaedic field.^{211–233} They can also be used to produce partially degradable bone cements and hydrogels,^{221–223} and microparticles for controlled release of drugs.²²⁴ Furthermore, these polymers have also been extensively studied for applications in the tissue engineering field.^{225–229} Several techniques have been developed to produce scaffolds for tissue engineering applications with a wide range of mechanical properties and porous architectures.^{225,226} These scaffolds have been used in tissue engineering experiments using osteoblastic-like cells and rat bone marrow cells, which demonstrate their ability to support cell adhesion and proliferation.^{227–229}

Examples of polymeric systems that have been studied for use in tissue engineering related applications are given in Table 2.

Concluding remarks

Recent developments in biomaterials have provided many biodegradable polymers having interesting properties for varied biomedical applications. However, this variety remains limited in view of the wide range of materials properties required to fulfil the almost unlimited requirements inherent in these potential medical applications. Thus, research on new or modified biodegradable polymers remains a challenge.

Another important aspect of research on biodegradable biomaterials is that few of the biodegradable polymers proposed for specific applications have been extensively characterised in the light of these applications; such assessments are vital to establish the credibility of new biomaterials.

Table 2 Examples of natural origin and synthetic polymers that have been used, or that are under consideration for use, in tissue engineering applications

Polymeric systems	Ref.
Natural origin	
Type I collagen	7, 19
Hyaluronic acid	186, 187
Alginate	188–196
Chitosan	197–201
Starch based polymers	225–229
Synthetic*	
PGA, PLA and their co-polymers	19, 53, 102, 203
Poly(ϵ -caprolactone)	140–142
Poly(propylene fumarate)	163–166
PEO/PBT block co-polymers	207

*PGA: poly(glycolic acid); PLA: poly(lactic acid); PEO: poly-ethylene oxide; PBT: polybutylene terephthalate.

Finally, only a minute fraction of all biodegradable polymers are routinely used in a very small range of applications in human medicine and very few have been approved by the Food and Drug Administration (FDA), or equivalent authorities, for clinical studies in human patients.

All these factors provide a driving force for continuing research on biodegradable polymers, as well as for the development of new materials and for more systematic characterisation of existing materials in terms of their target applications.

Tissue engineering, in particular, is expected to drive development of novel biodegradable polymers, as is discussed in part 2 of the present review.²³⁴ Nevertheless, it is clear that much progress has been made since the days of catgut sutures.

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