Plastics Topics – Bioabsorbable plastics

TANGRAM TECHNOLOGY Consulting Engineers

Tangram Technology Ltd.

33 Gaping Lane, Hitchin, Herts., SG5 2DF

Phone: 01462 437 686

E-mail: sales@tangram.co.uk

Web Pages: www.tangram.co.uk

Plastics Topics – Bioabsorbable plastics

Contents:

Plastics Topics – Bioabsorbable plastics

1. Introduction

Polymers are often seen as ultimate in man-made materials but polymers are simply 'long chain molecules formed by combining many smaller molecules (monomers) in a regular pattern' and like many inventions, nature got there well before man. In fact, many of the basic building blocks of nature can be considered to be polymers, e.g., collagen, the most prevalent protein in mammals, can be considered to be a polymer, amber is actually a thermoplastic resin from trees and the horn from most animals can be formed and moulded to shape just like the synthetic polymers. In fact, the Horners' Company of London (one of the Royal Livery Companies) is first mentioned in 1284 and can be regarded as the first plastics trade association, albeit for the manufacture of products from animal horn.

Polymers and biopolymers have a long history but one of the most exciting areas for new developments in polymers is in bioabsorbable polymers; where polymers can be used to perform vital functions in the body and simply disappear after they have carried out their function. As Arthur C. Clarke wrote in his Laws of Prediction: 'Any sufficiently advanced technology is indistinguishable from magic'. Bioabsorbable polymers are truly magic and are currently providing the driving force for medical advances that have the possibility to change our lives.

2. Getting the words right

As with any new area where two or more areas are being combined there are considerable differences in the language used and this can often lead to confusion. We will try to clarify some of the words before starting to describe the magic of bioabsorbables.

- Bio-based plastic – this is a general term which refers to polymers made from biological materials, e.g., plant or other feedstock instead of the conventional petroleum feedstock.
- Biodegradable – this means that the polymer can be degraded by a biological agent such as an enzyme or microorganism. The source of the raw material, i.e., bio-based or oil based, does not define biodegradability. Bio-based does NOT equal biodegradability. Some biopolymers are not biodegradable, e.g., Polyamide 11 is a biopolymer made from vegetable oil but it is not biodegradable. Equally some conventional polymers can be made to be degradable, e.g., PE can be compounded to degrade under UV light, but this is not strictly biodegradation as there is no biological agent present in the initial degradation. Even stating that a polymer is biodegradable does not guarantee that it will break down under all conditions and many nominally biodegradable plastics will only fully biodegrade under very hot conditions.
- Bioresorbable – this is when the polymer degrades in the physiological environment and the by-products are disposed of by standard metabolic pathways.
- Bioabsorbable – this is when the polymer degrades in the physiological environment and the by-products are excreted through one of the organ systems. A bioabsorbable material may be degraded and lose weight by either the action of enzymes and other microorganisms (in which case it is biodegradable) or by simple non-enzyme hydrolysis (in which case it is not strictly biodegradable as no biological agent is involved). Bio-based plastic does NOT equal bioabsorbable and biodegradable does NOT equal bioabsorbable (although there are many cases where they are the same thing). Bioabsorbable is sometimes used to generally describe 'polymers that break down in the physiological environment' and this broader definition can then include bioresorbable polymers as well.
- Biocompatible – this means that the material does not produce a harmful immunological response in the host tissues or body as a whole. A material is biocompatible if the body undergoes the normal recovery process after implantation (inflammation, tissue formation and healing) with no side effects caused by impurities such as unreacted monomers or processing aids.

3. The mechanism of bioabsorption

The primary mechanism for bioabsorption is hydrolysis and bioabsorbable polymers generally have linkages in the main backbone chain that are unstable in the presence of water. Water in the body can then break the main backbone into progressively smaller units through chain scission at these unstable linkages. Bioabsorption generally takes place in two stages:

- Chain scission to cause a loss in molecular weight of the polymer. Water attacks the weak linkages to convert the long backbone chain into smaller water-soluble fragments
- Erosion of the small chain segments to cause a loss of mass of the implant as the small fragments are broken down into products that can be removed naturally by the body through natural pathways.

The location of the bioabsorption mechanism depends on the relative rates of water penetration and material erosion. The chain scission and loss of mass will be at the surface of the material if the rate of erosion is faster than the rate of water penetration into the bulk material or in the bulk of the polymer if the rate of erosion is slower than the rate of water penetration into the bulk polymer.

The final products of bioabsorption after metabolization are generally CO_2 and water which are naturally removed by the body.

4. Factors affecting bioabsorption

Bioabsorption is a complex process that is affected by both the basic structure of the polymer and the implant itself. The main factors are:

Crystallinity

In another Plastics Topic we discuss crystallinity in polymers and the significant effect this has on mechanical properties. It will therefore come as no surprise to learn that bioabsorption is also strongly dependent on the crystallinity. Crystallinity in polymers is short-range order and higher crystallinity means that it is more difficult for water to be absorbed and therefore bioabsorption is slower for highly crystalline materials than for amorphous materials.

An additional concern with crystalline polymers is that the degradation process can release small crystalline particles into the body before the polymer is completely broken down. In some circumstances this can cause later biocompatibility reactions. Amorphous polymers obviously degrade with no crystalline particle remnants.

Hydrophobic/hydrophilic

Polymers can also be grouped according to their affinity for water molecules. Some polymers are hydrophobic, i.e., they do not absorb water and others are hydrophilic, i.e., they absorb water. As the primary mechanism of bioabsorption depends on chain scission in the presence of water it is obvious that hydrophilic polymers will be more rapidly bioabsorbed than hydrophobic polymers.

Polymer structure

Bioabsorption rates can be modified by changing the basic structure of the polymer during production to change the molecular weight, the molecular weight distribution, the location and number of hydrophilic groups and, in the case of copolymers, the distribution and amount of the various copolymer constituents.

Surface roughness

The crystallinity, hydrophilicity and structure are functions of the base polymer but bioabsorption is also affected by the product itself, i.e., the surface roughness of the product. A rough surface means:

- Better tissue growth on the surface (more attachment points).
- More surface area to be attacked by the degradation mechanism.

The convention in the production of polymer products is to aim for a smooth surface but for bioabsorbable products this is reversed. A rough surface gives faster bioabsorption than a smooth surface.

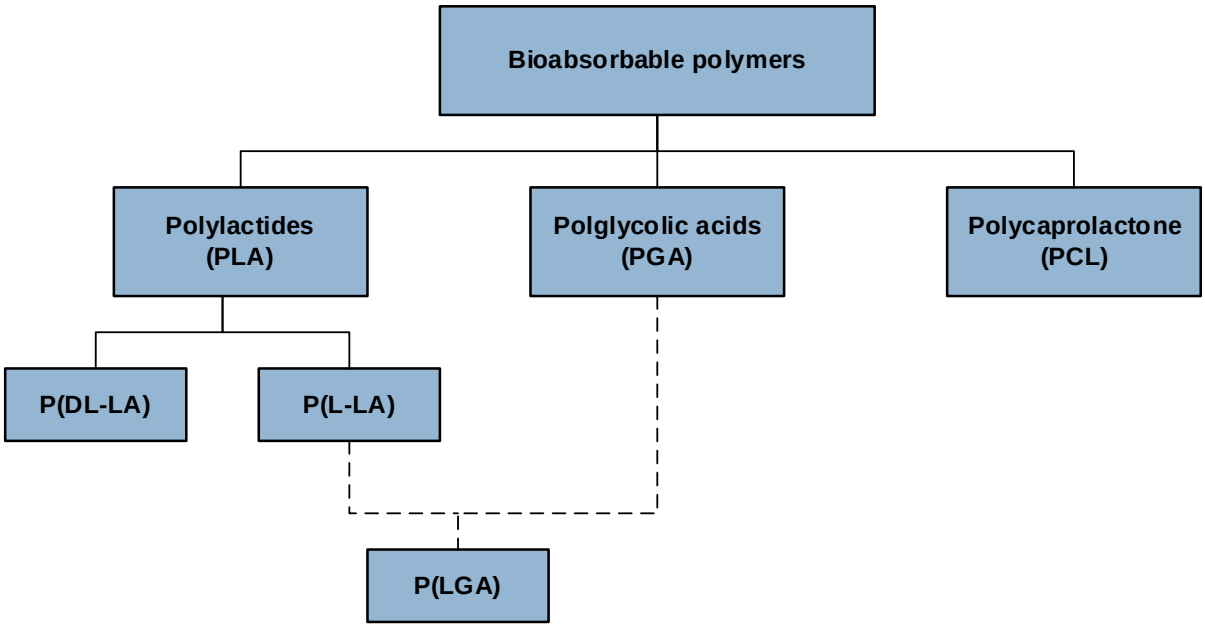
5. Types of bioabsorbable polymers

Bioabsorbable polymers must be:

- Biocompatible with the host and leave no trace after being bioabsorbed.

- Sterilizable by methods that are compatible with implantation and which do not initiate the bioabsorption process, i.e., heat sterilization can start degradation, EtO can leave residues and radiation can damage the polymer structure in some cases (see the Plastics Topic on the sterilization of plastics). As with any medical device, the sterilization method to be used needs to be defined at an early stage.
- Have adequate mechanical and physical properties for the application and remain strong enough to support the loads until the tissue or bone has healed.
- Be capable of being processed into the desired product.

The main families of bioabsorbable polymers currently used are the lactide polymers, the glycolide polymers as well as copolymers based on the basic polymers.



The main bioabsorbable polymers

Polylactides – PLA

Lactide exists in three distinct stereoisomeric forms, L-lactide (Levo-lactide), D-lactide (Dexo-lactide) and Meso-lactide that can be used to produce polymers.

Poly (L-lactide) – P(L-LA)

P(L-LA) was first made in the 1890's but is only now being developed for substantial numbers of applications. It is a semi-crystalline polymer (37% crystallinity) which has a high tensile strength and a high modulus. The melting point is approximately 170-178˚C and the glass transition temperature is in the range 50-80˚C.

The good mechanical properties make P(L-LA) suitable for load-bearing applications such as orthopaedic fixation and sutures but the highly crystalline nature means that bioabsorption times are long and that crystalline remnants can be a potential concern.

Poly (D-lactide) – P(D-LA)

P(D-LA) is the dexo isomeric form of the polylactides and has a much faster bioabsorption rate than the P(L-LA) form.

Poly (DL-lactide) – P(DL-LA)

P(DL-LA) is a random copolymer of an equimolar mixture of L- and D-lactides. This random polymerization produces an amorphous polymer with lower tensile strength and lower modulus than the crystalline P(L-LA). The melting point is approximately 140-150˚C and the glass transition temperature is between 45-60˚C.

The amorphous nature of P(DL-LA) makes it highly suitable for applications needing very short bioabsorption times such as drug delivery systems.

Polyglycolic acid – PGA

PGA is a semi-crystalline polymer (45-55% crystallinity) which has a high tensile strength and a high modulus. The melting point is approximately 225-230˚C and the glass transition temperature is in the range 35-40˚C. Despite the high crystallinity, PGA has very short bioabsorption times which may present concerns with removal of the products of bioabsorption.

Polycaprolactone – PCL

PCL is a semi-crystalline polymer which has a low tensile strength and is ductile under loads. The melting point s approximately 50-65˚C and the glass transition temperature is in the range -65 to -55˚C. PCL has a slower bioabsorption rate than P(L-LA).

Copolymers and blends

As with most polymers, bioabsorbable polymers can be copolymerized to modify and improve the properties. P(DL-LA) is the most common copolymer but it is also possible to produce:

- Copolymers of PLA and PGA.
- Copolymers of PGA and caprolactone.
- Copolymers of PGA and trimethylene carbonate (TMC).
- Copolymers of PCL and PLA.

The production of copolymers allows the mechanical and bioabsorption properties to be tailored to the application demands.

It is also possible to blend (mechanically mix as opposed to copolymerize) the basic bioabsorbable polymers to produce even more options, i.e., it is possible to blend P(D-LA) and P(L-LA) polymers in ratios of up to 1:1 to produce a very highly crystalline polymer that has an even slower bioabsorption rate than P(L-LA).

6. Advantages of bioabsorbables

- Bioabsorbables are slowly removed from the body to allow gradual load transfer to body structures as the bioabsorbable is removed, e.g., bioabsorbable fracture fixings gradually lose stiffness and encourage the bone to take the load whereas metal plates shield the bone and can cause bone atrophy.
- Bioabsorbable polymers remove themselves from the body and there is no need for additional procedures to remove the implant. This is particularly relevant for children when they are growing rapidly.
- Bioabsorbable polymers present no concerns of undesirable interactions with the body, i.e., no corrosion of metals.
- Bioabsorbable polymers form no harmful debris from wear during use.
- Bioabsorbable polymers can be used to deliver bioactive agents during bioabsorption, i.e., long-term drug release.
- Bioabsorbable polymers are MRI compatible for post-operation diagnosis.
- Bioabsorbable products are cost effective to manufacture and process compared to metal equivalents.

7. Timing the disappearance

The rate of bioabsorbtion depends on several factors and cannot always be given with any certainty. The bioabsorbtion time depends on:

- The surface area of the product (at both the macro and micro levels)

- The overall volume of the product.
- The polymer used and the molecular weight of the polymer.
- The implantation site.

This presents a concern because it is essential to match the mechanical properties and the time to absorption to the specific application. Much of the development work in bioabsorbables is concerned with controlling the rate of bioabsorbtion to produce the best result for the specific application.

Polymer		Time to start of bioabsorption (months)	Time to complete bioabsorption (months)
Lactides	Poly (L-lactide) P(L-LA)	6-12	36-60
	Poly (DL-lactide) P(DL-LA)	1-2	12-16
Glycolides	Poly (glycolide) P(GA)	< 1	6-12
Caprolactones	Polycaprolactone PCL	4 - 6	> 36
Copolymers	P(LGA) Co-polymer of P(L-LA) and PGA	1-2	3-6

Bioabsorption rates for the main bioabsorbable polymers

8. Uses of bioabsorbables

Bioabsorbable materials are ideal for the manufacture of devices and products that are only required to function for a short time and can then be removed from the body by absorption. Applications for bioabsorbables are rapidly increasing as the benefits are being recognized and exploited. Current and future applications include:

- Sutures and films for soft tissue repair – this is probably the most common historical and current use of bioabsorbables.
- Short term or transient implants for fixings and load bearing elements in bone repair, e.g., bone plates, screws, pins and threaded rods.
- Fixings to attach soft tissue to bone, e.g., staples.
- Screws and fixings for ligament or tendon repair.
- Many other applications in trauma surgery.
- Vascular grafts.
- Drug delivery via injectable microspheres, rod or pellets direct to the desired site and in a very controlled manner.
- Manufacture of stents for cardiovascular treatments that not only provide a bioabsorbable stent but also use the stent material to deliver required drugs at the point of use.

- Tissue engineering applications to provide scaffolds for the growth of new tissue.

This list is increasing almost daily as medical professionals recognize the benefits offered by bioabsorbables and as the polymer industry develops the polymers and technologies necessary to process them. The market for bioabsorbables is currently estimated by Frost and Sullivan to be growing at 7.5% per year and this rate is forecast to increase as current development work completes clinical trials and is approved for use.

9. Summary

Bioabsorbables are a new and rapidly growing field of polymer technology where the skills of the polymer technologist are combined with the skills of the surgeon. Plastic was once used as a derogatory term for cheap and nasty – this perception is rapidly changing as plastic parts are used to save lives and to improve the quality of life of large numbers of people. Bioabsorbables are part of the driving force for this changing attitude.