The Biocompatibility, Biological Safety and Clinical Applications of PURASORB® Resorbable Polymers

An Independent Report Compiled for Purac Biomaterials

by

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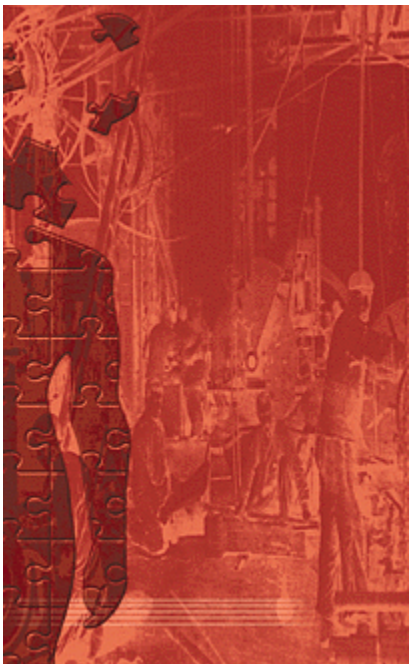


May 2010

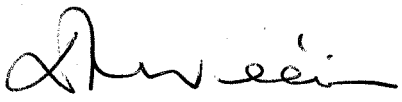
Executive Summary

PURASORB® resorbable polymers are based on platforms of homopolymers and copolymers of lactides, glycolide and ε-caprolactone. They comprise a group of polymers with tunable degradation rates and mechanical properties. They degrade over a period of time ranging from a few weeks to a few years. They degrade by hydrolysis, a process that takes place in water but which may be influenced by the precise nature of the tissue environment, and the products of the degradation are readily metabolized during normal physiological processes. They can be processed by a variety of routes, yielding molded or extruded solid objects such as plates, screws and pins, spun fibers, porous scaffolds or micro- or nano-particles. It is no surprise, therefore, that these materials have found many uses in medical and pharmaceutical technology, with applications including trauma devices in orthopedics, maxillofacial and craniofacial surgery and sports medicine, and sutures and other soft-tissue closure devices. They have been approved for clinical use in many situations. As the benefits of resorbable devices over permanently implantable devices become clearer, they are being considered for use in critical applications such as spinal fusion devices and intravascular stents. They have become prime contenders for scaffolds required for tissue engineering applications, are already used for a variety of drug and vaccine delivery systems and are likely to be used in some form as non-viral vectors for gene therapy.

There is a long track record of compliance with regulatory procedures world-wide, including those of the FDA, with extensive testing performed to ISO and equivalent standards. Great care has to be taken to minimize the possibility of adverse events associated with this process of degradation; experiences to date emphasize the minimal nature of the tissue responses in the vast majority of the applications and the consistently good clinical outcomes that are achieved. There is no evidence of any cytotoxicity, systemic toxicity, genotoxicity, carcinogenicity, reproductive toxicity or hypersensitivity with these materials, nor should any be expected. Both soft and hard tissue responses are among the most acceptable seen with resorbable polymers and no causes for concern about biological safety arise.

This report discusses the properties of the lactide, glycolide and ε-caprolactone based materials, with an emphasis on their biological properties. The evidence from pre-clinical studies and clinical experiences points overwhelmingly to the excellent biocompatibility and biological safety of the PURASORB materials, which have proven track records and which provide, in the vast majority of patients, excellent clinical outcomes.

Professor David Williams, May 2010



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1 General Introduction

Medical devices have been placed within the human body for a variety of reconstructive, therapeutic and cosmetic purposes for many decades. For most of these applications, it has been the intention for the device to remain in the patient's body for a long time, often for the rest of his or her life. That seems eminently sensible if the device is replacing the structure and function of a critical part of the body, for example an articular joint such as the hip, a part of the eye as in an intraocular lens or a valve of the heart. However, there are many other situations, and indeed an increasingly large percentage of these applications, where the function is not intended to last forever. This may occur when the device is providing support during a healing process, or where it is delivering a drug to the body over a defined but limited duration.

The question naturally arises as to whether it is desirable for a device to remain in the body if its function has terminated. Since we know that all devices, and all materials, placed in the body have a propensity to cause some response from the body, and that the severity of that response could increase with duration in the body, it is intuitively obvious that such non-functioning devices should, if at all possible, be removed once the function is complete. That, however, is not always feasible since it would require a further invasive procedure and because it would not necessarily be easy to locate and retrieve the material.

These considerations have naturally lead to the possible option of constructing the device from a material that dissolves, or otherwise disappears through a chemical, or more likely biochemical, process within the body. One of the more obvious types of device here is the suture used for sewing internal tissues together after trauma or surgery, where it would be self-defeating to re-open a wound to take out the suture. Early surgeons used plant or animal tissues to make such sutures in the 19th Century, including cotton, silk and catgut. In view of the overall impact of synthetic polymers in engineering and consumer goods after the middle of the 20th Century, it is not surprising that synthetic versions of these sutures were developed, and clinical application started in the early 1970's.

It is not a trivial matter developing, manufacturing and using clinically an entirely new material, taking into account a relatively good acceptance of these forerunner natural products and the new regulatory environment that was being introduced into medical device technology. It was necessary for these new sutures to have good handling characteristics and be cost effective, as well as producing at least as good clinical outcomes. The response from the patient's tissue was an important consideration. The human body is exquisitively sensitive to the presence of a foreign body, and a material that was actively being degraded by those tissues has a considerable ability to irritate those tissues. It became obvious that it was not sufficient to produce a synthetic polymer that was degradable; it had to degrade with minimal biological consequences to the patient. This was unlikely to happen with synthetic polymers that

degraded in the body leaving degradation products that were themselves toxic or irritant, with adverse effects either or both at the local site of application or systemically. Importantly, it was necessary for the degradation process to yield products that were metabolized within the body, leaving no traces of irritable products. Such materials were then described as resorbable or absorbable.

Since that time, a major industry platform has been established based on the need to provide the medical profession with a range of resorbable materials, and especially resorbable polymers, for an increasing number and diversity of applications. Just because a material is resorbable does not mean that it will always have the desired and most favorable response from the body, and considerable effort has been expended in order to optimize the performance of these resorbable polymers and minimize any possible adverse effects.

From the very beginning of this era of resorbable polymers, one group of materials has stood out as having very attractive properties, these being the polymers based on lactic and glycolic acid. Also, although there have been many industrial companies engaged in the development and supply of these polymers, a small number have reached some positions of eminence. One of these is Purac, a global company with its headquarters in the Netherlands which is the worlds largest producer of natural lactic acid and its derivatives, the lactides and polylactides. Purac Biomaterials, a business unit of Purac, produces a wide range of monomers and polymers within this family for medical and pharmaceutical applications, under the general brand name PURASORB.

Because of the rapidly growing interest in the use of these resorbable materials in wide ranging areas of medical technology, including medical devices, tissue engineering / regenerative medicine and drug / gene delivery, and the need to consolidate the evidence and experience associated with the varying uses in one place, this independent report has been compiled for the purpose of educating and informing the users of these products on the biocompatibility, biological safety and clinical applications of PURASORB resorbable polymers.

2 Resorbable Polymers; Mechanisms and Properties

This section is intended to provide a basic overview of the chemistry of resorbable polymers in general and a discussion of the mechanisms of degradation and resorption, such that the potential applications and the possible physiological consequences of these processes can be understood.

2.1 The Essentials of Polymer Structure

Polymers are macromolecular structures that contain very large numbers of long chain molecules. In the vast majority of polymers, the molecules are based upon the carbon atom.

Many polymers are simply formed by the end-to-end addition of monomer units so that ethylene, C_2H_4, polymerizes to polyethylene, vinyl chloride, C_2H_3 Cl, polymerizes to poly(vinyl chloride) and so on. There are many variations to this theme. Other atoms or groups may replace some of the carbon atoms in the backbone of the chain; for example in the very common medical textile poly(ethylene terephthalate), a benzene ring is inserted into the backbone. A further major variation concerns the arrangement of individual polymer chains. A polymer which exists solely with very long chains is, not surprisingly, called a linear polymer. The length of the chains, which effectively controls the molecular weight, can vary considerably. Some polymers consist of rather short chains with molecular weights of a few thousand Daltons, whilst others can have molecular weights of several million Daltons. If the polymer chains are effectively arranged side by side with a great deal of regularity and symmetry, the polymer will have a crystalline or semi-crystalline structure – solid polymers of this form will usually be opaque. If it is impossible for the rows of molecules to take up a regular form they will be amorphous, and nearly always these polymers are transparent. In many cases individual molecules will become attached or linked to each other, giving a so-called cross-linked structure.

The crystallinity varies with temperature, and here we must introduce the concept of the glass transition temperature. All polymers have temperatures at which they are rigid, brittle and glassy materials. As the temperature rises, there will be a point where the behavior of the polymer changes from glassy to tough behavior, with a drop in stiffness and an increase in toughness. This occurs in the glass transition region and the temperature at the midpoint of the transition is defined as the glass transition temperature, Tg. If a polymer's glass transition temperature is well above ambient room temperature, the material will normally behave like a brittle glassy polymer, but if the Tg is well below room temperature, the material is usually softer and more flexible. Those materials whose Tg is reasonably close to the ambient temperature may exhibit plastic behavior, being strong and tough. In practice, polymers are rarely completely crystalline or amorphous and will exist in partially crystalline states. It is also often the case that properties desirable for given applications cannot be obtained in one polymer, and modifications may be required. It may be that optimal properties can be obtained

by starting with more than one monomer and building up a polymer that has some large molecules based on one monomer and some based on another. Such polymers are referred to as copolymers. This is an extremely important point with respect to PURASORB polymers. The sections based on the different monomers may be microscopically indistinguishable or they may form quite discreet zones. In cases where the different parts are immiscible, and therefore quite separate, the material may be referred to as a polymer blend.

We should also mention here that the final properties may well be refined by using additives that themselves are not polymeric. The fabrication of polymers is often assisted by additives which optimize the processes of extrusion, molding, spinning and so on. These are relevant points since the presence of such additives may well control the tissue response to the polymers, as we will note below. As a final point here, the polymerization process itself (as distinct from the fabrication of articles from the polymer) is usually achieved through the use of catalysts. By definition, these are reactive chemicals that facilitate certain chemical reactions during various steps in the polymerization, so they have the potential to be biologically active in the final product. Equally importantly, and again by definition, they are very likely to be retained in the final product because catalysts are not consumed in chemical reactions; great care has to be taken over the potential role of residual catalysts in the performance of the resulting polymer.

2.2 Polymer Degradation and Resorption

The nature of the individual atoms and groups within the polymer structure, and the manner in which they are arranged within these molecular and crystalline structures, control most of the properties of the resulting material. For example, amorphous polymers and highly cross-linked polymers are usually brittle because their molecular form cannot be easily re-arranged when mechanical forces are applied, and they break rather than deform. Highly crystalline polymers usually have high strength and elasticity.

Of crucial importance to the discussion of degradable and resorbable polymers is the environmental stability of the structures. It is appropriate to carefully define the relevant terms here – many terms used within the field of biomedical polymer degradation and resorption have some widely used generic meanings as well as precise meanings. The basis for this discussion of definitions is the Williams Dictionary of Biomaterials [1]. 'Degradation' is a general term used in materials science that means '*deleterious changes in the chemical structure, physical properties or appearance of a material*'. 'Biodegradation' means '*the breakdown of a material mediated by a biological system'*. These are very general terms and are not sufficiently precise or focused to allow a clear understanding of what is required, or achieved, in intentionally degradable medical devices. Neither term mentions at all the nature of any degradation products ('*products of a material, either particulate or molecular, that are generated by degradation of that material*') or their fate, either within the body, or associated with their elimination from the body. The

intention of the polymers that are the subject of this report is that they are fully and harmlessly eliminated from the body as the end-stage of the degradation process. Historically, such polymers were initially described as absorbable polymers but, as discussed by Vert [2], this term is not entirely appropriate since 'absorb' is a simple verb that describes the process of taking in or assimilating a substance. Common usage has determined that 'absorbable' and 'bioabsorbable' are still used in this area, and the latter term has come to be associated with the phenomenon of being '*capable of being degraded or dissolved or subsequently metabolized within an organism'*. The terms 'resorbable' and 'bioresorbable' are more appropriate although there is no clear consensus of the distinction between them. I prefer the noun 'bioresorption' and its adjective 'bioresorbable', the former being defined as '*the process of removal by cellular activity and /or dissolution of a material in a biological system*'. When the term 'resorbable polymer' is used in the context of medical applications, it, de facto, becomes synonymous with 'bioresorbable polymer', which for the purpose of this report can be taken to mean *' a polymer which is capable of removal by cellular activity and / or dissolution in a biological system such as the human body'*.

A polymer which is designed to degrade in an aqueous environment such as the human body must have linkages between atoms and between molecules that can be broken in that environment. The simple polymers with all-carbon backbones are usually stable because the carbon-carbon bond is very strong and not easily broken by thermal or chemical energy; no biodegradable polymer exists that has such a structure. On the other hand there are several bonds which are quite readily broken by such energies. In polymers, wherever carboxyl groups are found there will be susceptibility to degradation, as there will in polymers based on ester and amide structures. Inherently biodegradable polymers will usually contain one or more of these structures.

Polymers in general are susceptible to degradation through the effects of heat, light and ionizing radiations and in certain chemical environments. Within the human body, we are not concerned with excesses of heat or exposure to light or radiation, but implanted biomaterials will be constantly bathed in tissue fluids. Their biodegradation is therefore largely dependent on interactions with these fluids and the ions and molecules they contain. Water is the main constituent of these fluids, and hydrolysis, which is the breakdown of any substance caused by interaction with water, is the main mechanism by which degradable polymers break down in the body. As a general rule, hydrolysis of organic substances takes place minimally under neutral conditions, that is when the pH of the environment is around 7.0, but proceeds much faster under acidic (low pH) or alkaline (high pH) conditions, a fact which becomes very important in the design of biodegradable biomedical polymers.

In order for the water of tissue fluids to cause the molecules of a polymer to degrade, it has to gain access to the susceptible bonds. Within any one type of polymer system, much will depend on the ability of the water to diffuse into the polymer. For a polymer that is very resistant to

water absorption, there will be limited opportunity for hydrolysis to take place and it may well be that the degradation process is confined to the surface. In other words, the polymer degrades slowly by a process of continual erosion of the surface, the polymer essentially degrading from the outside towards the centre. For polymers that readily allow the take up of water, we would expect the degradation process to be more uniform and faster. This characteristic of absorbing water is controlled by the structure and chemical form of the molecules themselves and the molecular arrangement. The degree of crystallinity is one important factor, as is the overall hydrophilic / hydrophobic nature of the material. Some polymers such as PTFE, poly(tetrafluoroethylene) are extremely hydrophobic, giving the non-stick quality to domestic products made of Teflon®, and do not absorb water at all. It is interesting to note that this polymer has many applications in long term implantable devices because it is so biologically inert through the combination of this hydrophobicity and the presence within the molecular structure of only high strength carbon-carbon and carbon-fluorine bonds. The better biodegradable materials are those which are both hydrophilic and contain hydrolysable bonds.

It is also necessary to take into account the nature of end groups of the polymer chains. The repeating units in the polymer backbone control overall properties, but each molecule have ends that will usually be of a different structure to these repeating units, and these will play some role in the initiation of the degradation. Manipulation of polymer end group chemistry is one way that biodegradable polymers can be fine-tuned with respect to degradation rates. In addition, since all medical devices have to be sterilized, the effect of the sterilization process (often γ irradiation or electron beam) on the polymer has to be taken into account. Such processes often cause up to 50% drop in molecular weight of the polymer, with a consequent effect on the degradation rate.

Of course the tissue fluids of the body are not constituted solely by water; there are many ions and molecules, both large and small, within the fluids. There are also many types of cell, which can be highly active structures. Many of these entities can contribute to polymer degradation processes, and it is important to note that the constitution and activity of this tissue environment are changeable, both with time and from one location to another. For example, inflammation is the response of the body to injury or irritation, which is mediated by a series of cells and molecules that are present in the tissue fluids. At its simplest, we can consider inflammation as a defensive process where cellular and humoral components combine synergistically to remove the cause of the irritation.

The significance of the existence of these complex inflammatory and immune responses is that the tissues of the body may well contain, at any one place and at any one time, a myriad of very active and aggressive molecules and cells. It is usual for the placement of a biomaterial in tissues to be accompanied by an inflammatory response. We should therefore expect that these

active species to be present at the site of a biodegradable polymer where they may assist the hydrolysis process, or introduce another mechanism of degradation such as oxidation.

We therefore have an immensely interesting situation where the implantation of a degradable polymer into the body may stimulate an inflammatory reaction and where that inflammatory reaction may influence the way in which the polymer degrades. Polymer degradation within the body may therefore be autocatalytic, which makes the understanding of the degradation process difficult and adds considerable uncertainty to the prediction of in vivo performance and, in consequence, the design of biodegradable, bioresorbable, biomedical polymers.

To add to this complexity, there are some additional factors that influence polymer degradation mechanisms and their kinetics. First, there are some molecular species other than the products of cell activation which may accelerate the degradation process, principal amongst these being metal ions such as iron and cobalt. Secondly, the degradation process is likely to be influenced by the mechanical stresses applied to the polymer. Stress will influence the molecular conformation, and the stretching of bonds within and between molecular chains may increase susceptibility to environmental attack. This may happen with applied stress, for example associated with tying the knot of a suture, or with residual stress following a manufacturing process.

Summarizing this section, we may see that at least five steps are involved in the full resorption of a polymer from the human body.

- Hydration – the absorption into the polymer of water from the surrounding tissue, either directly into the bulk of the polymer or slowly through surface dominated processes.
- Cleavage of the polymer backbone.
- Fragmentation and loss of mass of the polymer.
- Solubilization of the products of degradation.
- Metabolism of the products of solubilization.

2.3 Biocompatibility and the Mechanisms of the Tissue Response to Implanted Polymers

It is necessary to expand this general introduction on inflammation to lay the foundation for the discussion about the details of the tissue response to biomaterials. This is part of the subject that we refer to as 'biocompatibility'. For many years, this term had been defined as '*the ability of a material to perform with an appropriate response in a specific situation'* [3]. This has been

updated recently to a more comprehensive statement '*Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy* [4].

There are several important messages within these definitions. First, the performance of a function by the biomaterial is an important part of biocompatibility; when discussing the biocompatibility of PURASORB materials, it is necessary to take into account what function any one of the materials is actually performing, be that as a surgical suture or a drug delivery depot. Secondly, the material shall do no harm to the patient, either locally or systemically when carrying out that function. This is a very important issue with biodegradable materials since it is imperative that the products of the degradation do not cause harm, at any time and at any place in the body. Thirdly, biocompatibility is concerned with generating the desired, beneficial tissue response. Again this is vital to the resorbable polymer since it should, inherently and initially, elicit the most desirable response at the site of implantation but also it should continue to elicit the desirable response whilst it is undergoing degradation and resorption, right up to the point that every last residue has been eliminated from the body. Finally, these definitions refer to the host response in a specific situation. It is vital to appreciate that different tissues respond to biomaterials in different ways and exactly the same material may induce quite different responses in different situations. It follows from this that no material has universally good biocompatibility, and just because a biomaterial performs well in one situation does not mean in will do well in another. On many occasions we see a material being described as 'biocompatible'. This is an erroneous concept and no material can be described as biocompatible.

So what does happen when a biomaterial is placed within the human body, starting with the situation where it is soft tissue such as muscle that is the site of insertion? If the material in question is the resorbable suture used to close a wound, the overall response will depend on the nature of the wound being closed; there will be some degree of injury and the response to this will be inflammation, which, in the absence of infection or other confounding conditions, will lead to a repair process. A simple incision through the skin will elicit the clotting of blood that exudes from the microvasculature, followed by a mild inflammatory response, which is why it gets red and swollen, and then the repair. Fibroblast cells are attracted to the site where they produce new collagen fibers which close the wound through the formation of scar tissue.

If we now place a biomaterial within the incision / injection site, it may interfere both mechanically and biologically with these processes. In the simplest case, there are minimal effects and the early, or acute, inflammatory and healing processes follow normal patterns and the end result is the formation of a thin zone of scar tissue around the material, this often being referred to as a fibrous capsule, and the phenomenon as 'the foreign body response'.

If the biomaterial is initially significantly irritating, then the acute inflammatory response will be more severe and more prolonged, and the fibrous capsule may eventually be thicker. It may be that the inflammation is never fully resolved and it remains as a chronic inflammation. Severe cases of chronic inflammation, including those that involve extensive inflammatory tissue known as a granuloma, are rarely helpful to the patient [5-7].

It is fairly straightforward to design biomaterials which are not inherently pro-inflammatory in this way. Greater difficulties are found where an initially non-inflammatory material becomes pro-inflammatory at a later stage. This can happen when some inflammatory components are released from the material over time. These components could be wear particles released from a joint replacement prosthesis, or polymer additives that are slowly leached out of the material. Of greater relevance here are the products of the degradation of the material, which could be the corrosion of a metal or the degradation of a polymer. It is quite possible for the early tissue response to a degradable polymer to be quite unremarkable, but for the inflammatory response to be re-stimulated as the products of degradation are released. These products could be the monomers or very low molecular weight ingredients from which the polymer was synthesized and which are re-constituted during the degradation process. Alternatively, they could be particles that are released during the fragmentation process that accompanies the degradation. If the returning chronic inflammation is profound then it can be very detrimental, causing swelling and pain; it should be borne in mind that a fragmenting or degrading device may not be easy to remove should the tissue reaction be such as to cause clinical problems. It is also important to note that many polymers have extremely low toxicity but their precursors and/or ultimate degradation products may have powerful toxic effect

Many implantable devices are used in the context of injuries and diseases of bones, involving either the long bones of the skeleton, the articular joints, the bones of the head (in the so-called craniofacial or maxillofacial areas), the bones of the extremities (hands and feet) and the spinal column. Very often devices are used to assist in the stabilization and repair of these bones or to assist in the regeneration of diseased or removed bone. The response of bone tissue is therefore very important. Luckily bone is one of the few tissues that does have the capacity to regenerate and remodel; the main requirement of any device here is to hold the segments of bone steady whist the repair process takes place, which under normal circumstances will be between 8 and 10 weeks. The bone healing process involves its own type of inflammatory response followed by the regeneration of a new collagen matrix which becomes mineralized. This process of new bone formation is regulated by the bone cells called osteoblasts. Also present in bone are the osteoclasts. In normal healthy bone there is a constant turnover of bone, caused by the continual resorption of bone by the osteoclasts and formation of new bone by osteoblasts. When biomaterials are used in the context of assisting bone healing it is very important that the material does not interfere with these normal processes, which work by themselves very well [8,9].

In the context of blood, we have to consider how foreign materials may interact with some critical mechanisms of the coagulation process. Blood is a complex composition of active molecules and cells in water and it obviously has a number of functions, including the transport of oxygen and nutrients, the transport of cells and molecules of the inflammatory and immune systems, and the defense of the body after injury through the clotting process. When we use biomaterials in direct contact with blood it is essential that they do not interfere with these processes. Of particular importance is the fact that most foreign materials are able to initiate the clotting process [10,11], which can be a highly unfortunate experience if it causes a local blockage (a thrombosis) or if the clot is released into the circulation where it, now referred to as an embolus, can cause blockage elsewhere, for example in a blood vessel in the brain. If degradable polymers are used in any blood-contacting situation, the manner in which its degradation products interact with blood components has to be seriously considered.

If an implanted material is placed in one discreet position, it is normally the local host response that is seen to be critical to the overall biocompatibility. If, however, either that material releases components (degradation or wear products, for example) into the tissues, or if the material is itself composed on fine particles, then the systemic distribution becomes an important issue. Small particles may be taken up in the lymphatic system [12] or within the circulating blood. In the former case, the particles are likely to be deposited in lymph nodes, often without any significant harm. Small particles or large molecules circulating in the blood, however, may represent a quite different risk as they may be deposited at distant sites, for example in the liver or spleen. The brain is well protected from circulating entities because it is protected by the blood brain barrier, but certain types of substance, especially very small nanoparticles, may be able to pass this barrier and have direct access to the brain [13]. Again, these become very important considerations with degrading polymers. In many of these situations it is easy to see why the degradation products should be resorbable, with the shortest possible residence time in the body before complete resorption has taken place.

2.4 The Selection of Resorbable Polymers

We now piece together the above background information on biomedical polymers and the degradation / biocompatibility phenomena in order to set out the rationale for the selection of resorbable materials for clinical use. One point to make here, and then put on one side, is that is not inevitable that resorbable biomedical materials have to be polymers. There is now extensive use of resorbable calcium phosphate ceramics in medicine, these having variable degradation rates, with ultimate degradation products based on the calcium and phosphate ions which are readily assimilated into the tissues through metabolic routes [14]. There is also strong interest in some quarters in using corrodible metals based upon essential, and therefore potentially assimilated, metals such as magnesium [15]. The vast majority of applications, however, are concerned with polymeric structures.

The essential requirements for a resorbable biomedical polymer can be summarized as follows: the polymer should have -

- appropriate mechanical and physical properties suitable for the desired function,
- a molecular structure that is capable of hydrolysis at pH 7.4 with the desired kinetics,
- a hydrophilicity that allows for the required degree and kinetics of water absorption,
- a degradation process that results in the predictable formation of degradation products
- a chemical composition that reliably results in degradation products that are readily assimilated and/or metabolized within the body without any significant pro-inflammatory or cytotoxic characteristics
- a structure and form that can be conveniently fabricated without the need for any processing additives that would compromise the biocompatibility of the polymer as it degraded.

It should not be surprising that, given the history of surgical sutures, where synthetic polymers eventually superseded the materials derived from plant or animal tissues, the polymeric materials that are able to satisfy the above requirements could be grouped as either naturally derived or synthetic. This is not an entirely accurate division since some polymers that are based on structures found in nature may actually be prepared by synthetic routes, including recombinant technology, but it useful for present purposes. This document is not concerned with the former group, usually known as biopolymers, but it is important to recognize their existence, primarily because one trend in biomedical polymer design involves the development of blends between biopolymers and synthetic polymers. Within this group of biopolymers we find proteins and peptides, such as collagen, elastin, keratin and silk, polysaccharides such as chitosan, alginate and hyaluronan, and lipids [16-19].

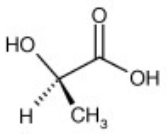
Over the last few decades, several groups of biodegradable / resorbable polymers have been developed or adapted for medical use. There is no straightforward way of classifying these and it is better to consider each group as a separate entity, although there will be some similarities between many of the groups. First and foremost of these groups are the polymers based on lactic acid and glycolic acid, and it is these which this document is mainly concerned. The second type is based on polycaprolactone, and these are also discussed here. In no particular order, the other clinically used or experimental degradable biomedical polymers are the polyanhydrides [20], polydioxanone [21], polyorthoesters [22], polyglycerols [23], sebacate polymers [24], fumarate polymers [25], cyanoacrylate polymers [26], degradable polyurethanes [27] and the polyhydroxyalkanoates [28]. Several good reviews of biodegradable polymers may be found in the recent literature [29-31].

3 PURASORB Resorbable Polymers and their Characteristics

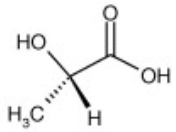
This report is specifically concerned with the PURASORB series of resorbable polymers, but will also draw on the general literature and knowledge about polylactides, polyglycolide and polycaprolactone based polymers. The product line consists of a series of lactide, glycolide and caprolactone monomers and a series of polymers and co-polymers based on these monomers.

3.1 The monomers

The best place to start the discussion is with lactic acid, otherwise known as 2-hydroxy propanoic acid. This is a simple hydroxy acid, and has an asymmetric carbon atom. Of special interest is the fact that this molecule can exist in two different forms based on this symmetry, known as isomers. These have identical molecular formulae but different arrangements of atoms within the molecules. There are several different forms of isomerism. The isomerism that occurs with lactic acid is called stereo-isomerism, which means that there are two different forms that are mirror images of each other. Molecules of this form are said to be chiral and the two different forms are called enantiomers. The two different enantiomers of lactic acid are L-lactic acid and D-lactic acid, as shown below.



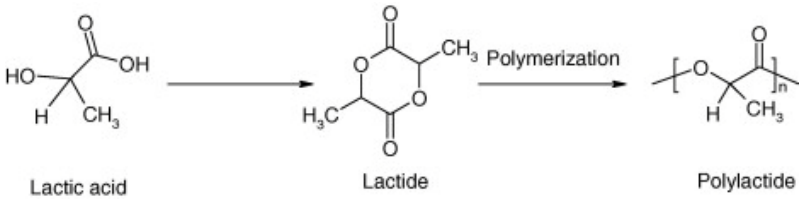
L - Lactic acid



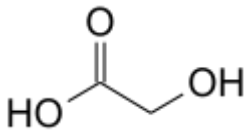
D - Lactic acid

These are optical isomers which can rotate the plane of polarization of plane-polarized light. One enantiomer rotates the polarized light clockwise and is the L (+) enantiomer; the other rotates it anticlockwise and is the D (-) enantiomer. Lactic acid can be polymerized to poly(lactic acid). Generally the term poly(lactic acid) is used when the polymer is produced by direct polymerization. It is more common to produce the polymer via the formation of lactide, followed by ring opening polymerization, in which case it is usually referred to as polylactide. Lactic acid itself has some trouble taking part in chemical reactions because the hydroxyl group

(-OH) is so close to the carboxylic group (-COOH). It may however, form a dimer by the combination of two molecules, which forms a cyclic compound, which is called lactide;

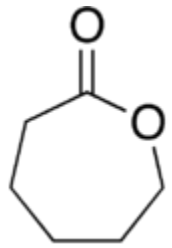


Glycolic acid is a even simpler hydroxyl acid.



It does not exist in isomeric forms and so the chemistry is simpler. As with the lactic acid polymers, we have the same terminology issues, with either poly(glycolic acid) or polyglycolide.

Caprolactone is a cyclic ester, $C_6H_{10}O_2$, with the structure:



There are different forms depending on the position of the oxygen atom in the ring, and these are described by Greek letters. The most widely encountered form, and that used for the synthesis of biodegradable polymers is epsilon caprolactone (ε-caprolactone).

It is not necessary to discuss the polymerization processes in any detail here. Several good reviews of these processes have been published, including that of Albertsson and Varma [32].

As noted above, there are different methods of polymerization of the lactic acid. One is the direct polycondensation route in which lactic acid in aqueous solution is converted directly into

poly(lactic acid), in the presence of a catalyst, through the elimination of water. The resulting polymers tend to have low molecular weight and low mechanical properties. They may be used for consumer goods but not, in general, for high performance applications.

The more popular method, and the one used for the production of the PURASORB polymers, is that of ring opening polymerization. This involves the generation of the cyclic dimers and then the opening of the rings and their subsequent attachment to each other, under high temperature and low pressure in the presence of a suitable catalyst. These methods produce high molecular weights, a high conversion rate (or yield) and very attractive properties. The choice of catalyst is very important and many are available. For many years metal-based catalysts were preferred, including those based on iron, tin and zinc. Developments in catalyst systems, especially with organocatalysts have become significant, including guanidines and amidines. Different catalysts and different variations of the ring opening polymerization mechanism give rise to different characteristics of the resulting polymer chain and the material properties. Among the more significant features are the molecular lengths and the nature of the groups that terminate the molecules. These end groups can include those of carboxylate, alkoxide, hydroxyalkyl or acidic nature. As noted before, the nature of the end groups can have a significant effect on the degradation rate.

3.2 The Polymers

A wide range of polymers and co-polymers based on the combinations of the different lactides glycolides and ε-caprolactone have been developed over the last fifty years. We are concerned here primarily with the poly(L-lactide)s, poly(D-lactide)s, poly(DL-lactide)s, polyglycolides, L-lactide/DL-lactide copolymers, DL-lactide/glycolide copolymers, L-lactide/ε-caprolactone copolymers, D-lactide/ε-caprolactone copolymers, DL-lactide/ε-caprolactone copolymers and glycolide/ε-caprolactone copolymers. The variations within these come from the different ratios of L and D forms of lactic acid and the different ratios of lactic acid, glycolic acid and ε-caprolactone in the copolymers. These groupings of polymers may be referred to as polylactides, polyglycolide and polycaprolactone platforms.

As earlier, it is convenient to start the discussion with the polylactide platform. We shall refer to these by the PLA shorthand, with PLLA, PDLA being used for the homopolymers of the L and D forms respectively and PDLLA for polymers of mixed enantiomers. Enantiomerically pure PLA are semi-crystalline polymers, that is they contain crystalline and amorphous regions. PLLA is generally about 40% crystalline, the glass transition temperature is around 55-60^{o}C and the melting temperature around 180^{o}C. Racemic PDLLA, that is containing equal amounts of L and D forms, is a completely amorphous polymer. Because of this, PLLA tends to have higher tensile strength. However, the mechanical properties of both PLLA and PDLLA can be varied quite considerably by modifying the molecular weight and crystallinity, for example by annealing. Tensile strengths in the range 20-70 MPa can be achieved. The tensile modulus of the semi-

crystalline PLA is in the region of 3GPa. Elongations are usually below 10%, which implies that PLA is rather brittle. PLA is also hydrophobic, with a contact angle of around 80°. This does inhibit cell attachment and activity at the surface, which may be a disadvantage in some applications.

With respect to co-polymers, there are several options. We may start with the co-polymers derived from the two enantiomers of the lactides, with compositions usually in the range 70/30 L-lactide/DL –lactide to 80/20 L-lactide/DL–lactide. Copolymers of lactide/glycolide range from 10/90 L-lactide/glycolide to 85/15 L-lactide/glycolide, and from 50/50 DL-lactide/glycolide to 75/25 DL-lactide/glycolide. Copolymers with caprolactone are typically in the ratio of 70/30 L-lactide/caprolactone. Other compositions are possible, including 95/5 and 85/15, these intermediate ratios giving intermediate properties. The lactides/glycolide copolymers have tensile strengths in the range 40 – 70 MPa, with elongations usually below 6%. Tensile moduli are in the same range as the homopolymers, between 3 and 3.8 GPa. The lactides/caprolactone copolymers have much lower moduli, in the region of 0.03 GPa, and lower tensile strengths of 20 MPa, but elongations over 100%.

PLA degrades through the hydrolysis of backbone ester groups and the degradation rate depends on the degree of crystallinity, the molecular weight and its distribution, morphology, water diffusion rate into the polymer, and the stereoisomeric content [33]. The amorphous parts of the polymer have a higher rate of water uptake and a higher rate of hydrolysis than the crystalline regions. The amorphous racemic PLA therefore degrades faster than PLLA. The degradation rates are rather slow and could lead to long residence times in the body, up to many years in some situations [34]. One of the interesting points about PLA degradation is that the process is essentially random in terms of which ester groups are hydrolyzed at any one time, which means that the material suffers a gradual reduction in molecular weight over a long period of time, but without any appreciable mass loss for most of the time. However, with solid masses of polymer, it may be noticed that the inside degrades faster as the later stages of the process leads to a buildup of compounds containing carboxylic end groups. These cannot easily diffuse to the surface and contribute to an autocatalytic reaction through acid-catalyzed chain-end scission in the centre [35].

Polyglycolide or polyglycolic acid (PGA) is the analogous polymer to PLA, and is the simplest of all aliphatic polyesters. It has a lower Tg but a higher melting temperature and has a crystallinity in the region of 45-55% depending on molecular weight. This gives the polymer good mechanical properties. The polymer degrades by random chain scission of the ester backbone and will lose strength over a few months and lose all mass within a year. Because of its initial strength and fast rate of degradation, couple with very good fiber forming ability it has been used in surgical sutures; indeed the first FDA approved synthetic surgical sutures were made from PGA.

Poly(lactic-co-glycolic acid), PLGA, is probably the best known biodegradable platform, with widespread commercial uses. These polymers are usually prepared by the random co-ring opening polymerization of lactide (either L or DL forms) and glycolide dimers, again using a variety of possible catalysts. The result is a copolymer with ester linkages between lactic and glycolic acid units. Most often it is the racemic DL mixture of PLA that is used, and the ratios of lactide to glycolide may vary from 10/90, 50/50, 70/30, 75-25 and up to 85/15. The variety of properties that are obtainable with PLGA gives this platform a strong position in the field of resorbable medical polymers; this is not surprising since they should be able to combine the better characteristics of the individual homopolymers, giving blends of strength and degradability suitable for many situations. In general, the 50/50 copolymers degrade over a couple of months, with the 75/25 doing so in 4-5 months and 85/15 in 5-6 months. Again the degradation is produced by bulk hydrolytic attack on the ester backbones.

Polycaprolactone is also a semi-crystalline polymer that can be synthesized by ring opening polymerization. It has a very low Tg, at -60^{o}C, which gives it a low tensile strength of around 20 MPa and an elongation in excess of 600%. The degradation mechanism is the same but is slow, typically taking more than a few years for complete mass loss to occur. For this reason, caprolactone is often co-polymerized for use in medical devices. The caprolactone platform here is typified by a poly(L-lactide/caprolactone) at a ratio of 70/30. These polymers have faster degradation times and also much better mechanical properties.

4 Existing and Potential Clinical Applications of Resorbable Polymers

In this Chapter, the rationale for using resorbable polymers in various clinical applications will be discussed, covering a variety of clinical areas and ranging from the established applications to those which are recent and still under exploration and investigation.

4.1 Wound Closure

We start with a discussion of sutures and staples in wound closure, but this will be dealt with briefly since these applications are now well known. In wound closure there are situations in which either non-absorbable sutures, absorbable sutures, clips, staples, ligatures and other devices are used to hold tissues together during healing, either after soft tissue trauma or invasive operative procedures. In addition, there are procedures where implants and prostheses have to be attached to the relevant tissues of the body. The decision of which closure or attachment material or device to use is based on many factors that are associated with the required mechanical and handling characteristics as well as the length of time the material has to remain functional. There are clearly some situations where permanence is required, as in suturing a prosthetic valve to the heart, but in many other situations it is desirable for the material to be removed once healing is complete.

For very many years the materials of choice for absorbable surgical sutures were the various forms of catgut, a proteinaceous material derived from animal's intestines, usually bovine. The material could be treated in a number of ways to control strength and resorption rate, and it had good handling characteristics. Synthetic materials were introduced in the 1970s and gradually superseded the catgut. There were some concerns over the safety of catgut following the emergence of prion diseases such as bovine spongiform encephalopathy, and there were also issues of reproducibility with the naturally derived material. The synthetic polymers had no such disease transmission risks and were also far more reproducible in their properties. Although some surgeons maintained their preference for the handling of catgut, and issues of cost did affect the introduction of the synthetics into markets in some parts of the world, as the better qualities of the new materials became clear, the use of catgut significantly declined [36].

The polyglycolide and polylactide materials were rather obvious choices for these sutures, and indeed their early commercial development was directed at this market [37]. Dexon™ was the first commercial product, being made from PGA homopolymers. It was a little stiff and not amenable to monofilament form, and so was made available as a multifilament, losing strength over around 3 weeks and total mass loss by 120 days. Variations on the original material have been introduced over the years, including a form that has the PGA coated with a glycolide-ε-caprolactone copolymer. Vicryl™ was introduced soon after, being a 90% glycolide-10%lactide copolymer, sometimes referred to as Polyglactin 910. Also used in multifilament form, this degrades slightly quicker, losing mass between 60 and 90 days. A faster degrading form, Vicryl Rapide™, produced by irradiating the copolymer is available, as is a form which is coated with an

antibacterial layer. PDS™ is a monofilament absorbable suture made from polydioxanone; this is one of the more long lasting sutures, losing mass over 120 days. Maxon™ is a made from a co-polymer of glycolide and trimethylene carbonate (referred to as polyglyconate); it is a monofilament, loses 75% strength over 4 weeks and total mass loss by 180 days. Biosyn™ is a terpolymer of 60% glycolide, 14% dioxanone and 26% trimethylene carbonate; the degradation is faster and total mass loss is seen around 100 days. Caprosyn™ is a copolymer of lactides, glycolide, caprolactone and trimethylene carbonate and degrades even faster, with all strength lost by 21 days and mass loss by 56 days. Monocryl™ is a monofilament suture based on a copolymer of glycolide and caprolactone (sometimes referred to as poliglecaprone 25), and resorbs fast, with strength loss by two weeks and mass loss by 90 days. These aliphatic based polyester absorbable sutures obviously provide a wide range of forms and properties. They each have preferred applications and appear to cover most needs of wound closure.

4.2 Orthopedic, Maxillofacial and Spinal Surgery.

There are several areas of orthopedics, maxillofacial / craniofacial surgery and spinal surgery where the potential to use resorbable polymers is very attractive. These are primarily concerned with the stabilization of fractured bones, (including those associated with pediatric craniofacial and orthognathic reconstructive procedures) and the attachment of various devices to bone. Much of the early work on resorbable polymers in fracture fixation was carried out in Finland [38] but other centers were involved [39]. The concept is simple and follows on from the discussion in the first Chapter of this report. Bones are capable of healing when fractured but usually need some stabilization equipment to maintain the opposing fracture surfaces in close proximity whilst the healing takes place, usually over a period of 6-8 weeks. This may be done with an external plaster cast, but in complex cases, either by virtue of the location of the fracture or the multiple parts of bone produced during the process, optimal stability can be better produced by an implantable device. This could be a plate secured to the outside of the bone, or a rod placed internally within the medullary space, or individual screws. There are some very good metallic devices, such as those made of titanium alloys, which do this very well. However, there are several significant disadvantages of this technique of metallic internal fixation. First, if the device is retained in place for the duration of the patient's life, this foreign body could have long term effects on the body through a maintained foreign body response [40]. Secondly, since metallic materials have much higher elastic moduli than bone, the device will be more rigid and will substantially alter the stress patterns in the bone. It is widely appreciated that bone needs the stimulus of mechanical stress to maintain optimal morphology and density, and the continued presence of the metallic device may lead to osteoporotic effects in the adjacent bone [41]. Thirdly, the metallic device may well be quite bulky and, if the affected bone is superficial, may be palpable and unsightly. For these reasons, internal fracture devices are often removed once the bone has united, which is obviously a further operation, with additional risks of morbidity and significant cost implications. It is for these reasons that degradable devices have been introduced.

One issue with the comparison between degradable polymers and alloys such as those of titanium is immediately obvious; the mechanical properties. Titanium alloys have yield strengths (i.e. the stress at which they deform permanently) of around 800 MPa and ultimate tensile strengths (the stress at which they break) of around 900 MPa. Values for most degradable polymers are usually less than 10% of these figures. For highly stressed long bones such as the femur and tibia, this is a significant disadvantage – even titanium plates and rods can bend under the applied forces. Most attention has therefore been paid to the bones that are not so highly stressed, including the proximal humerus, the humeral, tibial and femoral condyles, the olecranon, the radial head, the talus, metatarsal bones and phalanges of the toes and facial fractures [42].

Within the area of maxillofacial trauma, polylactides plates and screws have been used for fracture stabilization [43,44]. Although patients of all ages may be suitable for resorbable plates, young children are especially suitable because of the fact that rigid internal fixation with metal plates may adversely affect skeleton growth and development. In older patients, resorbable devices tend to be used in cases of low velocity trauma. In the series reported by Bell et al using 70/30 PLDLA [44], all patients healed in a satisfactory manner and there were few complications; indeed only 3% of patients with resorbable plates had any complications compared to about 6% for the control group with titanium plates. Only one case of significant inflammation was seen, which did not require surgical intervention. As noted earlier, the resorbable plates are weaker than titanium plates, which does restrict their use with respect to the type of patient and type of fracture. The plates usually have to be thicker than titanium in order to compensate for this; also polymer screws are not self-tapping so that additional bone preparation is necessary. In general the mid-face is more appropriate for resorbable devices compared to the mandible, where forces are higher.

The same type of experience is seen with pediatric craniofacial, or orthognathic surgery, as reviewed by Haug et al [45]. Early experiences with the use of resorbable devices for the treatment of conditions such as encephalocele, which is a congenital gap in the skull, and craniosynostosis, the premature fusion of cranial sutures that prevents normal cranial growth, were described by Goldstein et al [46]. An extensive follow up of orthognathic patients has been reported by Eppley [47] who used poly(L-lactide-co-glycolide plates and screws. This group of patients was treated with either maxillary or mandibular osteotomies or genioplasty and uneventful healing was seen with all but three patients, where some para-nasal swelling occurred that could be treated by anti-inflammatory medication alone. Cheung et al [48] reported a larger series of 87 craniofacial osteotomies treated with titanium and 90 with resorbable plates, finding that infection rates (less than 2%) plate exposure rates (around 1%) and 1 year plate removal rates (1.5-3.5%) were statistically similar for both groups and the overall satisfaction rates were the same.

Osteochondral fractures of the knee (osteochondritis dissecans) quite frequently occur in young patients with high levels of sporting activity, where the traditional management regimes require extensive rest, usually over a year and involving immobilization. Early arthroscopic fixation of the lesions with resorbable pins is attractive as it could allow for a much early return to activity. Din et al [49] reported on a series of 12 knees, involving 1 cm^3 size lesions, with surrounding edema, in which this technique was used. Patients were between 12 and 16 years and 2-6 PLA pins were used for the lesions. All patients had excellent or good outcomes; the pins took around 18 months to resorb, and patients were allowed non-contact sport at 3 months. Adachi et al [50] have recently reported follow up studies with similar patients. In no patient were there any post-operative complications and there was no subsequent synovitis. Healthy regenerative changes were seen in the cartilage on subsequent arthroscopy, showing that stable fixation with resorbable pins had a beneficial regenerative effect as well as reducing the time of inactivity.

Resorbable screws have been used to treat flexible flatfoot in children, in which there is excessive flexibility at the sub-talar joint. The screws may be used to restrict this movement. Giannini et al have reported on the use of PLLA screws in children followed over a four year period [51]. No sinus formation or any osseous alterations in the sinus tarsi were seen. The implant began to change after six months and fragmentation was seen at one year. Structural integrity was lost at eighteen months and by four years the implant was completely absorbed. All patients had an effective and lasting functional outcome.

Large bony defects can pose many difficulties in treatment and post-operative care, especially with the problems of complete bone filling and the potential for infection. Several materials have been used for the coverage of large defects in order to minimize infection risk and soft tissue ingress into the site. Both poly(LD-lactide) and 70/30 poly(LD-L-lactide) have been used with successful outcomes with respect to these parameters [52].

In the spine, the main area of interest with resorbable polymers at this time is in interbody fusion. Problems with degenerating intervertebral discs are becoming more prevalent, and spinal arthrodesis, or fusion of adjacent vertebrae, is now a common procedure. For some time autogenous bone grafts were the preferred option, but the morbidity of harvesting the bone and the fact that they do not always succeed has led to the search for alternative materials, either as a replacement or adjunct to the bone. Interbody cages became popular, made for example out of titanium; nevertheless they are not ideal, having a significant modulus mismatch with respect to bone and, being radiopaque, making it difficult to visualize the tissue in the fusion zone on subsequent radiological examination. Some of these drawbacks may be obviated by the use of thermoplastics such as PEEK, polyetheretherketone, but this still leaves one outstanding issue and that is the cage remains in place once the bone has fused. Cages made of resorbable polymers have been introduced, with some clinical trials starting in the early 2000's. Polylactides have been favored since an extended resorption time is required. It is important that only bone forms in the intervertebral space, and not fibrous tissue, and so the whole of the

disc has to be completely excised and the cartilage endplate removed. The design of the cage and the precise position of placement are important variables [53].

One of the clinically used PLA cages is SOLIS™ RS from Stryker. This is a PLLA cage for use in the cervical spine; it should be noted that the different segments of the spine vary with respect to the incidence of disease, the forces involved with movement, and the optimal surgical approach. The cervical spine is subjected to lower forces, especially compression forces than the lumbar spine and is amenable to an anterior approach. Soderland et al [54] have published a report following 17 patients with cervical spondylotic myelopathy treated with these cages between C3 and C6. All patients experienced good neurological recovery and fusion, with just 2 cases of incomplete fusion and three cage breakages, none of these requiring operative intervention.

Some of the injuries and conditions of the musculoskeletal system discussed above may be sustained during sporting activity, and a major use of resorbable polymers is found in the general field of sports medicine. The advantages of resorbable devices that assist in the repair of damaged tissues, especially compared to permanent devices are seen to be particularly important in young active individuals. The advantages and disadvantages of resorbable materials in sports medicine were reviewed by Weiler at al [55]. We may see the benefits of resorbable polymers in meniscus repair [56] and potential benefits in anterior cruciate ligament reconstruction [57]. Post-traumatic, recurrent, unidirectional shoulder instability is a serious problem for many sportsmen and good results have been achieved with arthroscopic reconstruction using resorbable polymers [58].

4.3 The Cardiovascular System

Within the cardiovascular system, there are at present fewer opportunities and indications for resorbable polymers that have reached the clinical stage. The use of these materials in bone is largely predicated on the inherent regenerative properties of bone, and the need of these mechanisms to be reinforced by a supporting material in some circumstances. This is not the case with cardiovascular tissues, which suffer many diseases but have little power of self regeneration. The uses of resorbable materials has largely been limited to minor support roles in vascular interventions.

One of these areas is within vascular closure after interventions such as angioplasty or other situations where temporary access is needed to the vasculature, but where the access site has to be effectively sealed after finishing the procedure. There are a number of vascular closure devices, which usually involve a shape memory alloy in order to give the relevant mechanical properties, bearing in mind the high blood flow rates and forces that are involved, or a substance that has good intrinsic thrombogenic properties to facilitate clotting within the vessel wall, such as collagen. At least one device, the Angio-Seal ™ closure device of St Jude Medical, incorporates a resorbable polymer anchor to assist in the performance of their bovine collagen

haemostatic agent. Obviously in this situation great care has to be taken with the degradation rate and mechanism, since the anchor should not separate from the vessel prematurely and flow away in the blood stream, as happens in a small number of cases [59].

In another situation, resorbable polymers, and specifically PLGA, have been used to coat platinum coils used for the endovascular treatment of intracranial aneurysms [60]. These coils are made of platinum and are inserted into the site of the aneurysm, where they occlude the relevant artery. However, a significant number of these vessels re-canalize; the intention of the PLGA layer is to optimize the host response within the coil area to minimize this risk.

Undoubtedly the most important potential intravascular area for biodegradable polymers is that of stents. It is well known that intravascular stents are used to hold blood vessels, especially the coronary arteries, open after angioplasty therapy. Whilst metals, including stainless steel, cobalt-chromium alloys and shape memory alloy are very good from the mechanical perspective, they do tend to permit or even promote intimal hyperplasia and restenosis. There are several issues here. First there is inevitably an irritation caused to the endothelium by the metal framework, which stimulates that endothelium to proliferate. Secondly the continued presence of the device inside these small arteries allows for the continuation of the chronic response, and may also allow the device to initiate a thromboembolic event at any time.

Polymers may feature in the two possible solutions to these continuing problems. The first, and so far, major contribution, has been with the technology of drug eluting stents. Highly anti-proliferative drugs such as the chemotherapeutic agents paclitaxel and sirolimus can be released from the surfaces of metallic stents. Although it is possible to coat the stent directly with the drug, it is more usual to coat the stent with a polymer – drug complex. The drug can then be released by, for example, diffusion-controlled or degradation-controlled processes. Most widely used drug eluting stents utilize hydrophobic biostable polymers for this, as reviewed by Wykrzykowska et al [61] . The Cypher stent uses a poly-n-butyl methacrylate based system with sirolimus. Taxus uses polystyrene-b-isobutyl-b-styrene (SIBS) with paclitaxel. These combinations appear to give good drug-polymer miscibility and release kinetics, with minimal stimulation of the tissue. There does remain the potential problem that the polymer-coated stent is still present in the artery once the drug has been eluted, which occurs over a few weeks. This has been associated with a small but finite risk of serious thromboembolic events occurring soon after.

The potential solution to this is to use a biodegradable / resorbable polymer coating. Several animal studies have demonstrated this possibility [62,63]. A further possibility is to use a wholly resorbable drug eluting device. In 2008 Ormiston et al published first stage results of a clinical trial using a resorbable everolimus eluting stent [64]. The major part of this is made from PLLA which is coated with PDLLA containing the everolimus. Animal studies had suggested a mass loss of 30% at six months and 60% by 18 months. 80% of the drug should be released by 28 days.

Excellent clinical outcomes were found at 1 year with only one Major Adverse Clinical Event. There was an acceptable in-stent late loss, minimal intra-stent neointimal hyperplasia, and a low stent area obstruction. Obviously these results appear very promising for the role in polylactides in intravascular stents.

4.4 Plastic and Reconstructive Surgery and Cosmetic Technologies

In plastic and reconstructive surgery, a wide variety of materials are used to alter shape, form and size of parts of the body. In most situations it would be counter-intuitive to use a degradable material for this purpose. Often, however, there is a need to alter the features of the skin and underlying tissues in order to give a more aesthetic appearance, where the surgical implantation of solid objects is not a good option. Biomaterials that are capable of injection into the sub-dermal space in relatively small amounts, where they eventually resorb but leave behind some volume filling fibrous tissue, provide a better alternative. Collagen is often used for this purpose but synthetic resorbable polymers also have a place. PLLA has been used in this form of cosmetic technology for a few years [65], especially in attempts to reverse the signs of ageing. It has also been approved for use in patients with the human immunodeficiency virus condition for the restoration of facial features following fat loss, or lipoatrophy [66]. The PLLA is micronized, and a suspension of particles around 50 microns in diameter in carboxymethylcellulose is used for the injection(s). The PLLA is resorbed over a period of around 2 years, which is a much longer timescale than collagen preparations. The vast majority of patients have very acceptable outcomes. A small number, usually less than 10%, do experience the formation of subcutaneous inflammatory nodules, which are responsive to anti-inflammatory agents such as steroids.

4.5 Pharmaceutical Applications

The rationale for alternative drug delivery systems to the conventional oral route is very well known and need not be discussed at length here. Oral administration of most drugs is poorly controlled and directed such that the bioavailability of the drug is rarely ideal. It would be much better if there were far greater control over precisely where the drug was to be delivered and over the length of time that the drug was present in the appropriate tissues within its therapeutic window. It has long been considered an attractive possibility for the drug to be contained within some delivery system that could control the release and the site of delivery of the drug. One problem has been, however, that the health care industry is very price sensitive and the cost per tablet is a critical factor in the reimbursement strategy and, therefore, the commercial success of a drug. Additional costs of the control system are unlikely to be realistic with low cost drugs. In addition, issues have arisen over drug tolerance; if a patient has a mild adverse reaction to an orally delivered drug, they can stop taking the drug and try something else. If, however, the drug had been implanted in the patient within a delivery device, then rapid and difficult steps may have to be taken if a reaction occurs.

Some attempts were made to introduce alternative methods for some very widely used contraceptive agents, which could be delivered from an implantable depot, such as a silicone capsule, over a matter of weeks or months. In general, these have not survived in the market place; some reactions did occur and the retrieval of the capsules was not always easy. Some other, more profound reason has to be present for controlled release systems to be effective and useful. These reasons can be found in either the need to place a powerful drug in a precise place in order to treat a life – threatening disease, or in situations where the drug characteristics, for example hydrophobicity or molecular size, preclude the use of normal administration route with solid or water-soluble forms, or where a very precise pharmacological or genetic manipulation is required in which the active agent has to be combined with an agent that has special powers of targeting and release.

We shall consider the first of these just briefly. The main application here is likely to be in the localized delivery of powerful ant-cancer drugs to tumors, especially brain tumors. Primary malignant gliomas are very difficult to treat, there being a median survival of under 1 year even with the most aggressive combination of surgery, radiation and chemotherapy, with a very high rate of recurrence. One of the most effective drugs is carmustine (BCNU) but with systemic administration does not yield adequate brain tumor penetration, and there are significant cytotoxic responses to the level that has to be used. In view of this, the technology has been developed to deliver the drug to the site of the tumor at the time of surgical removal. The drug is contained within wafers of the biodegradable poly-[bis-p-(carboxyphenoxy)propane-sebacic acid). After extensive pre-clinical tests, clinical trials were undertaken with the device as an adjunct to the treatment of patients with recurrent malignant glioma, leading to US approval in 1996 [67]. This and other combinations have now been used in other cancers. Although this particular pivotal combination did not use any of the lactide or glycolide platforms, others have. Manome et al [68] have reported the experimental use of a doxorubicin – PLGA system in the brain. Menei et al [69] also reported on the use of PLGA for the controlled release of 5-fluorouracil into the brain.

Other clinical areas in which the lactide/glycolide platforms are used for drug delivery implants include ophthalmology, where the product Posurdex is in clinical use for intravitreal placement for the treatment of macular edema and retinal vein occlusion. The device is made from PLGA and delivers dexamethasone to the posterior segment of the eye. It has been in clinical trials for the treatment of age-related macular degeneration [70].

In the second group, we concentrate on polymeric drug delivery devices where large molecules and / or molecules with low solubility are encapsulated within microspheres, or, increasingly within nanoparticles. The large molecules include peptides, proteins and DNA / RNA complexes. There are many recently developed poorly soluble drugs that would appear to have little possibility of administration by conventional routes, but if they have a broad therapeutic window with a requirement of a low daily dose to treat a long-term disease, then

microencapsulation in a degradable polymer offers considerable potential [71]. Even if there is sufficient solubility to realize good oral bioavailability, the controlled release from injected microparticles has significant value if highly constant plasma concentrations are required, if highly localized delivery is required or if poor patient compliance over the long term is expected.

Most of the drugs in question will normally have poor solubility in water but good solubility in one or more solvents. One of the better types of method of preparing microparticles involves aqueous phase emulsion technology, so that the solubility of a drug in both water and the emulsifier are important factors [71]. Drug stability during the emulsification techniques that often apply high temperatures and shear forces is also very important, as are polymer-drug interactions during all phases of preparation and storage. During microencapsulation, the drug has to be dissolved or dispersed in a solvent and may eventual be found within the microcapsules as a solid solution, as amorphous or crystalline solids, or as a molecular dispersion.

It is perhaps not surprising that the hydrophobic PLA was very popular in the early developments of microencapsulated drugs. As with some other applications of the lactide and glycolide platforms, however, the long residence time in the body was perceived as a disadvantage in many situations, and there was a move towards the faster degrading poly(lactide-co-glycolide) materials. This degradation time was one of the more important deciding factors in biodegradable polymer choice. Typically a 50/50 PLGA, of medium molecular weight was chosen, although longer release times could be achieved with higher lactides content. The swelling of the microcapsules in water could be controlled by choice of the end groups and particle size. It is also possible to use block co-polymers based on PLGA and PEG, polyethylene glycol, to give faster drug release. Care has to be taken with the acidic by-products of the hydrolysis of PLGA within the capsule and their effects on the drugs, and also with the possibility of aggregation of the microparticles.

A major amount of research has been performed on biodegradable materials for particulate drug delivery over the last decade, much of it on PLA and PLGA. The translation of this into clinically used products takes a long time, of course, and the impact of this technology has yet to be realized. One of the first products to obtain FDA approval and clinical application was Nutropin Depot, a PLGA encapsulated form of a recombinant human growth factor. It received approval in 1998 but manufacturing and marketing ceased in 2004 since it was uneconomical. The major focus on chemotherapy, where patient numbers will always be high and the health economics arguments are far more favorable, has led to a significant interest here, especially with the move towards nanoscale particles. The first nanoparticle based chemotherapeutic agents were Abraxane, introduced in 2005, as paclitaxel conjugated albumin nanoparticles [72] and Doxil, a doxorubicin loaded liposome preparation embedded in a methoxypolyethylene glycol gel [73]. The real potential for PLGA and PLA has been recognized here [74], with much attention being focused on prostate cancer. Farokhzad et al [75] and Dhar et al [76] have

successfully experimented with the targeted delivery of cisplatin to prostate cancer cells through the use of aptamer functionalized platinum prodrug – PLGA – polyethylene nanoparticles, giving a ten-fold increase in effectiveness over free cisplatin. The power of such systems is clear; the encapsulation of the drug within the interior of the particles protects it from the tissue environment before it reaches its target. Engineering of the surface of the PLGA nanoparticles by the introduction of ligands such as peptides, antibodies or nucleic acid aptamers allow targeting of the cancer cells to the cancer cells of interest. This approach has moved on to clinical trials aimed at prostate cancer and breast cancer.

The third area where PLGA and similar biodegradable and resorbable polymers have great potential in delivering pharmaceutical payloads to precise locations is in gene therapy. This is some way from clinical reality, but the opportunities are profound. Gene therapy in general aims to insert genes into cells of a patient in order to treat a disease that is caused by genetic error. The technology of gene insertion has been developed for some time, but the key issue of being able to carry out this gene transfer safely has not fully been resolved, and it is well known that some early clinical attempts at the therapy had serious, including fatal, consequences [77].

Gene transfer requires that the relevant gene is carried into the cell by some agent, or vector. Early attention focused on the use of viral vectors, but it was these that caused safety concerns and it is widely recognized that non-viral vectors should be much safer [78]. Several different forms of non-viral vector have been investigated and, although many can certainly deliver the genes safely, they often do so with very low efficiency. There are two main groups of non-viral vector based on cationic lipids and cationic polymers. These polymers, such as polyethylenimine and poly-L-lysine have good transfection characteristics but are non-degradable and have risks of long term accumulation and cytotoxic side effects [79]. A significant need for biodegradable polymeric gene vectors has therefore arisen. In answer to this, two broad classes of biomaterial have emerged. One is based on the self assembly of DNA on cationic polymers; these complexes are referred to as polyplexes and will not be considered further here. The second is the group based on degradable micro- and nanoparticles, and at this stage this group is dominated by PLGA [80]. PLGA particles, especially at the nanoscale, enter the cell efficiently through a combination of specific and non-specific endocytic mechanisms [81]. Following uptake, some of the nanoparticles escape from the lysosomal compartment and reach the cytosol, a process that is facilitated by the increasing cationic charge on the nanoparticles in their acidic environment. Following the lysosomal escape, the nanoparticles remain in the cytoplasm, where they release their plasmid DNA (or other forms of RNA) as the PLGA degrades, over a matter of weeks. There are some drawbacks with the PLGA, and successful applications are requiring some modifications. For example, encapsulation of the plasmid DNA, which is large and hydrophilic, within the hydrophobic micro- or nanoparticles is not easy. The pH change associated with the hydrolysis of the PLGA may also result in DNA degradation. Co-polymerization of the lactide-co-glycolide with other monomers may overcome some of these issues [82].

4.6 Regenerative Medicine

The final clinical application to consider is that of regenerative medicine.

There are several conclusions that can be drawn from any analysis of the merits of long term implantable medical devices. First, although they can give very good performance in many situations, they will always be limited to situations involving mechanical or physical functions and will not, by themselves, be able to deal with conditions which require biological solutions. Secondly, even in those situations where the performance is good, it will always be less than 100% effective because so many variables impose themselves on the process, especially in the context of biocompatibility and the influence of clinical skill and patient compliance. Outcomes are variable and often unpredictable.

In this context, biomaterials scientists, while working to optimize the applications and performance of their materials, have to recognize the implicit limitations to the concepts and practice of the long term replacement of tissues and organs by synthetic materials. Put quite simply, a natural hip joint does not look like, or behave like, a combination of metals, polymers and ceramics. Natural tissues are usually heterogeneous, anisotropic, hydrated living substances; synthetic materials are not.

One of the alternatives to tissue replacement by synthetic biomaterials / medical devices involves the use of transplanted tissues, which are living structures derived from a human donor site. These could be small pieces of tissue (for example a cornea or piece of skin) or major organs (such as the heart, kidney or liver). They may be derived from a recently deceased donor, a living, closely matched donor such as a close relative, or from a site within the patient themselves, as with bone, skin or nerve grafts. Such transplants or grafts have the major advantage of being living, natural structures. Disadvantages include the logistics of donor supply, which is extremely limited, and the possibility of immunological rejection. In view of these difficulties, transplantation remains a minor option.

In between these two extremes of synthetic non-living replacements and living transplants are some more recent options for therapies which reply on the use of various methods and tools that result in the regeneration of the patients own tissue, either physically or functionally. This area of clinical medicine has been termed ‘regenerative medicine’. There are currently three main strands of regenerative medicine. The first, usually called ‘cell therapy’ involves the use of groups of cells, derived from the patient or elsewhere, that can be injected or otherwise placed at the site of disease or injury in the expectation that they will facilitate the spontaneous regeneration of the required tissue. Stem cells are often discussed in this context, and potential applications include the use of dopamine producing cells in the treatment of Parkinson’s disease, chondrocytes in the treatment of cartilage lesions and cardiomyocytes in the treatment of myocardial infarctions. At its conceptually simplest level, cell therapy does not involve conventional biomaterials.

The second strand is that of gene therapy where specific genes are inserted into specific cells in order to correct deficiencies in those cells; this has already been discussed in the previous section. The third strand is that of tissue engineering, which is now a major factor in the development of new biomaterials. Tissue engineering may be defined as ''*the creation of new tissue for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals* '' [83]. The simple concept underpinning tissue engineering is based on the fact that adult humans have very limited capacity to regenerate damaged tissue. Clearly, as a fetus, embryo or infant we have the capacity for new tissue growth but much of this capacity is lost once we reach maturity. It is possible, however, to switch these mechanisms back on under some circumstances, these processes involving delivery of the right signals to the affected tissue. The two most important forms of signals are those involving active biomolecules such as growth factors and those involving mechanical stimuli [84].

Molecular and mechanical signals do not directly imply the use of biomaterials, and indeed tissue engineering may in theory be carried out in the absence of biomaterials. Three factors, however, determine that biomaterials are most likely to involved in tissue engineering processes. The first is that regenerated tissue needs form and structure, and injected cells by themselves are unlikely to provide this – a material template is very useful here, especially if it is biodegradable. Secondly, molecular signals are not easy to deliver with the appropriate spatial and temporal characteristics; a material template that contains and delivers such signals to the required cells in the requisite format would also be very beneficial. Thirdly, mechanical signals may be equally difficult to deliver, and again it is likely that better delivery could be sustained via a material construct.

It is obvious that as tissue engineering attracts some of the spotlight away from medical devices, a new role for biomaterials is being developed. The material construct that is used in tissue engineering is usually called a scaffold, although often the term 'matrix' is more appropriate. This is where the PURASORB materials are having an impact.

It should be noted that at this stage, although there have been some successes with tissue engineering and regenerative medicine, it is taking a long while for this new section of medicine to become routinely successful, either clinically or commercially. From a technical point of view, it is proving very difficult to regenerate the optimal amount and quality of tissue. The principles appear to be sound, but the translation is proving difficult. The essential tissue engineering paradigm [84] is one where healthy cells are derived, either from the intended patient or another source. Under sterile conditions these are cultured so that multiply and grow, or are differentiated, until they are sufficient in number and phenotype to express new tissue. To do this, they may be placed in a suitable bioreactor, and seeded into a material construct, the scaffold. It is this scaffold that gives structure to the intended newly formed tissue and which facilitates both mechanical signaling (through either structural or fluid stresses) and molecular

signaling, through the delivery of drugs such as growth factors. When sufficient tissue has formed, the construct may be implanted into the patient where, hopefully, it will integrate with the host tissue. There are several possible variations to this process. First, the cells may either be autologous, that is derived from the patient, or allogeneic, which means that they could be obtained from a donor, which, in the case of stem cells, could be an embryo. It is not necessary for the whole process to take place in a bioreactor *ex vivo*, and there is much interest in directing much of the regeneration to take place in the host, *in vivo*. Whatever the precise technique, the nature of the scaffold material will be crucial.

As yet there are few clearly described specifications for these scaffolds. As noted above, these could be matrices or gels, but we will concentrate here on the more relevant solid polymer scaffolds. Because of the need for regulatory approval for tissue engineering products, including scaffolds, much of the emphasis has been on those materials that are already used in approved devices, especially FDA approved devices. Although it is not an absolute requirement that the material is fully degradable, and indeed there are some arguments in favor of hybrid scaffolds that contain both degradable and non-degradable components, FDA approved resorbable polymers have received most attention. It is not surprising, therefore, that the popular scaffolds have been the same polymers that have been used in sutures, drug delivery systems and so on, and the PLA, PLGA and polycaprolactone platforms have been among the most widely investigated. It is generally agreed that, although the precise requirements for these scaffolds will depend on the type of tissue involved, the polymer must be capable of preparation in a highly porous form and should degrade in a timescale usually measured in weeks, without any adverse effects on cells and tissues during the degradation [85]. Moreover, the material should be sufficiently hydrophilic to facilitate cell adhesion, should be capable of functionalization with active biomolecules and of releasing other biomolecules, such as growth factors in a controlled manner.

Mikos et al [86] were among the first to develop the technology for the preparation of highly porous PLA scaffolds, using a salt-leaching method. It became obvious, however, that for most applications, unmodified PLA homopolymers was not ideal because of its slow degradation rate and hydrophobicity. There have been many attempts to modify the polymer, either by surface modification or copolymerization and blending. Copolymerization with polyethylene glycol is a popular option [87]. The possible modification strategies have been reviewed by Wang et al [88] while the advent of electrospun nanofiber copolymer scaffolds has been discussed by Liu and Ma [89]. The need to optimize degradation rates for these polymers has led to extensive investigations into different copolymers with the lactide, glycolide, caprolactone platforms. The significance of the degradation rate on cellular responses within the scaffolds was elucidated by Sung et al [90. They found that fast degradation negatively affects cell viability and migration into the scaffold both in vitro and in vivo; the degradation of both PLGA and PCL is faster in vivo than in vitro because of the accumulation of carboxylic acid within the material in the former

case. Inflammation associated with the degradation also influences cell behavior. The nature of the porosity [91] and the bioreactor fluid flow [92] also affect the degradation. The trend has certainly been towards the use of porous poly(DL-lactide-co-glycolide) [93] and polycaprolactone based co-polymers [94]. Experimentally there have been good successes with nanostructured PCL in bone [95], 70-30 PLGA in blood vessel scaffolds [96], and nanofibrous PCL-PLLA in cartilage tissue engineering [97] amongst many other examples.

One of the factors that control the success of tissue engineering scaffolds is the ability of cells to adhere to scaffold surfaces and display the appropriate characteristics for the expression of new tissue. The lactides, glycolide, caprolactone materials are not particularly good in this respect, but they are capable of surface functionalization which may assist in these processes [98]. For example PCL has been functionalized with the collagen-mimetic peptide GFOGER, which enhances bone regeneration [99]. There are many other examples in the biomaterials literature where PCL and PLGA have been functionalized with these types of peptide, especially RGD. Interest has also been shown in combining these polymers with other components in composite scaffolds, for example with bioactive ceramics such as the calcium phosphates [100] and in various nanocomposites [101].

PLGA, PLA and PCL scaffolds and their hybrids and composites have been utilized, experimentally or clinically, in cartilage tissue engineering [102], bladder tissue engineering [103], bone tissue engineering [104], skin tissue engineering [105], nerve tissue engineering [106] and many other areas. It is noteworthy that of the few clinical success with tissue engineering products in critical situations in human patients, two of the most important, in arteries [107] and the bladder [108] have used these resorbable polymer scaffolds.

5 The Biocompatibility and Biological Safety of PURASORB Polymers

We have noted in section 2 of this report that the phenomenon of biocompatibility is rather complex and our understanding of mechanisms of biocompatibility have been evolving over the years. For many purposes, specially related to medical devices, biocompatibility has often been considered synonymous with biological safety. As discussed earlier, this is not strictly the case since biocompatibility usually means more than being safe to use in humans, but it is a good starting point for the discussion of the overall biological performance of resorbable polymers.

With respect to the use of biomaterials in medical devices, a series of International Standards exists which set out the tests that may be performed to evaluate the biological responses that are relevant to establishing the safety of devices and materials [109]. It can be seen from the list of the different parts of this Standard that these tests have been established to determine that the materials and devices do no harm to the patients, and indeed materials are considered to either pass the tests, in which case they are suitable for use in the body, or fail the tests, in which case they are deemed to be unsafe for use. It is useful to consider how resorbable polymers fare when tested according to these criteria. In the following sections, evidence from studies using these types of test, both *in vitro* and *in vivo*, are reviewed, and the overall performance of PURASORB materials discussed in terms of their individual characteristics.

5.1 Interactions with Cells and Cytotoxicity

The most widely used type of basic test is that of cytotoxicity, which is used to determine whether a material has any significant and deleterious effect on cells in culture. The tests may be performed on the material directly, where the material is placed within the cell culture medium, or indirectly, in which case the material is incubated for a defined period of time in a suitable solvent and then that solvent, containing any soluble components extracted from the material, is incubated with the test cells. The end-point of a test could be the determination of the number of cells that die, or some measure of the health of the cells, for example their respiration rate. It would not be expected that polymers derived from naturally occurring substances such as lactic or glycolic acid would have any adverse, direct effect on cells. With most polymeric systems, the prospects of cytotoxicity generally depend on additives or residues that may be present and available for extraction during these tests. It is also important to note that cytotoxicity should not really be expected from the PURASORB materials since they contain no additives and since residual catalysts, mostly tin-based, are at a very low level, approaching 50 ppm.

Ignatius and Claes have reported on cytotoxicity tests for some polylactides and lactide-glycolide copolymers, specifically a 70/30 poly(L-D/L-lactide) and a 90/10 poly(L-lactide-co-glycolide) [110]. A variety of tests were carried out with mouse fibroblasts. No cytotoxicity was seen with either material in direct tests. Cells treated with extracts obtained in phosphate buffer saline at 37^{o}C actually marginally improved cell respiration. Higher temperature extracts did have some

negative effects on cells, but this would not be relevant to human applications. Overall these resorbable materials display negligible cytotoxic effects of cells *in vitro*. Polycaprolactone has been tested extensively for cytotoxicity using the same types of tests, without evidence of any adverse effects on cells; for example, Domingos et al [111] have recently evaluated polycaprolactone tissue engineering scaffold materials and found them to be non-cytotoxic with respect to fibroblasts. Similar results were reported by Serrano et al for ε-polycaprolactone with fibroblasts [112]. Poly(65/35(85/15 L/D) lactide-ε-caprolactone) nerve guides were assessed for cytotoxicity by Meek et al and found to have no adverse effects at all on mouse fibroblasts [113].

The interactions between resorbable polymers and cells is also of importance in tissue engineering applications, where, as noted in the previous section, the functionality of cells on polymer scaffold surfaces is an important controlling factor in tissue regeneration. Poly (ε-caprolactone) is widely employed in scaffold construction. Salerno et al have demonstrated the excellent performance of poly(ε-caprolactone) with respect to the promotion of activity of human mesenchymal stem cells [114]. Similar results have been shown when poly(ε-caprolactone) nanowires were coated onto polymer surfaces and cultured with bone marrow derived stem cells [115]. Osteoblasts grow and proliferate on poly(ε-caprolactone) surfaces [116]. Elgendy et al studied the response of an osteogenic cell line on 50/50 poly(lactide –co-glycolide) surfaces, finding that cell attachment and growth was significantly higher compared with the surfaces of several other polymers and composites [117].

Interactions between cells and the lactides – glycolide polymers do vary, largely as a result of the varying hydrophilicity of the materials. Pamula et al found that the adhesion, viability and morphology of fibroblasts on a glycolide-L-lactide copolymer was very similar to that on control glass surfaces, but the viability was reduced on a glycolide – L-lactide- ε-caprolactone terpolymer and a glycolide-ε-caprolactone copolymer [118].

The effect of polymers of red blood cells is also widely evaluated, since red cells come into direct contact with implantable devices and their sensitive cell membranes can easily be disrupted, in the process known as hemolysis. These effects may well be influenced by the nature of the polymer, for example whether it is presented as a solid surface or as particles. The PURASORB materials do not have any hemolytic effects. Even when presented to red cells in the form of nanoparticles, no hemolysis is seen [119].

5.2 Blood Compatibility

Several different types of test are available to investigate the blood compatibility of biomaterials more broadly, with an emphasis on thrombogenicity, that is the ability of a material to initiate the formation of a blood clot. Two inter-related mechanisms may be involved here, the initiation of the clotting cascade and the activation of platelets. There are, however, very few published studies of the blood compatibility of resorbable polymers. The overall thrombogenic

potential of polycaprolactone scaffolds has been determined to be very low [120] and the same would be expected of the other PURASORB materials.

5.3 Systemic and Reproductive Toxicology, Genotoxicity and Carcinogenicity

With implantable biomaterials, it is essential that tests are performed to assess the potential for adverse events on the patient as a whole, in addition to local adverse events. Included in a large series of tests that may be performed are those that address issues of reproductive toxicity, the fate of systemically distributed products of the material, and those issues concerned with genotoxicity and carcinogenicity. With bioresorbable materials that are based on naturally occurring substances, and which are readily metabolized and eliminated from the body, these concerns should be minimal. Indeed there are very few studies reported in the literature concerning these matters since it is usually considered irrelevant or unnecessary to carry out such tests.

An extensive search of the literature reveals no reports of adverse events related to any of these processes with the lactide, glycolide, caprolactone platform polymers. Because of the possibility of greater risks with polymers in nanoparticulate form, some attention has been paid to the potential of genotoxicity with resorbable polymers, but again without identifying any such effects. Huang et al have carried out genotoxicity studies on nanoparticles of ε-caprolactone – ethylene glycol copolymers using the standard chromosomal aberration and mouse micronucleus tests and found no effects at all [121].

5.4 Tissue responses in Animal Models

Over the last 40 years, many papers have been published on the tissue responses to resorbable polymers observed in pre-clinical testing. Many of the studies have involved laboratory synthesized versions of these polymers, often without a great deal of detailed characterization and indeed quite often without a clear description of the polymer involved, so that comparisons are difficult. Some of the more relevant reports are summarized here; clearly this cannot be an exhaustive and comprehensive review.

Several early studies focused on the suture materials that were being commercialized in the 1970's. Kulkarni et al [122], Postlethwaite [123], Frazza and Schmitt [37] and Cutright et al [124] all published very favorable reports on the soft tissue responses to polylactide, polyglycolide and various co-polymer sutures, usually showing a minimal response and, as was the clinical objective, a milder response than with existing sutures.

With implants placed in soft tissue, such as in intramuscular or subcutaneous sites, the responses have usually been very mild. Schakenraad et al observed a very mild foreign body response to subcutaneously implanted poly(DL-lactide) [125]. Visscher et al reported just slight reactions after 480 days with rat intramuscular implantation of both polylactides and polyglycolide materials [126]. Galgut et al showed minimal response to polylactides in the soft

tissue of rats [127], although Rozema et al did report a greater level of cellular response to poly(L-lactide) in similar experiments [128] whilst Lam et al also showed some cell damage with this material in soft tissue of mice [129]. When implanted in the rat abdominal wall, polylactides materials gave excellent biocompatibility, with a slightly greater response to the polyglycolide [130]. In the skin of rats, which is very relevant for scaffolds for skin tissue engineering, Cooper et al [131] showed that there was little or no inflammation to either polylactide or polyglycolide materials.

Within the rabbit cornea, Kobayashi et al [132] demonstrated the absence of any adverse tissue responses with polylactide but a little greater reaction with polyglycolide. Wong et al [133 have studied the response of the rat brain to both poly(L-lactide-co-glycolide) and poly(ε-caprolactone). Porous scaffolds were implanted into the cerebral cortex. PCL induced a lower inflammatory response than PLGA and greater tissue ingrowth. Both polymers alleviated astrocytic activation and prevented enlargement of the defect and both demonstrated permissiveness to neural ingrowth. Both polymers were seen to attenuate secondary death and scarring and PCL appeared to have some advantages over PLGA.

Ng et al [134] investigated the response to ultra-thin polycaprolactone films in wound healing models, using full and partial thickness wounds in rats and pigs. Wounds re-epithelialized completely with the formation of a neo-dermal layer and a low level of fibrosis. No inflammation was seen and the PCL supported the healing process.

With respect to bone, variable responses have been seen depending on factors relating to the polymer and the site of implantation. Poly L-lactide rods were placed in the medullary cavity of rabbit femora for 52 weeks by Matsusue et al [135] and no inflammatory responses were seen. When polyglycolide rods were placed within experimental osteochondral fractures of the medial femoral condyle in rabbits, some inflammatory responses were seen at around 12 weeks, even though all fractures healed reliably [136]. When both polylactides and polyglycolides were placed in defects in rabbit calvaria by Schmitz and Hollinger, no inflammatory or adverse responses were noted [137].

Most studies of polylactide and polyglycolide materials in the fixation of bones in the rat have shown very little inflammatory responses, or other indications of adverse local effects [138-140]. In larger animals there have been some experiments that show similar minimal responses and some that show some extent of inflammatory reactions. Leenslag et al carried out fracture fixation in dogs and sheep with poly(L-lactide) and reported some increased cellular activity but otherwise acceptable responses and good outcomes [141]. In the rabbit, Bostman et al showed variable tissue responses but no serious adverse events [142-143]. Paivarinta et al showed minimal inflammatory responses with poly(L-lactide) and polyglycolide in the fixation of rabbit femora [144]. Suganuma and Alexander reported significant foreign body responses to poly(L-lactide) plates in the dog femur [145] . Reviews of the published pre-clinical studies of

resorbable polymers, with an emphasis on bone models, have been published by Athanasiou et al [146] and An et al [147].

5.5 Clinical Studies of Biocompatibility

The clinical applications of resorbable polymers reviewed in Section 4 indicated widespread clinical acceptability of these materials, with few situations in which adverse events should be expected or have been observed. The actual clinical observations in certain areas of surgery do require some consideration since there have been some differences of opinion and variations in clinical outcomes. It was alluded to in the previous section that there have been differences in the host response in some animal models, especially relating to the use of these materials in contact with bone.

The main issues that have arisen relate to inflammatory reactions seen in response to fracture plates and screws used in maxillofacial surgery. In 1993, Bergsma et al reported some cases of clinically significant foreign body responses to poly(L-lactide) devices used in the treatment of unstable zygomatic factures [148]. They discussed the three year postoperative findings in a series of 10 patients; four of the patients had intermittent swelling at the site of implantation. Six of the patients had the wound site re-opened, where polymer particles were found within the cytoplasm of cells in the fibrous capsule. A review of progress with biodegradable polymers in oral and maxillofacial surgery from the same institution over a decade later [149] indicated that there were other reports of adverse tissue reactions, in some cases with 'painful erythematous papules with sinus discharge containing remnants of the implant material' [150], osteolytic changes in a high percentage of patients [151] and abundant polymeric debris surrounded by mononuclear phagocytes and multi-nucleated foreign body giant cells [152]. However, in the same review paper [149] a systematic study of published papers in which resorbable polymers (of varying commercial sources) were compared with titanium plates was reported. Evidence was available from a number of randomized controlled trials, the conclusion being that there were no significant differences between biodegradable and titanium devices with respect to short-term clinical outcomes, complication rates and infection rates. Re-operation rates did not differ between the groups. Included in the clinical studies were those of Ueki et al [153], Norholt et al [154], Cheung et al [155] and Ferretti et al [156], the clinical applications being either Le Fort I or mandibular split osteotomies. These observations are important since if there were any consistent adverse events with these polymeric materials, the clinical outcomes would have not been the same as with titanium, usually considered to be the gold standard osteosynthetic material.

It should also be said that there are many other studies and reviews that indicate consistently good clinical outcomes with resorbable polymers in orthopedic and maxillofacial / craniofacial areas. Both Waris et al [157] and Peltoniemi et al [158] have published review papers which point to the clinical successes without significant adverse effects. Ambrose and Clanton have

reviewed the overall evidence of bioabsorbable implants in orthopedic surgery and concluded that some complications do exist but that they rarely have an adverse effect on long term outcomes [159].

In recent years, resorbable polymers have been used increasingly as interference screws in anterior cruciate ligament reconstruction surgery. The overall performance of these devices, as of 2009, has been reviewed by Konan and Haddad [160]. This is a difficult area of surgery and mistakes with materials can have significant effects, as seen with the calcium carbonate reinforced poly-DL-lactide-co-glycolide material, which had to be withdrawn from clinical use because of repeated cases of wound discharge and breakdown [160]. There is extensive experience with poly(L-lactide) screws and most studies show comparable clinical outcomes compared to metallic interference screws with the exception that up to 7% of the polymer screws may fracture on insertion and late stage fracture and migration can also occur [161,162]. There are no consistent adverse events related to the biodegradation or host response [163, 164].

5.6 Summary of Biological Performance

Clearly there is a great deal of data derived from in vitro experiments, pre-clinical animal studies and clinical evaluations about the biocompatibility, biological safety and overall biological performance of the bioresorbable materials in general, including the PURASORB materials. There are a few caveats that should be added to any general comments about this performance. First, since it is necessary to rely on the published literature, we have to recognize that much of the experimental work is performed on materials that may be imprecisely defined or characterized. Secondly, not all studies cover the full period of the material degradation, which in some cases can be measured in years. Thirdly, in those situations where the materials are used clinically, it is important to recognize that some apparent adverse events may have little to do with the quality or performance of the material, but instead are caused by differences in clinical technique or idiosyncratic features of individual patients.

Even with those caveats in mind, the evidence points overwhelmingly to the excellent biocompatibility and confirmed biological safety of the PURASORB materials. The range of polymers discussed in this Report, represent degradation times varying from a few weeks to several years and mechanical properties ranging from the highly elastomeric to the rather brittle.

Under *in vitro* conditions, the materials display no significant cytotoxicity. The products of degradation and resorption are clearly well tolerated by the human body, and there is no evidence of systemic effects arising from their distribution or elimination, of any reproductive toxicological effects, or of any genotoxicity or carcinogenicity. This situation should be expected from the composition and their resorption / metabolism, but it is helpful to have this confirmed by pre-clinical testing.

Equally we should not expect to see any allergic or hypersensitivity effects with these materials. There is a little confusion in the literature about the relationship between the immune system and inflammation, which was introduced in Section 3 of this Report, and which is discussed a little further below, but it should be emphasized here that, although it is quite clear that the particulate products of polymer degradation can give rise to inflammatory responses under some circumstances, these do not involve stimulation of the immune system or the generation of any allergic reactions. It is interesting to note that the mild inflammatory response to poly(lactides-co-glycolide) microparticles can be put to use in the development of injectable delivery vehicles for vaccine antigens [165].

All of this evidence points to the excellent general biological safety of these materials. There are three important points to consider when assessing the overall biocompatibility, which relate to the influences of polymer structure, surface characteristics and degradation rate on the cellular responses to the materials and their degradation products.

The first concerns the observations that have been reported on the cellular, and especially the inflammatory cell, responses to certain polylactide or polyglycolide based polymers, especially with bone fracture plates. As noted earlier, the degradation of a synthetic polymer within the body will inevitably result in some form of cellular response. This may range from a short-term and transient acute inflammation that is quickly resolved to a more sustained chronic response. The evidence within the clinical literature suggests that this range of responses is seen with the types of polymer represented by the PURASORB platforms. Various arguments have been put forward to explain this type of response. Proposed mechanisms include the effect of the low pH that may be associated with the release of lactic or glycolic acids, the putative toxicity of residual catalysts that may be released during late stages of degradation, the putative pro-inflammatory nature of micro-crystallites that are the last parts of the polymer to degrade, and the non-specific inflammatory character of fragments of polymer that are inevitably formed during the degradation process. None of these mechanisms can be confirmed as being responsible for any host response, although equally none can be shown to be entirely implausible. It is of relevance to note that some degree of inflammation has been seen with different forms of the polymers and at different times, ranging from a few weeks to several years, so that there is no one obvious, sole mechanism responsible. It is of considerable significance, however, that the clinical observations of inflammation are rare, and usually without any detrimental effect on the patient. Even in those few cases where late stage swelling has been seen with fracture devices, the effects are usually transient and do not impede fracture healing nor influence the patient's well being. It may be concluded that, since all implantable medical devices, whether degradable or not, have the ability to induce a detectable foreign body response in some patients, under some conditions, the effects seen with the PURASORB platform of materials are minimal and of no clinical significance in the vast majority of cases.

The second point concerns the interactions between the PURASORB materials and cells that are intended to express new tissue in regenerative medicine processes. The ability of a cell to adhere to a polymer surface depends on several factors but especially the surface energetic and the hydrophobic / hydrophilic balance. The surface energy, and therefore wettability, of the PURASORB range of polymers, does vary, and it should be noted that cells do have difficulty in attaching and functioning on some of these materials. The effects will vary from cell type to cell type, and with the culture conditions, so that it is difficult to generalize. However, we should note that there are several good options within this material range that provide acceptable conditions for cell attachment, and that a series of surface modifications are available that enhance this behavior considerably. Again it clear that these materials are amongst the better available to tissue engineers, the best clinical success stories in regenerative medicine having already been based on some of these resorbable materials.

The third point concerns the increasing trend towards the use in microparticles, and especially, nanoparticles, in drug and gene delivery, and in diagnostic agents. It is frequently the case that a pharmaceutical application requires that the active component, say a powerful chemotherapeutic agent or DNA, be delivered precisely to target cells, where it is internalized in order for it to exert its effect. The best vectors for these processes appear to be nanoparticles that are fabricated from a resorbable polymer combined with the active agent. Once internalized, the polymer should degrade rapidly and safely. The biological characteristics of the PURASORB polymers make them very attractive options here.

As a final point, we may address the issue of whether any further testing for the biological safety of the PURASORB materials is required. Biocompatibility always has to be considered in the context of the precise situation in which a material will be used. The inherent biological safety, however, is dependent on the constituents of a biomaterial and the manner in which these constituents or their derivatives are released into the tissue environment. The PURASORB polymers have been evaluated exhaustively by numerous tests, both within the ISO guidelines and in other situations; since no concerns arise from these pre-clinical tests, it is suggested that nothing would be gained by carrying out further testing on these previously validated materials.

6 Conclusions

This review of the properties of the polylactide, polyglycolide and caprolactone based polymers, and especially their biological properties, has clearly shown that they provide excellent material platforms for an increasingly wide variety of medical and pharmaceutical applications. These materials have several decades of proven clinical success in areas of trauma and reconstructive surgery, sports medicine and pharmaceutical technology. They have been tested extensively according to established International Standards, and indeed subjected to many different types of evaluation and investigation. They have been approved for clinical use in many situations, and in many regulatory jurisdictions. The basis for their excellent clinical performance lies in their chemical structure, which allows for hydrolysis and complete resorption under physiological conditions, coupled with versatility with respect to mechanical properties and process technologies. The degradation and resorption processes, although inevitably being associated with some degree of cellular response, are well tolerated by tissues, and lead, in the vast majority of patients, to excellent clinical outcomes. Their biological safety has been conclusively demonstrated. The available evidence clearly points to excellent general biocompatibility. In addition, in some recent developments in new areas of medicine, including tissue engineering and gene therapy, these materials may be considered to be the most attractive of all synthetic resorbable polymers in which biological functionality may be added to biological safety.

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