Structural considerations and new polymers for biomedical applications

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(Received 8 November 1984)

Polymers intended for surgical implantation must satisfy the double requirement of adequate long-term mechanical properties and surface compatibility. Earlier concepts of inertness are being modified to ascribe a more interactive role to polymers mainly resulting from studies on blood compatibility and controlled drug release. The interfacial reactions implied by interactive behaviour determine immediate compatibility whereas longer-term functional acceptance is more related to bulk properties. The relationship between these two requirements in terms of polymer structure is discussed with reference to new polymers in use, studies of polymer orientation and uses of polymer composites containing carbon fibre. Structural order is an important consideration for biomedical applications and when this is achieved in conjunction with composites, interesting developments are possible.

(Keywords: biomaterials; surgery; implants; interfacial reactions; polymers; compatability)

The science of polymers used for medical applications is catching up slowly with the applications, mainly in areas of polymer chemistry rather than technology or material science. The applications have been dominated by the suitability of available materials and only in recent years have there been serious attempts to use chemical modification to make materials specifically for a particular use. The exception was the development of hydrophilic poly-(hydroxyethyl methacrylate) – polyHEMA – for contact lenses by Wichterle[1].

The development of prostheses for total joint replacement is a good illustration of the way the process of polymeric materials selection has worked, by a series of sometimes spectacular 'mistakes' which, fortunately, did not damage the process. In another context words of Bertrand Russell are applicable '...an important truth, namely that the worse your logic, the more interesting the consequences to which it gives rise'[2].

Apart from early uses of foreign materials the first modern milepost was the use of poly(methyl methacrylate) by Judet[3] to make a replacement for the head of the femur. This 'petit champignon' failed in two ways. It cracked at the junction between the metal stem insert and the acrylic and the bearing surface crazed and abraded. Apart from the breakage there were adverse tissue reactions. This served to demonstrate that the form in which a plastics material was introduced to the tissues determined the cellular response and in this case the abraded particles were unacceptable, whereas the bulk material was well tolerated, as other uses showed. It was of course the wrong material for a bearing surface. The next milestone was the use by John Charnley of poly(tetrafluorethylene) (ptfe) as the acetabular cup component of a total hip prosthesis, articulating against a stainless steel ball which made the opposite component of the bearing. Rapid abrasion and severe tissue reactions led to the abandonment of this system after about 100 had been put into patients. Ptfe is well accepted in the body in fibre or other forms for situations in which wear does not occur.

In the meantime, the all-metal prosthesis was being developed by McKee but Charnley did not abandon his concept for a low friction joint and turned to ultra high molecular weight polyethylene (UHMWPE-RCH1000) for the acetabular component. Both femoral and acetabular components were grouted in using a room temperature hardening acrylic based on a suspension polymerized poly(methyl methacrylate) powder containing unreacted peroxide and a monomer activated with dimethyl *p*-toluidine. The dough resulting from mixture of the two is packed into the bone cavities followed by insertion of the prosthetic components[4]. Hardening in 5–6 min is accompanied by an exothermic temperature rise and liberation of free monomer into the blood stream[5]. Both effects are undesirable leading to cell death and blood pressure decrease. The former does not appear to be a problem and in fact the new fibrous tissue growth replacing the dead cells may act in the same supporting way as the periodontal membrane serves for teeth. Careful anaesthesia controls the blood pressure effect. Bactericidal effects of the monomer have been studied[6]. Several variants in cement and application technique are now available.

The UHMWPE-metal-acrylic combination is now a well-accepted system for different joint prostheses although deficiencies are recognized. In the hip joint more than 20 years service has been reported but wear and creep are observed in UHMWPE. This is a greater problem in other joints (*Figure 1*) in which loadings are more severe and complex[7] and carbon fibre reinforcement has been used but optimization of mechanical properties may reduce the wear characteristics[8]. Acrylic cement fragments and this can lead to loosening and possibly failure. As many as 20% of acetabular components are estimated to loosen and it is believed that loosening may be the major problem to be resolved in joint replacement surgery.

For these reasons changes in the components are proposed with alumina ceramic or silicon carbide replacing the metal ball to reduce the frictional component and cementless fixation being achieved by changing surface characteristics or structure to encourage tissue ingrowth. Additionally, the gross mechanical

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mismatch between device and tissue is being overcome by the developments of so-called 'iso-elastic' prostheses using polyacetal[9] or of carbon fibre composites[10].

This brief review of one line of development in implant surgery emphasizes the engineering materials approach towards using plastics materials in load-bearing applications. These are only a part of the spectrum[11] (*Table 1*). However, this approach has been apparent in other surgical areas. Vascular prosthesis development concentrated on a non-kinkable tube which was leakproof but permitted tissue ingrowth and did not block up with thrombi. The problems were more those of textile technology than polymer science once polyester (Dacron®) was found to be suitable. It is only more recently that the subtle chemistry affecting thrombus production at foreign surfaces has begun to be understood although the pioneer work of Gott[12] in attaching heparin to polymer surfaces must be acknowledged as preparing the way for this.

Similarly, in heart valve prosthesis design major attention has focused on the flow dynamics of the valve although the problems encountered with silicone rubbers and the adverse effects of blood lipid absorption showed up the influence of other factors.

The search for materials which were mechanically durable and blood compatible for use as vessel and valve replacements and latterly for the implantable ventricular assist device or artificial heart has concentrated much more attention on surface properties – in particular the study of reactions at the interface between synthetic material and tissue has become more significant.

BIOCOMPATIBILITY

Any attempt to study the factors which determine the suitability or otherwise of a material for medical use reveals a complex problem which encompasses more than the usual material design interactions. These interactions may indeed be a first consideration and therefore will require a knowledge of structure–property relationships. The broad classifications of macromolecules into elastomers, plastics and fibres is an expression of the underlying molecular basis for these groupings but in the classical approach to implant material selection with plastics little attention has been given to this molecular basis[11]. Phenomenology governed much of the earlier selection processes and to a certain extent this is still apparent in the use of the term 'biocompatible', often taken to express biological reactions caused by the material. It is much broader than that. The action of the implant on the tissues is complemented by that of the tissues on the implant[13]. *Figure 2* shows that, of these two aspects, the former is governed primarily by surface interactions since the initial reaction is one of protein deposition which will be affected by surface energy considerations. These determine the way in which the protein bonds to the surface, thus the extent of its denaturation and the 'naturalness' of the consequent interface presented to the external environment. Bulk polymer properties are secondary in so far as leaching of components or degradation are longer-term events. The latter aspect is primarily a bulk effect since it is degradative processes (hydrolysis, oxidation, enzymic) that represent the effects of long-duration exposure to body media upon the polymer.

Imposed on the above considerations are those of functional acceptability. Wear resistance and fatigue properties must be adequate but the mechanical interaction with tissue will also affect the result. Correct transmission of pulsatile flow in a blood vessel, or the time-dependent properties of a tendon illustrate well the close relationship between structure, mechanical properties and function. One attribute of acrylic bone cement is that it provides a layer of intermediate elastic modulus between bone and metallic implant which distributes stress more evenly (*Figure 3*).

Only when a plastics material satisfies all these criteria can it be judged biocompatible and then only for a particular site and application as Black points out[14]. The

Table 1 Typical applications of polymers in medicine

Load bearing	–	Composites, polyethylene
Moving parts	–	Polyethylene (UHMW)
Blood contact	–	Polyurethane (segmented)
Soft tissue	–	Silicone elastomers
Ophthalmic	–	Acrylics, hydrogels, silicones
Disposables	–	PVC, polystyrene, polycarbonate, acrylics

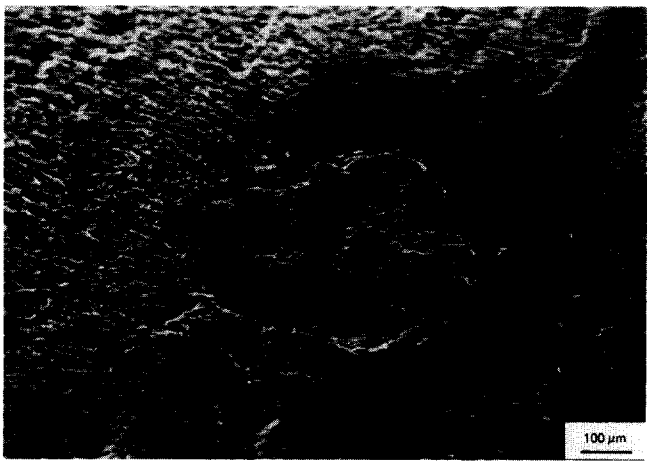

Figure 1 Typical wear in ultra high molecular weight polyethylene taken from the tibial component of a knee prosthesis. Note particle in process of dislodgement

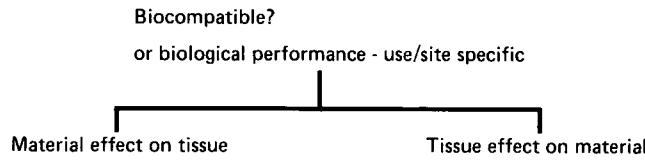

Figure 2 Factors in biological performance assessment

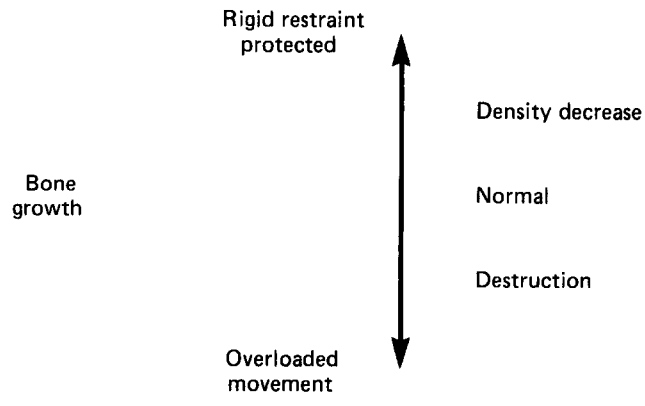

Figure 3 Mechanical effects on bone growth

orthopaedic experience with poly(methyl methacrylate) referred to earlier illustrates the point.

Identification of biocompatible or 'biological performance'[14] with inertness is a misconception. There is no truly inert implant material in the sense of chemical inertness but it is the level of interaction that is important (*Figure 4*). A 'benign reactivity'[15] implies that the reactivity is appropriate to the intended use. It may be a high level in a macromolecular drug but low in a joint replacement. Generally for implants used for reconstruction or repair it is hoped that the adjacent tissues will act as they would if no implant were present, following the initial reactions to surgery.

The body's own macromolecular biomaterials are not inert yet are obviously acceptable. Collagen, for example, has a very specific reactivity as calcification studies on reconstructed forms show[15]. The 640 Å repeating structure is the only conformation that will calcify. The molecular weight of the basic collagen unit, tropocollagen is ≈ 300 000 and it appears to be a rigid rod 3000 × 14 Å in size. It is a triple coil structure (*Figure 5*), stabilized by various cross linkages which may well account for its function as a reinforcing fibre in the bone composite material. Tropocollagen units link to form fibrils which then accrete into bundles up to 5 μm in thickness.

There are distinct structural differences between collagens in bone, cartilage (including the cartilage of the growth plate in bone), blood vessels and skin. Bone collagen is classified type I, joint cartilage is type II, cartilage associated with the growth plate and length extension of bone is type III. Other types are also recognized.

Each type can be distinguished by chain composition and immunological response. In the normal process of bone fracture healing it appears that there is a progression from type II to III to I and recent work indicates that in non-healing fractures there are raised levels of type III[16]. The healing has stopped at an intermediate collagen structure possibly either because type III production was overstimulated, perhaps by excessive mechanical stimuli (movement) or that the level is normal but no substitution by type I occurred.

These observations illustrate:

1. that a biologically acceptable material is not necessarily non-reactive; and
2. that subtle changes in composition and structure can have profound effects on function (calcification in this example) and on tissue reaction (immunology).

EXTERNAL INFLUENCES ON *IN VIVO* POLYMER REACTIONS

If the premise is accepted that a biologically acceptable polymer does not need to be non-reactive in terms of immediate tissue response, then there is the possibility that other factors may also be important. Williams[17] has reviewed the ways in which inorganic entities interact with organic molecules and influence cellular activity by means of a range of feed-back control systems and switches, many of which are site- or function-specific. The membranes of cells are a mobile array of macromolecules. The various parts of the protein polysaccharide complex are affected *inter alia* by ionic flux and density, redox reactions or enzyme processes and the membrane dimensions vary to permit transport across. Conversely

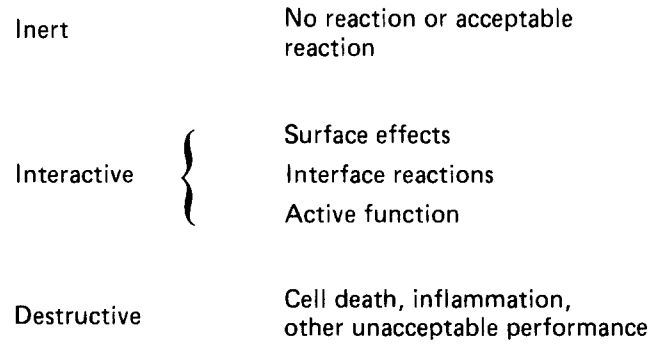

Figure 4 Types of tissue reaction

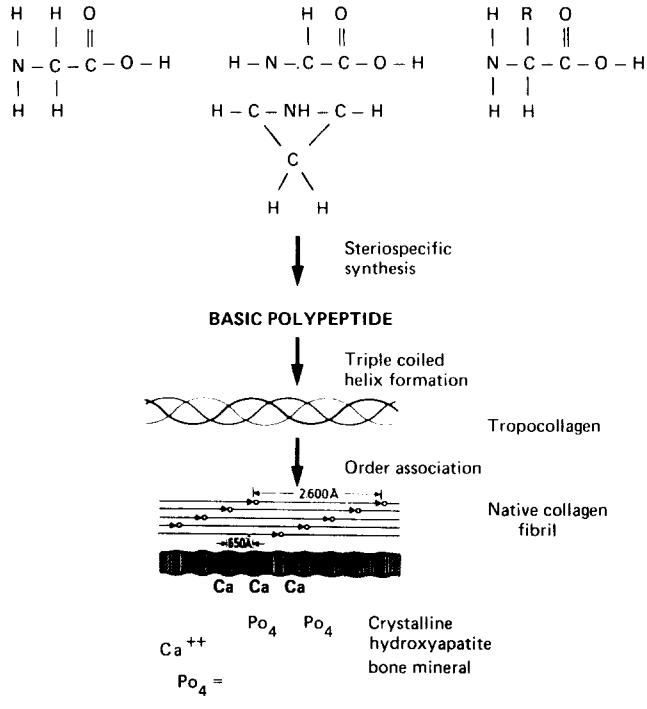

Figure 5 Collagen – a biocompatible but reactive macromolecule. Tissue acceptance does not depend on inertness

mechanical deformation would also be expected to modify transport phenomena.

These localized effects may also be influenced by more generalized external factors, e.g. why do bone cells differentiate to produce either bone-forming or bone-removing cells (osteoblasts or osteoclasts) under the influence of mechanical deformation. It is supposed that electrical fields may mediate these mechanical factors to the cells following the observations that collagen in bone is the source of its piezo-electric behaviour though other electrical responses are more likely to be significant in living situations (e.g. streaming potentials).

The studies on collagen type (see above) arose from an interest in the effect claimed on ununited fractures by external application of pulsed electromagnetic fields. The method is not without controversy[18] and the mechanism by which it can proceed is unknown. It might be by an effect on collagen formation or subsequent orientation although studies on synthetic model polymer systems and on reconstructed collagen *in vitro* showed no effect[19] with magnetic fields of the level used clinically (1–2 gauss). Higher static field strength (3000 gauss) did appear to modify collagen orientation slightly and it is known that very high ($>10^4$ gauss) fields do influence macromolecule

orientation[20]. Magnetic fields applied to poly(vinylidene-fluoride) produce electrets which have been studied for their effect on bone formation.

Conformational changes, analogous to shape memory alloy behaviour and reactivity changes initiated by external agencies introduces a new dimension into polymeric biomaterials development. Re-chargeable systems, thermal generators, magnetic field systems and modifiable drug release systems controlled in the same way as a cardiac pacemaker are all future possibilities. Biosensors which monitor and provide control of biological processes are products of multi-layer polymers on suitable substrates and with progress in Langmuir–Blodgett techniques a very powerful method is available for their development.

APPLICATIONS

Bulk polymer properties

Long-term durability *in vivo* for polymer implant materials depends mainly on the properties of the bulk material. The suitability of e.g. UHMWPE is closely dependent on the combination of linear high molecular weight molecules for its load-bearing and wear properties, whereas the crystalline, amorphous combination gives a certain degree of elastomeric-type behaviour producing resilience in the artificial joint. However, the typical creep properties of a thermoplastic material are shown which is a disadvantage.

The material used extensively in the UK is Ruhr Chemie RCH 1000 made by large-scale compression moulding of polymer powder. Prosthetic components are machined from blocks which are themselves cut from very large slabs. Experience shows a certain degree of inhomogeneity in the product. This is evidenced by regions of greater opacity, sometimes seen as bands, yellowing and whiter particles scattered throughout the sample. The method of manufacture may result in incomplete fusion of particles or regional fluctuations in extent of heating or rates of heating and cooling. Calcium stearate lubricant is used during processing and some inhomogeneities may result from incompletely blended powder. Observations of retrieved implants reveal the results of these bulk variations in the types of wear[7]. A surface delamination effect may be a result of gamma irradiation-induced changes in surface chain structure.

Attempts to modify the properties have been made by incorporating carbon fibres but there is a compromise between creep and wear performance which is unsatisfactory[8]. A fibre-polymer incompatibility was also apparent. In fact, the combination of a thermoplastic material in which the polymer matrix comprises linear very high molecular weight partially oriented chains (crystalline) and a low polydispersity is an interesting material for studying composite behaviour where a more usual matrix is a highly crosslinked resin or a glassy amorphous polymer (acrylics for example). It may be noted that some of the body tissues are of this type with protein fibres in a polysaccharide matrix. Bone has a highly crystalline inorganic matrix of calcium hydroxyapatite (calcium phosphate) and represents a different type of composite and one which has a remarkably complex internal order. A composite material which has mechanical properties suitable for use in bone has been developed from polyethylene and calcium hydroxyapatite powder[21].

Our own studies of composites have mainly concentrated on epoxy resin matrices for carbon fibre[22,23] and have been primarily concerned with the dynamic mechanical relationship between such implant materials and bone. In clinical practice used for internal fixation of fractures in the tibia and in the forearm bones, composite plates have afforded stability, more than adequate fatigue properties and, arising from the closer-to-normal mechanical strain possible at the fracture with this system, a very acceptable healing pattern.

Silicone elastomers, widely accepted for soft tissue implants are cross-linked networks with a –Si–O–Si–O– backbone carrying two methyl or sometimes other groups on the Si atoms. Although relatively non-reactive *in vivo* they are lipophilic and also have a high permeability to moisture and oxygen. The gas permeability has led to their investigation as contact lenses and membranes. Mechanical property enhancement is achieved by addition of very fine silica which is thought responsible for adverse fibrotic reactions. Permeability to a silicone gel is another source of unacceptable reactivity and there are now reports of immune reactions in certain people, and sensitization reactions[24]. Despite the criticisms, various forms of silicone polymers continue to be used effectively in implant surgery.

The effect that molecular structural modification has on polymer properties has been well utilized with polyurethanes in artificial implantable heart and blood contact areas. The balance between rigid and flexible chain segments[25] affects flexibility, flex life and dimensional stability among the requirements for this implant programme.

Most devices are made by dip casting and control of chemistry of polymerization is important to avoid bubble formation from interaction with water. Blood compatibility is a function of bulk polymer properties (to provide pumping without red cell damage), chemical methods (since bubbles provide a locus for calcification and failure by cracking) but also of surface chemistry which is a feature of chain composition.

Interfacial effects

Apart from biological acceptability which although being a cell-interaction effect is 'long range' and often rather imprecise in its consequences and interpretation, there is the consideration of specific site interactions typified in the use of polymers as carriers for therapeutic agents. The now classical representation of the polymer drug system (*Figure 6*) shows that the polymer chain carries three types of active attachment; a hydrophilic moiety as solubilizer, a transport system to assist in location to a specific tissue site and a pharmacon which is the bound therapeutic agent. These systems can operate either completely in the fluid phase or by adsorptive processes at cell sites. Such systems avoid the problems of low molecular weight drugs which can produce generalized toxic reactions. The drug is bound via a degradable link which is stable until affected by the digestive enzymes within the cells. The polymer may be taken into the cell without interaction with the cell membrane or may be adsorbed at the surface and this can be made specific to the cell type. In the cell, fusion with lysosymes occurs with the subsequent release of drug. Typical of the polymers used is poly(hydroxypropylmethacrylamide)[26] and galactose has been used to target the

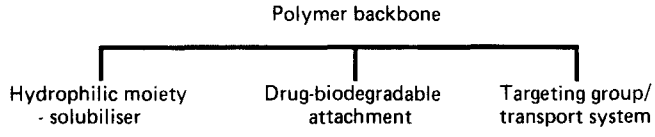

Figure 6 Schematic representation of a polymer drug

molecule to liver hepatocytes which have receptor sites.

Polymeric liposomes are being studied extensively by Ringsdorff and his co-workers[27] as carrier systems for drugs and in attempts to model cell membrane processes. Diacetylenes form the basis of the system and are polymerized in monolayers to stabilize the synthetic liposome against the cell contact. Having a stable liposome which is a polymer network makes possible introduction of moieties which will recognize cells (sugars or antibodies) and others which will destroy cells by destabilization of the membrane[27]. Incorporation of drugs into the polymeric liposome which contains a removable 'cork' has attracted interest and led to drug systems active against leukemic cells.

As discussed in detail previously by the author[28] there is still a need for an adhesive which can be used to replace sutures in delicate tissue or to assist in device fixation (*Table 2*). There are grave disadvantages with adhesives used up to the present, generally related to toxicity of components reacting together during hardening or of degradation products.

The concepts of commercial adhesives do not apply to biological uses, mainly because the substrates to which the adhesive is to be applied are aqueous, multi-component and constantly changing, a decided contrast to an engineered section. In the simplest understanding the need is for a readily polymerizable monomer which is itself non-toxic, does not require heat or other physical agencies to promote polymerization and after providing for adequate bonding is then degraded without toxic products. However, it is more subtle than that. Whereas acrylic cement works within bone as a mechanical grout some form of chemical binding is desirable to stabilize the adhesive and improve its function. Many biological adhesives are polysaccharides and the structures are far from being rigid. The structural stabilization is provided for by ionic or hydrogen bonds and by chelation processes. One of the features of living systems is the ability to respond rapidly to change and an adhesive should be designed to show similar characteristics in terms of the bonds by which adhesion is obtained. It would therefore seem that the principles being applied to drug transport and targetting could be applied equally successfully to adhesives.

SUMMARY

Biological use of polymers has advanced far beyond the initial concept of them as 'inert' replacements. Even though the mechanisms of biological acceptability (referred to as biocompatibility) are imperfectly understood, a significant part is played in implant surgery by several polymers. However, when bulk structure and surface reactivity are considered in more depth the control of interfacial reactions is possible. Polymers are therefore moving from a purely passive to a more interactive, even aggressive role. In drug therapy, systems are now in use based on polymers. The related field of biotechnology has an actual and potential use for polymers in the various stages of genetic and cell engineering to produce diagnostic or therapeutic agents, as well as in other processes. This is one of the most interesting areas and takes polymer chemists into interdisciplinary areas. In engineering there are still possibilities in composite materials with highly structured matrix polymers.

Table 2 Possible uses of surgical adhesives

Implant attachment	–Cementless –Sutureless
Vessel anastomosis	
Nerve repair	
Haemostasis	
Wound closure	
Skin attachment of devices	
Small bone fragment fixation	
Maxillo facial region	

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