Chapter One

Biomaterials

1.1 Introduction

Biomaterials may be defined as those engineered materials used specifically for medical applications. Biomaterials share with all other engineering materials the classification into the traditional categories of metals, ceramics, polymers and composites. The history of biomaterials can be represented by the use of metallic implants. Metallic alloys like Co-Cr alloys, 316L stainless steel and Ti alloys have found application in orthopedics. Polymers are another category of materials widely used for biomedical applications. From linen sutures for closing wounds 4000 years ago to modern tissue adhesives, heart valves and lenses, biopolymers have found wide-ranging application.

1.2 Requirements for Biomaterials

Replacement for worn or injured body parts is the area wherein biomaterials are predominantly used. Artificial joints require complete body stability and biocompatibility. This holds for the implant as well as the wear debris. High mechanical strength, particularly fatigue strength is required and for the articulating parts, high wear resistance is also necessary. The joints are also required to bear high loads. In addition to structural requirements being met by the material under consideration, survivability of the material is an important aspect that has to be taken into account. Implants which replace body parts have to survive for long periods, typically more than 20 years, under

conditions of use that are especially harsh: corrosive saline body fluids under varying multiaxial and cyclical mechanical loading.

1.3 Biocompatibility

In addition to satisfying the mechanical requirements for the application, if a material is to be used as a biomedical device, it will have to have a specific set of properties [1]

- The material should be non-toxic
- The device should be stable during implantation
- The material should not corrode or degrade *in vivo*; and
- The material should not be carcinogenic

The biocompatibility of the material is tested by the means of *in vivo* and/or *in vitro* tests.

In vivo tests involve testing by actual implantation in humans or animals. *In vitro* tests on the other hand, use tissue and cell cultures to determine the biocompatibility of the material. To mimic the environment in which the material will have to survive, it is also exposed to Simulated Body Fluids (SBF) and saline environments. If the application so requires, the material is also tested in acidic and basic environments to gauge the extent of degradation, if any. *In vitro* biocompatibility testing is used because it is less complicated, cheaper and more reproducible.

Chapter Two

Bioceramics

The use of ceramics for biomedical applications is a relatively recent phenomenon. The inherent brittleness of ceramics has limited their competition with ductile metals and polymers. Advances in ceramic processing have contributed to increased possibility of modifying the materials for use in biomedicine.

Bioceramics are used for the repair and reconstruction of diseased or damaged parts of the musculo-skeletal system. These materials include alumina, zirconia, hydroxyapatite and other calcium phosphate materials, bioactive glasses and glass ceramics.

Orthopedic bioceramics provide the advantage of chemical similarity to natural skeletal materials. Bone is 43% by weight hydroxyapatite, a common ceramic mineral. This has led to the widespread use of ceramics in restorative dentistry and repair of bone defects including hip and knee replacements.

2.1 Ceramic Tissue Interaction

The bioceramic must form a stable interface with body tissue to achieve attachment to the musculo-skeletal system. There are four types of response that the body may have to the implant material – [2]

1. If the material is toxic and surrounding tissue dies

2. If the material is non-toxic but biologically inactive, a non-adherent capsule of tissue is formed around the implant
3. If the material is non-toxic and biologically active, a coherent interfacial bond is formed by the body with the implant
4. If the material is non-toxic and dissolves, tissue grows to the surface of the material to replace it

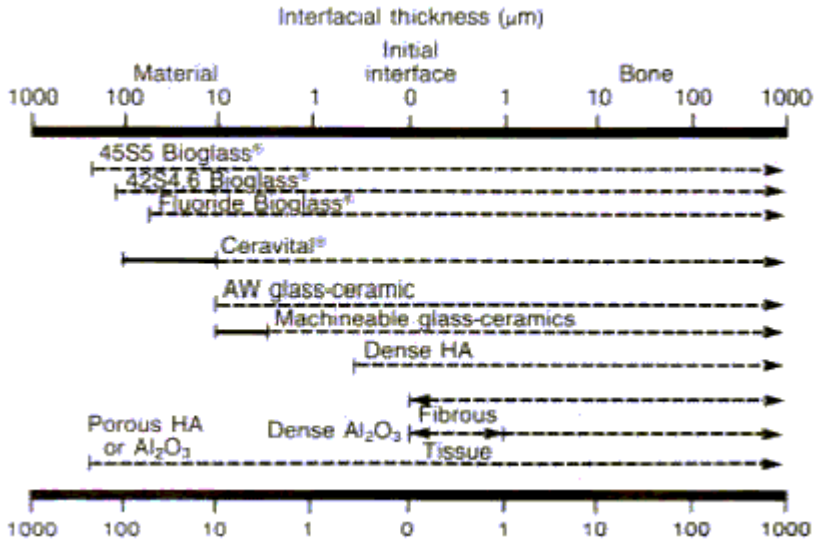


Figure 2.1 Comparison of interfacial thickness of reaction layer of bioactive implants or fibrous tissue of inactive bioceramics in bone [2]

2.2 Classification of Bioceramics

The relative reactivity of the material influences the thickness of the interfacial zone between the tissue and the implant. When the interface is not chemically or biologically bonded, there is relative movement which eventually leads to deterioration in function.

The following table lists the classification of bioceramics based on tissue response –

Table 2.1 – Types of Bioceramic tissue attachment and bioceramic classification [2]

Type of attachment	Type of bioceramic
Non-porous, almost inert ceramics attach by bone growth into surface irregularities cementing the device into the tissue or by press fitting into a defect (morphological fixation)	Al_2O_3, ZrO_2
Porous implants; bone ingrowth mechanically attaches the bone to the tissue (biological fixation)	Porous Hydroxyapatite
Surface reactive ceramics, glasses and glass-ceramics attach directly by chemical bonding with the bone (bioactive fixation)	Dense Hydroxyapatite, Bioactive glasses and glass-ceramics
Resorbable ceramics and glasses designed to be slowly replaced	Tricalcium Phosphate, Calcium Phosphate and its' salts

2.2.1 Inert Bioceramics

The fibrous capsule at the interface with dense Al_2O_3 implants can be very thin. Consequently, Al_2O_3 implants that are implanted with a very tight mechanical fit are very successful. In contrast, if an inert implant loaded such that interfacial movement can occur, the capsule can become a few hundred micrometers thick leading to loosening of the implant.

2.2.2 Porous Bioceramics

The concept behind micro porous bioceramics (type 2 in Table 2.1) is the ingrowth of tissue on the surface or throughout the implant. The increased interfacial area results in increased resistance to movement of the device. This method of attachment is termed "biological fixation".

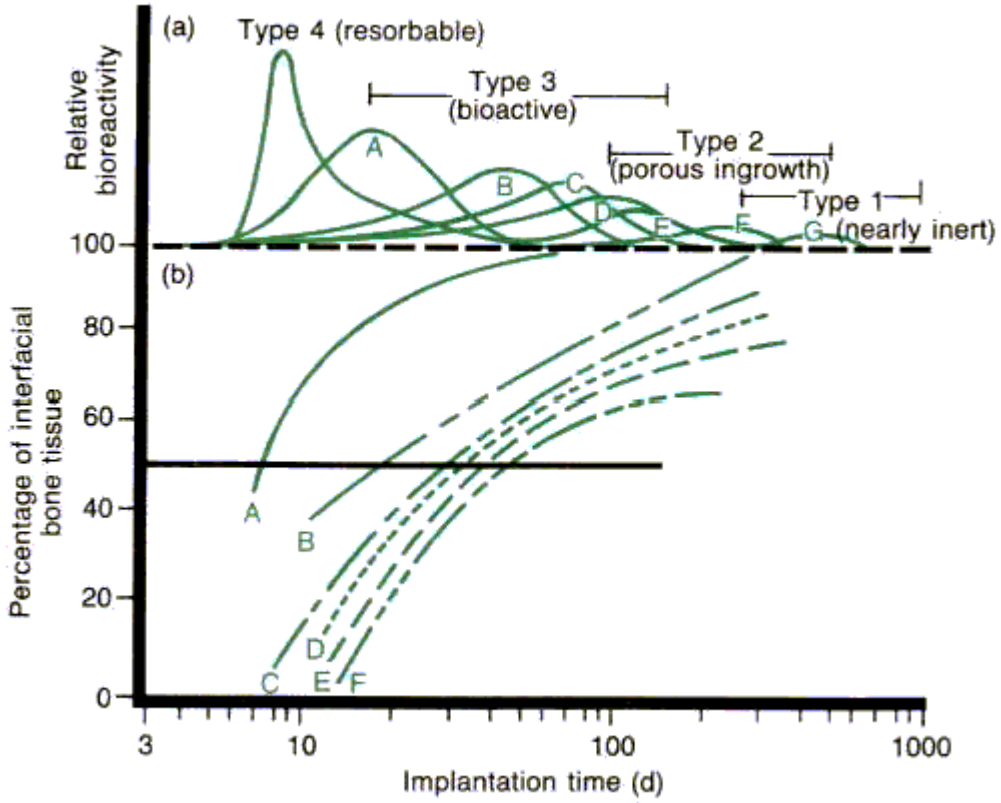


Figure 2.2 – Reactivity of Ceramic Biomaterials [2]

2.2.3 Resorbable Bioceramics

Resorbable biomaterials (type 4 in Table 2.1 and type C in Figure 2.1) are designed to degrade gradually and be replaced by host tissue. This leads to a thin or non-existent interfacial thickness and is the optimal solution to biomaterial problems. However, there are complications in the development of resorbable ceramics –

- Maintenance of interface strength and stability during the degradation period
- Matching rates of resorption to repair rates of body tissue, which vary enormously depending on the age and condition of tissue.

Resorbable tricalcium phosphate (TCP) has been successfully used for hard tissue replacement in repair of the jaw.

2.2.4 Bioactive Materials

Bioactive materials (type 3 in Table 2.1 and type B in Figure 2.1) are intermediate between inert and resorbable materials. *A bioactive material is one that elicits a specific biological response at the interface of the material that results in the formation of a bond between tissues and the material.* [3] Bioceramics with a wide range of bonding rates and interface layer thickness have been produced. Commercially available bioactive materials include Bioglass and apatite-wollastonite (AW) glass ceramics. It is important to recognize that small variations in composition can dramatically change the behavior of the material from bioinert to bioactive or resorbable.

Chapter Three

Inert Bioceramics

The most commonly used bioinert ceramics are alumina and zirconia-yttria ceramics. Alumina finds application in hip replacement and dental restoration while zirconia is used to manufacture ball heads for Total Hip Replacement.

There are some important prerequisites for a material to be selected for hip replacement applications, namely [4] –

- precise geometry and no change in geometry under corrosive body conditions
- high stiffness (i.e. Young's' Modulus)
- no porosity
- high density
- good surface finish

Both alumina and zirconia biomaterials are attractive for hip replacement applications.

3.1 Alumina Bioceramics

Alumina bioceramics are widely used in dental and implant applications because they satisfy the mechanical considerations required by a biomaterial as discussed in Section 1.2 The strength requirements can only be met by high-purity, high-density alumina ceramics with small grain size. High density is also important because each pore acts as a notch reducing the strength and influencing the sensitivity to body fluids.

3.1.1 Mechanical Properties

Strength, fatigue resistance and fracture toughness of polycrystalline alumina are a function of grain size and concentration of sintering aid. Al_2O_3 with and average grain size of < 4 um and a purity of >99.7% exhibit good flexural strength and excellent compressive strength. The mechanical properties of clinically used alumina ceramics are listed in Table 3.1

High concentrations of sintering aids must be avoided because they remain in the grain boundaries and degrade fatigue resistance especially in the corrosive physiological environment. Al_2O_3 devices implanted with a tight mechanical fit and loaded primarily in compression are successful clinically.

3.1.2 Applications

Alumina based ceramics are used in both dental as well as orthopaedic applications. Dental implants differ from orthopaedic implants by the fact that one part of the implant is outside the tissue in the oral cavity. In this environment they are exposed to fluids with varying pH values, ranging from acidic to basic. Therefore metal dental implants are highly susceptible to attack.

In order to protect the implant, attempts were made to cover the metallic implants with a layer of alumina. However, since the layers are porous, the protection is insufficient and the bond strength between the ceramic layer and the metal is low. High purity alumina ceramics have proved successful for dental implants. They offer a high corrosion

resistance leading to excellent biocompatibility. Another important advantage of alumina ceramics is that in contrast to metallic implant materials, no plaque or concrements can be deposited on the surface of the implant thus eliminating a major cause of inflammation.

3.2 Zirconia Bioceramics

Zirconia ceramics have several advantages over other ceramic materials due to the transformation toughening mechanisms operating in their microstructure. Good chemical and dimensional stability, mechanical strength and toughness was the origin of the interest in using zirconia as a bioceramic.

3.2.1 Microstructural properties

Zirconia is polymorphic and occurs in monoclinic (M), cubic (C) and tetragonal (T) forms. The monoclinic phase is stable upto 1170 °C above which it transforms into T and then to C at 2370 °C. The phase transformation during cooling is associated with a volume change of 3-4%.

The addition of stabilising oxides like CaO, MgO, CeO_2 and Y_2O_3 to pure zirconia allows the generation of multiphase materials known as Partially Stabilised Zirconia (PSZ) which comprise cubic zirconia as the major phase at room temperature. Monoclinic and tetragonal precipitates are present as the minor phase. In the ZrO_2-Y_2O_3 system, it is possible to obtain ceramics at room temperature with the tetragonal phase only called Tetragonal Zirconia Polycrystal (TZP). The mechanical properties of the TZP ceramics depend on the grain size and yttria content.

Several PSZ were tested as ceramic biomaterials especially Mg-PSZ which was tested extensively with favourable results. However, Mg-PSZ is characterized by a residual porosity which can influence negatively the wear rates of Ultrahigh Molecular Weight

Polyethylene (UHMWPE) sockets which were coupled with the ball heads made from zirconia. Mg-PSZ also sinter at higher temperature than TZP (1800°C vs. 1400°C) which would require special furnaces making it a little unfeasible. This, coupled with difficulty in obtaining the precursors free of SiO_2, Al_2O_3 and other impurities contributed towards the shift towards TZP materials.

3.2.2 Mechanical Properties

The mechanical properties of zirconia ceramics are better than other ceramic biomaterials as shown in Table 3.1.

Property	**Units**	**Alumina**	**Mg-PSZ**	**TZP**
Composition		99.9% Al_2O_3 +MgO	ZrO_2 +8-10%MgO	ZrO_2 +3%Y_2O_3
Density	g cm^{-3}	>3.97	5.74-6	>6
Porosity	%	<0.1	-	<0.1
Bending Strength	MPa	>500	450-700	900-1200
Compression Strength	MPa	4100	2000	2000
Young Modulus	Gpa	380	200	210
Fracture Toughness	M Pa m^{-1}	4	7-15	7-10

Table 3.1 Characteristics of some bioceramics [5]

The fracture toughness of zirconia ceramics also depends on the amount of stabilizing oxide added. Figure 3.1 depicts the variation in the fracture toughness of zirconia with the amount of yttria added to the material.

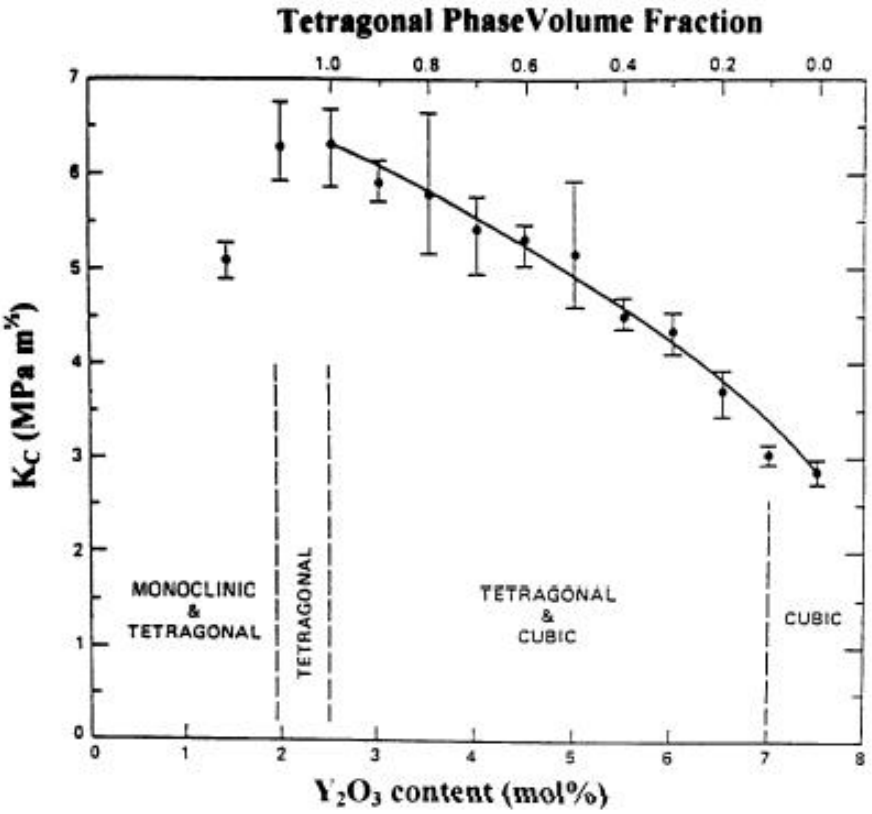


Figure 3.1 Fracture toughness vs. yttria content [5]

The stability of the zirconia microstructure is vital to the success of TZP based implant materials. Mechanical degradation, known as “ageing”, is due to the spontaneous transformation of the metastable tetragonal phase into the monoclinic phase.

Results of ageing tests conducted in water allow to predict a 25 year ageing period at 37°C to reach 20% M content. This lifetime is more than adequate for orthopaedic implants. [6]

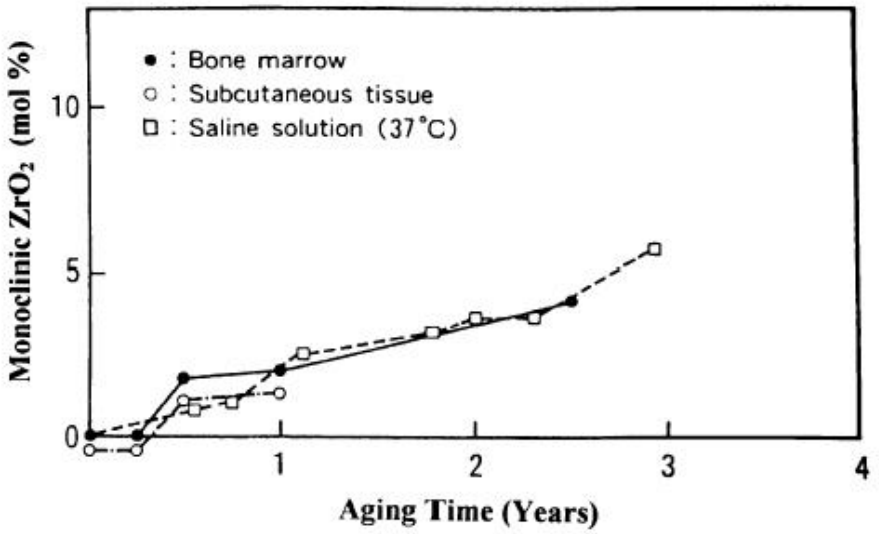


Figure 3.2 Tetragonal to monoclinic transformation of TZP in vivo and in saline medium [6]

The extent of strength degradation of TZPs in wet environments depends on the material microstructure and can be controlled by acting on the material manufacturing process. Evidence shows that TZP ceramics are able to maintain good mechanical properties in wet environments for expected implant lifetimes. Zirconia ceramics are however unsuited for use in an acid environment such as the oral cavity because yttrium and zirconium ions are released in such environments.

3.3 Zirconia Toughened Ceramics

The term Zirconia Toughened Ceramics (ZTC) represents a wide class of materials and microstructures. Besides PSZ and TZP, another promising bioceramic is Zirconia Toughened Alumina (ZTA).

ZTA structures can be formed by a fine and uniform dispersion of T-phase zirconia in the alumina matrix. Alternatively, metastable zirconia polycrystals may be introduced into the alumina matrix. In both cases, the zirconia concentration in the alumina is controlled so that the stresses due to the phase transformation of zirconia do not compromise the strength of the ceramic (Figure 3.3).

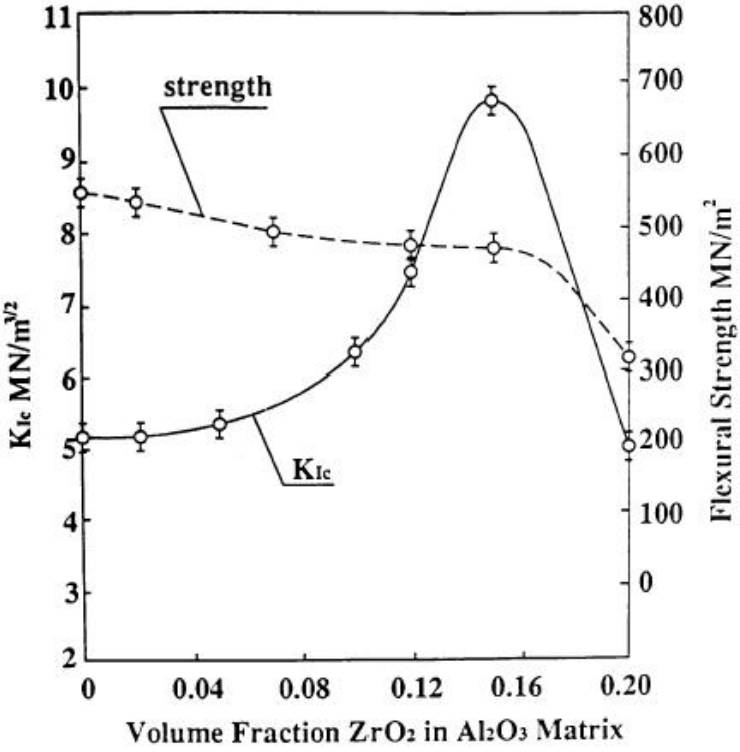


Figure 3.3 Strength of ZTA as a function of zirconia content [5]

Composites with hydroxyapatite (HAp) as the matrix and zirconia as the second phase have also been tested. Depending on sintering conditions and the final density and porosity, it was demonstrated that a maximum bending strength ranging from 100 to 150 MPa could be achieved. However, these materials degrade mechanically in wet environments and have therefore not yet found widespread clinical application.

Chapter Four

Glass Ceramics

Glass-ceramics are polycrystalline ceramics formed by controlled crystallization of glasses. In 1969, certain compositions of glasses and glass ceramics in the Na_2O-CaO-P_2O_5-SiO_2 system were discovered to form a mechanically strong bond to bone. [7] This behaviour, termed "bioactive bonding" is in marked contrast to that of other implant materials which elicit the formation of a thin fibrous capsule which isolates the implant from the bone.

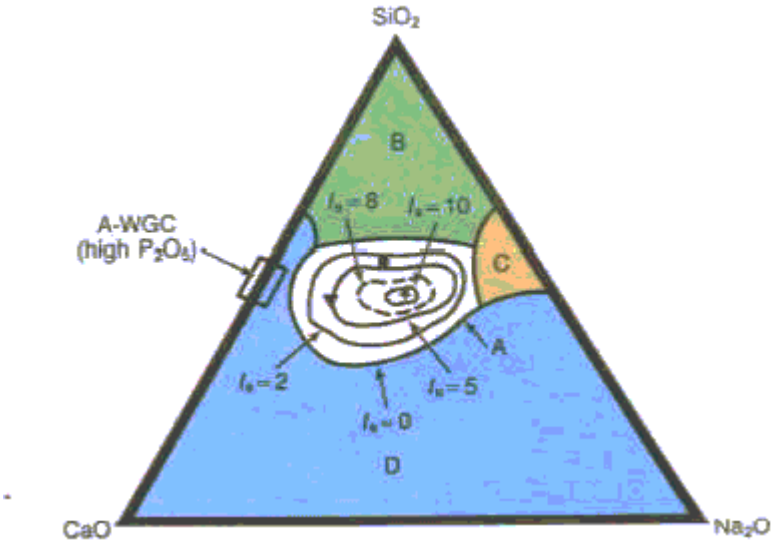
4.1 Mechanism of Bioactive Bonding

Analyses showed that the bioactive bonding was due to the formation of a layer of hydroxyapatite (HAp). Carboxyl bonds of collagen fibril end groups with calcium and phosphate sites on HAp crystals provided strong mechanical adherence. Further work showed that the bioactive material, termed Bioglass®, released soluble Si, Ca and P ions into solution very rapidly due to both ion exchange with H^+ and H_3O^+ and by silicate network dissolution. [7]

4.2 Formation of Glass-Ceramics

Two glass ceramics have been developed for implants, SiO_2-Cao-Na_2O-P_2O_5 and Li_2O-ZnO-SiO_2. Within the former system, the extent of implant-bone bonding which is observed is dependent on the composition. The bonding is related to the formation of calcium phosphate and a SiO_2 rich film on the material.

Figure 4.1 Composition boundaries for SiO_2-Cao-Na_2O bioactive glasses [7]



Compositions in the middle of region A form a bond to bone and hence this is termed the bioactive bone boundary. Glasses within region B elicit the formation of a fibrous capsule and those within region C are resorbable and disappear completely.

The glass ceramic which has found maximum clinical application is the three phase silica-phosphate material composed of apatite [$Ca_{10}(PO_4)_6(OHF_2)$] and wollastonite [CaO.SiO2] crystals and a residual glassy matrix rich in CaO-SiO_2. This material, termed A/W glass ceramic has excellent mechanical properties (Table 4.1) and forms a bond with bone which has a very high interfacial bond strength.

4.3 Properties

Table 4.1 outlines the composition and properties of some common glass ceramics.

Ceramic	SiO_2	Na_2O	CaO	P_2O_5	MgO	CaF_2	Young's Modulus	Strength	Density	Fracture Toughness	Hardness
Bioglass® (45S5 Glass)	45.0	24.5	24.5	6.0			35.0	42.0 (T)	2.66		458±9.4
Cervital (Glass-Ceramic)	40-50	5-10	30-35	10-50	2.5-5		100-150	500 (C)			
Cerabone (AW) Glass Ceramic	34		44.7	16.2	4.6	0.5	118	215(B) 1080(C)	3.07	2.0	680

(T) Tensile Strength (C) Compressive Strength (AW) Apatite Wollastonite (B) Bending

Table 4.1 – Composition and Properties of selected Glass Ceramics [7]

4.4 Applications

Bioactive glass-ceramics are used in three forms depending on the clinical function required: bulk, coatings, powders or composites.

4.4.1 Non Load Bearing Implants

Bulk Bioglass® implants have been used clinically for years as middle ear prostheses. There is very little tensile stress in the application and therefore mechanical strength or fatigue resistance is not a very important criterion. Only a narrow range of bioactive glass compositions form a bond with the collagen fibers of soft connective tissue. These typically fall in region A of figure 4.1

4.4.2 Load Bearing Implants

High strength bioactive apatite-wollastonite (A/W) glass ceramics are used for vertebral reconstruction in tumour patients. Developed by T. Yamamuro and T. Kokubo's

groups, A/W ceramics have a very uniform microstructure with small grain size and are resistant to interphase boundary attack. The mechanical properties of this material are excellent and it is widely used for clinical applications.

4.4.3 Bioactive Composites [7]

No implant material used matches the mechanical properties of bone. Orthopedic metals and alloys are much stiffer than bone and when they are used as implants, the bone is shielded from stress and resorbs. A solution to this is to use composites with a matrix of low elastic modulus and high strain to failure and a dispersed second phase with high elastic modulus. By use of bioactive fibres (HAp or Bioglass®) as the second phase it is possible to produce an anisotropic elastic modulus in a bioactive composite similar to that of bone. The uncertainty regarding composites is their reliability under cyclic fatigue in a corrosive physiological environment.

The major drawback for glass-ceramics is the restriction on composition for biocompatibility which prevents modifications for improvement in mechanical strength.

4.5 Novel Glass-Based Biomaterials [8]

Glass ceramics containing ferrimagnetic or ferromagnetic crystalline phases in a nearly inert or bioactive matrix are useful as thermoseeds for hyperthermia treatment of cancers. They are compatible with living tissue. When implanted around malignant tumours and placed under an alternating magnetic field, the tumours are locally heated up to temperatures above 43°C by magnetic hysteresis losses. This is effective for cancer treatment. A glass ceramic containing lithium ferrite ($LiFe_3O_8$) in a Al_2O_3-SiO_2-P_2O_5 glassy matrix precipitating a small amount of haematite (α-Fe_3O_4) in a CaO-SiO_2 glassy matrix precipitating wollastonite has been developed for this purpose.

Chemically durable glasses containing Y or P at high level are useful as radioactive seeds for in situ radiation of cancers. Microspheres 20 to 30 μm in size are entrapped in

the capillary bed of the tumours. When activated, they give large local radiation doses with little irradiation to the neighbouring normal tissues. If chemical durability of the glasses is high, the radioactive material is hardly released. A glass of the composition Y_2O_3 40, Al_2O_3 20, SiO_2 40 wt% shows high chemical durability and can easily be formed into microspheres.

Chapter 5

Hydroxyapatite

Hydroxyapatite (HAp, chemical formula $Ca_{10}(PO_4)_6(OH)_2$) is the main constituent of teeth and bones. HAp ceramics show excellent biocompatibility and can bond directly to the bone. However, its mechanical properties do not permit its use in heavy-loaded implants.

5.1 Dense HAp Ceramics

Preparation of pure dense HAp ceramics with superior mechanical properties is possible if the starting HAp powder is stoichiometric i.e. the Ca/P molar ratio is about 1.67 If the ratio exceeds this value, CaO forms during sintering and leads to a decrease in strength of the material and may even cause decohesion from stresses due to the formation of $Ca(OH)_2$. If the Ca/P molar ratio is lower than this value, β or α tri-calcium phosphate [TCP, $Ca_3(PO_4)_2$] forms. The presence of TCP increases slow crack growth susceptibility and biodegradability.

Low values of fracture toughness and high susceptibility to crack growth indicate low reliability of dense HAp implants. Therefore dense HAp implants are used in dentistry only as unloaded root substitutes. Presently, one of the most important applications of

dense HAp implants is as percutaneous devices for monitoring blood pressure and sugar or optical observation of body tissue.

5.2 Porous HAp Ceramics

Porous HAp exhibits strong bonding to the bone and is widely used as a bone substitute. Moreover, the pores provide a strong mechanical interlock leading to firmer fixation of the material. Bone tissue grows well into the pores and increases the strength of the implant. A minimum pore size is required to enable blood supply for bone ingrowth. These pores are typically 100 μm and decrease the strength of the implant significantly. Thus, porous HAp ceramics cannot be heavy loaded and are used to fill only small bone defects.

Bending strength, compressive strength and tensile strength of available porous HAp implants are in the range of 2-11 MPa, 2-100 MPa and 3 MPa respectively. Both strength and fracture toughness depend on the porosity as is illustrated by Figure 5.1 It is also important to note that porous HAp ceramics are less fatigue resistant than dense HAp ceramics.

5.3 HAp based Composites

HAp applications are limited by its low mechanical reliability. Preparation of HAp based composites can solve the problem since the composites can be fabricated to control the bioactivity, biodegradation and other biological properties of the implant.

5.3.1 Ceramic Composites

Many reinforcements including particles, whiskers, platelets, long fibres, partially stabilized zirconia and nano-particles have been used in HAp ceramics to improve its reliability. An advantage of the composite approach is an increase in the toughness and strength of the ceramics. However, inclusion of foreign materials may affect the biocompatibility and may promote the decomposition of HAp with the formation of TCP. Many ceramic materials like Al_2O_3, ZrO_2 and SiC have been used as reinforcements in HAp due to their corrosion and wear resistance and minimal tissue interaction.

5.3.2 Bioactive Glass Composites

Bioactive glasses exhibit high biocompatibility and have excellent bone and tissue bonding properties. The combination of bioactive glasses with HAp results in bioceramics with improved mechanical properties without degradation of biocompatibility and/or bioactivity. Composites with wollastonite and HAp as the crystallized phases exhibit strength of 100-200 MPa, K_{Ic} of 1.0-2.6 MPa $m^{1/2}$ and fracture energy of 6-26 J/m^2. They maintain strength for a longer duration than HAp. [9]

5.4 HAp Coatings

The use of HAp as coatings for metallic implants is a widespread and very useful clinical technique. This concept combines the mechanical advantages offered by the

metal alloys and the excellent biocompatibility and bioactivity of the HAp material. The HAp coatings fulfil several functions and most important of all, they provide stable fixation of the implant to bone and minimize adverse reaction by providing a biocompatible phase. Moreover, the HAp coatings prevent the release of metal ions from the implant and shield the metal surface from environmental attack. In case of porous metal implants, HAp coating enhances the ingrowth of bone.

HAp based biomaterials most importantly, HAp coated implants and HAp composites have found widespread clinical application owing to the excellent combination of mechanical properties and biocompatibility. Microstructurally controlled HAp ceramics and HAp reinforced polymers seem to be the most suitable ceramic materials for future applications in biomedicine.

Summary and Future Directions

Ceramics have become an integral part of orthopaedic medicine. With a theoretical foundation in place, a basis now exists for the development of a new generation of bioceramics. With the ability to tailor microstructure, composition and surface chemistry of the material, bioceramics can be produced to match the specific biological and metabolic requirements of the tissue or disease states. Coupled with tissue and genetic engineering, sensor technology and information processing, an unimaginable range of biomaterials could be produced to provide better relief to diseased and injured patients.

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