

Bioceramics — Clinical and Pharmaceutical Applications

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Bioceramics are widely used as implant materials in orthopaedics. Previously known to be materials in oxidized state, their use is well established now-a-days. In the present review main focus is on their compositions and types. Their behaviour upon implantation is discussed along with the chemical reactions taking place. Various factors affecting the interface formation are also discussed. These clinically important materials are being used in ear surgery, orthopaedics as drug carriers, and for controlled release of certain trace elements. The clinical applications of these materials are also described.

1 Introduction

Bioceramics were previously considered to be materials in oxidized state (e.g. alumina, zirconia, tricalcium phosphate). Being oxidized, ceramics would neither degrade in human body nor would they enter in any biological reaction. Bioinert ceramics are chemically inert with high hardness, while bioactive ceramics would elicit a host response upon implantation. As bioceramic materials are usually used for implant purposes, the performance of the material with regards to biocompatibility is important.¹

Bioceramic materials have since their discovery, proved to be an excellent bone substitute in orthopaedics as well as dentistry because of their resorbability, biocompatibility and osteoconductivity.² Recently, several studies have shown that many bioceramics could be used as a delivery system for therapeutic peptides,³ antibiotics, anticancer drugs⁴, anti inflammatory drugs⁵, and bone morphogenetic proteins.⁶ As bioceramic materials are usually intended for permanent residence in the body, their performance should be checked for time periods equalling the life expectancy of the patient. However, the interface between host and material cannot be analyzed theoretically, it has to be performed experimentally.

2 Various Compositions of Bioceramics

The various compositions of the bioceramics which are commonly been used include; hydroxyapatite, glass ceramic tricalcium phosphate, alumina and metals such as titanium, zirconium have also been included.⁷

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2.1 Bioactive Glass

The first to be developed was bioactive glass. Glasses containing specific proportions of silica, sodium oxide, calcium oxide and phosphorus pentoxide are termed as bioactive. Glass surface is stabilized by the incorporation of multivalent metal ions that form protective films on glass when exposed to body fluids.⁸

The nucleation and growth of crystals within the glass, converts the glass to glass ceramics, which still retain bioactivity. This ceraming process of converting glass to glass ceramic is carried out by increasing concentration of SiO₂ in glass above 60 per cent moles. Addition of multivalent elements such as aluminium, zirconium, titanium to glass ceramics eliminates bioactivity. Ceravital is a type of glass ceramic. The extensive studies by Gross and Strunz on ceravital implants have confirmed that bioactivity is primarily a function of composition of bioactive glasses as well as glass ceramic. Index of bioactivity (IB) is time required for more than 50 per cent interface to be bonded.⁹

2.2 Hydroxyapatite

Hydroxyapatite or more commonly known as hydroxyapatite cement is chemically calcium phosphate. Hydroxyapatite was developed soon after bioactive glasses. Hydroxyapatite could act as an excellent substrate for bone and tissue regeneration and in powder form it is an excellent bone filler.¹⁰ However, the use of hydroxyapatite for load bearing implant applications such as dental implants or total hip prostheses, is not feasible, because of its brittleness and relatively low strength. It has therefore been commonly used for coating purposes.¹¹

2.3 Tricalcium Phosphate Ceramics

Tricalcium phosphate ceramics is a subclass of calcium phosphate ceramics. These are widely used because of their extremely benign biocompatibility characteristics. Their composition is similar to that of the biological apatite and they also have an ability to form a strong bond with the bone. Tricalcium phosphate also has the added benefit of being resorbable.¹²

2.4 Metallic Ceramics

The metallic ceramics include alumina, zirconia and titanium oxide. Metal materials have problems such as corrosion and the deposition of metallic elements in the living body. Alumina ceramics have excessive hardness. Metallic ceramics are also noted to be cytotoxic, thus their biocompatibility is questionable.¹³ However, metallic ceramics can be coated with layers of hydroxyapatite or tricalcium phosphate and thus the drawbacks can be avoided.

Each ceramic has its own merits and demerits as a biomaterial, therefore in order to utilize only the good points of each, there is an increasing tendency for some materials to be combined and used as composites. Ceramic composite can be a matrix or only a filler or reinforcing material or both the matrix and the reinforcement material. The vast variety of matrix material used is generally polymers, but glasses, glass ceramics, carbon in polycrystalline or amorphous form and metal oxides are also used. Fillers or reinforcing materials can be glasses, glass ceramics, ceramics or even metals. Fillers or reinforcing material can be classified into particles and fibers on the basis of their shape.¹⁴ Particles behave isotropically as are irregularly distributed into a matrix. Particles improve abrasion resistance, reduce polymer shrinkage, influence thermal properties and also improve aesthetic value. The fibers on the other hand are properly oriented into the matrix and are anisotropic (strength variations with direction). Anisotropy increases with fiber length. The main purpose of the fibers is to increase the strength and thus they are normally called as reinforcement materials. Fibers may have high fracture toughness and increased Young's Modulus.¹⁴

Various materials are used as matrices and fillers, on the basis of which composites are classified as :

- (I) Ceramic particle filled composites .
- (II) Ceramic short fibre reinforced composites.
- (III) Ceramic long fibre reinforced composites.

Details of these classes are given in Tables 1 to 3 .

Table 1-- Ceramic particle-filled composites

Filler	Matrix	Application	Aim	Ref.
Glass, glass ceramic or HA	PMMA	Bone cement	Increase in stiffness and strength. Reduction of creep	2
Tricalcium phosphate	Polyethylene	Bone substitute	Increase in stiffness	14
Glass-ceramic quartz or glass	Bowen Polymer	Dental restoration	Brilliance, wear resistance, polishability, radiopacity	14

Table 2 — Ceramic short fibre reinforced composite

Filler	Matrix	Application	Aim	Ref.
Carbon	PMMA	Bone cement	Increase in Strength, reduction of creep.	14
Glass	PMMA	Dental	Increase in strength	15
Carbon	Epoxy	Dental	Increase in stiffness	14
Carbon	Triazin	Joint Replacement	Increase in stiffness, Reduction in creep and wear	14

Table 3 — Ceramic long fibre reinforced composites

Filler	Matrix	Application	Aim	Ref.
Carbon	Epoxy or PMMA	Dental implants	Increase in strength	14
Carbon	Triazin	Joint replacement	Increase in strength	14
Carbon	Polysulfone	Fracture stabilization	Increase in strength	14

*PMMA-Polymethylmethacrylate
(All matrices are of non-ceramic type)

3 Interface Formation

Hench proposed the hypothesis that the biocompatibility of the implant material would be optimum if it would establish a contiguous interface capable of supporting the loads that normally occur at the site of implantation.¹ Implantation of biomaterial involves the formation of surgical wound. Thus, the initial interfacial reaction involves the interaction of biomaterial surfaces

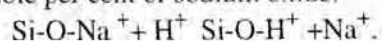
with serum components. The first organic materials that bind to the biomaterial are serum components which are present at the wound site. Proteins and carbohydrates are adsorbed first. Their relative adsorption influence the types of cells attracted towards the surface, their colonization and differentiation. The lipids, proteins, carbohydrates along with water bind to biomaterial in the form of layer. The flux of ions to and from the biomaterial occurs through this layer. The type of water, either free or bound, influences phosphate transformation. Depending upon the type of cells present at the interface different proteoglycan collagen, non-collagen and adhesion proteins can be synthesized. The type of glycosaminoglycan residues present here can alter the hydration of interfacial material, alters the implant's surface. The initial interface formed by the cells and organic constituents continue to mature throughout the initial phases.¹⁶

3.1 Migration, Growth and Differentiation of Cells at the Interface¹⁶

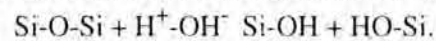
The implant immobilized in a bony implantation bed has its surface exposed to blood borne substances and fluid at the time of insertion. Blood borne cells migrate through surgical gap, which is filled with blood clot and cell debris and exudate from the surrounding tissue. Immunohistochemistry has shown that fibronectin forms a network connected with the fibrin network of blood clot within 3d of implantation. Macrophages and fibroblasts use this network to reach implant surface. After 7d of implantation, most of the space gets filled with the organization tissue, which contains capillaries and partially mineralized trabeculae of primary bone. Calcium phosphate ceramics are shown to contain glycosaminoglycans and proteins. After 60d most of the implant interface is covered by bone and cartilage like cells are no longer detected, thus bone formation occurs.

3.2 Interface Stabilization^{8,16}

Biomaterial tissue interface is dynamic throughout. After the effects of implantations and associated inflammation have dispersed the interface gets somewhat stabilized. Bioactive glass ceramics show mineralization, affected by multivalent cations. Glass ceramic implants undergo sufficient polymerization of silica (SiO₂). The sodium oxide glasses serve as highly effective flux creating two moles of nonbridging oxygen bonds for each mole per cent of sodium oxide.



Addition of calcium shows increase in flux. Cation exchange increases the hydroxyl ion concentration of the solution and an alkaline interfacial pH leads to glass network attack and additional silanol formation.



At intermediate pH, the rate of repolymerization of Si-O-Si bonds from SiO₂ gathers calcium oxide and phosphorus pentoxide from body fluid and nucleate to form Hydroxy Carbonate Apatite (HCA)^{1,8,16}. Thus, HCA mineralization forms the interface between ceramic and bone, and thus duplicates natural repair and growth of bone.

4 Factors Affecting Interface Formation

4.1 Particle Size

Particle size of the ceramic material has been observed to affect the properties of self setting cements. Thus, it affects the interface formation. Otsuka *et al.*⁵ have investigated a self-setting cement system for delivering antibiotics. The effect of the particle size of the metastable calcium phosphates as raw materials was studied. X-ray diffraction suggests that cement containing fine particles of dicalcium phosphate and tetracalcium phosphate are completely transformed to hydroxyapatite by nucleation and crystal growth at the interface, but larger particles are not transformed to hydroxyapatite.

4.2 Effect of Ions

Glass ceramics have shown soft tissue bonding through an apatite layer which is formed on its surface. Calcium and silicate ions are necessary for surface apatite layer formation. Non-bioactive glass ceramic containing apatite and wollastonite (a type of metal composite), in a glassy matrix of oxides of magnesium, calcium, silicon and aluminium do not form an apatite layer on its surface *in vivo*. Simultaneous addition of calcium and silicate ions in small amounts is required for efficient apatite layer formation. This dictates that ions dissolved from bioactive glass ceramics play an important role in the formation of an apatite layer on the surface, to give glass ceramic, a bioactivity.¹⁷

4.3 Porosity

Porosity of ceramics has significant effect on biodegradation and bioresorption of the implant materials. Changes in porosity change the mechanical strength, and thereby interfere in the possible transformations occur-

ing at the interface.¹⁸ Porosity depends upon and differs according to the specific structural needs of the implants. The different configuration of the ceramics based on different porosities, in turn, differs in their interfacial behaviour.¹⁹ The early host responses to hydroxy apatite and tricalcium phosphate porous ceramic implants, have been studied by Jianguo *et al.*²⁰ Mineralization was observed to have started directly on implant surface. Bone bonding was observed with or without amorphous intervening interface layer. These porous ceramics implanted for repair of rat femoral diaphyseal bone have shown bone formation within pores in direct contact with ceramic.

4.4 Volume of Mixing Solutions⁴

The volume of mixing solutions controls the release of drugs embedded into the ceramics and thus affect the interfacial reactions. The effects of mixing solution volume on *in vitro* drug release from a self-setting bioactive cement containing anticancer drug 6-Mercaptopurine was investigated. The drug release rate from the cement systems increased with increase in mixing solution volume. The drug release profiles were found to follow Higuchi and Cobby equation.

4.5 Cytotoxicity

Ceramics most widely used in the orthopaedics contain alumina, zirconia and titanium nitride. Screening of cell line was done following these implants and compared with blood haemolysis test. The results have shown that haemolysis of cells occurred due to the interfacial reactions occurring between the host and the implant material¹³. *In vitro* evaluation studies reflect that cytotoxicity was not observed at required concentrations of these ceramics.

5 Biomechanical Stability and Design

The introduction of the bioceramic implant into the musculoskeletal system can result in a perturbation of the strains acting on bones. Studies have indicated that bone remodelling occurs in the long term. Short term effects include altered rates of bone healing at the implant site. The design of the implants should be such that minimal structure alterations occur to bone due to implant induced remodelling. The biological performance of biomaterials implies the physicochemical potential of material on physiological and pathological aspects of the host response.²¹

The material response is mainly determined by the reactivity of the material in the physiological and pathological environment *in vivo* and *in vitro* (cell culture). The most important change of the material properties seems to be that of chemical composition and structure of the implant surface in the host environment as shown in case of bioactive glass ceramics.²²

6 Clinical Applications

Eversince their discovery, the bioactive ceramics have found various applications in orthopaedics. Now-a-days many novel methods have evolved that make use of ceramics in dentistry as drug carriers and also in controlled release of some elements. Following are the bio-medical applications of bioceramics:

6.1 Bioceramics in Orthopaedics

Bioactive ceramics in general have the characteristics of chemically binding to bone *in vivo*. Typical bioactive ceramics include tricalcium phosphate, calcium hydroxyapatite and bioglass ceravital. The mechanical strengths vary for different materials.

6.1.1 Application to the Vertebrae

Vertebrae damaged by the tumours and degenerative diseases were successfully treated by bone graft of apatite and glass ceramic. The graft makes a firm bond with the adjacent vertebral bone within six months, provided its dislocation did not occur at earlier stages.²³

6.1.2 Replacement of Diaphysis of Long Bone

Glass ceramic prothesis were introduced into the medullary canal of proximal and distal fragments after removing the diaphysis. The prothesis seemed to be bound chemically to the newly formed callus. Another method is to fix the prothesis with an intra-medullary nail through a hole made at its centre.²³

6.1.3 Reconstruction of Normal Configuration of Cortical Bone

In orthopaedic surgery, the iliac crest is often removed leaving a large bone defect. Various forms of artificial bone could be bound chemically to the surface of bone cortex. With an excellent bonding capacity to bone cortex, glass ceramics with apatite and wallstonite are used clinically to cure bone defects, to elevate bone depressions, and buildup new bony structures in neurosurgery and maxillofacial surgery.²³

6.2 Bioactive Glass Ceramics in Middle Ear Surgery

Elbrond and Elpren suggested the need of hard and stiff reconstruction material for optimum auditory results in reconstruction of ossicular chain²⁴. The remaining structures of the ossicular chain must have firm contact with the reconstruction material, bonded to it without tension. A bioactive glass ceramic-ceravital can be used to replace autologous or homologous ossicles. The ceravital ossicular prosthesis is also used for reconstruction of outer ear canal. The total ear canal prosthesis shows better hearing results.²⁴

6.3 Bioactive Ceramic as a Drug Delivery System

A novel skeletal self-setting hydroxyapatite cement system of antibacterial drugs has been proposed by Otsuka *et al.*⁹, as a drug delivery system. The novel approach using hydroxyapatite cement to achieve enough concentrations for desired therapeutic effects, of cephalexin and norfloxacin was proposed. After setting, the cement was transformed into hydroxyapatite which has strong affinity for hard bone tissues. In this approach, hydroxyapatite cement could be formed *in situ* and molded to fill the space created by the absence of the bone. It can also be used as bonding material between bones or bone and prosthesis. At the same time antibacterial drug gets dispersed in the cement while it is being fixed. Once formed and bonded with the bone tissue, controlled drug delivery can be achieved.

Another novel approach was gentamicin loaded hydraulic calcium phosphate bone cement as antibiotic delivery system.² Hydraulic calcium phosphate cement is made up of betatricalcium phosphate, monocalcium hydrate and water. Gentamicin sulphate added as powder or aqueous solution proved beneficial to the physico-chemical properties of the cement. To avoid costly and painful surgery, ceramic blocks loaded with gentamicin sulphate have been proposed. Beta tricalcium phosphate is resorbable and osteoconductive, so the block need not be removed after drug depletion.²⁵ Resorption rates of hydraulic calcium phosphate was intermediate. The reaction of and end product is dicalcium phosphate.

Another example is that of anticancer drug loaded selfsetting cement. Following surgical removal of the bone tumours, patients faced problems of poor mechanical integrity as well as possibility of the metsastasis. Both of these problems are corrected with a biocompatible artificial bone filler which also serves as a delivery system for a chemotherapeutic agent. Hydroxyapatite has an excellent bioaffinity for the hard tissues for

longterm use. 6-Mercaptopurine was incorporated into this self-setting cement. The release of drug from the cement would be determined by the factors such as porosity and geometry of the cement.⁴

6.4 Bioceramics As Carrier for Viral Antigen

Surface modified nanocrystalline ceramics have been used as carrier for viral antigens. This approach employs complex particulate multicomponent structures as carriers on which drug is immobilized or entrained.

The drug delivery system is an aqueous colloid comprising small solids from relatively few atoms clustered in solid crystals to which glassy carbohydrates are applied as surface coatings. This carbohydrate coated core serves as nondenaturing solid phase for subsequent attachment of various biochemically active molecules which then individually confer the final properties to colloids.²⁶

6.5 Controlled Release of Trace Elements

Novel acid base cements have been developed for the controlled release formulations. Many new acids and bases have been assessed. These include all those which release copper, selenium and cobalt, singly or in combinations. Drake and Amos were particularly associated with controlled release of metals and other ions. This class of cements were formed by reaction between an acid and a base which results in formation of saltlike binding matrix. This basic or proton acceptor component may be a metal oxide and acid can be bronsted acid. Release mechanisms involve, independent washoff of species adhering to surface, diffusion through the cement and erosion of material network to release the ions.²⁷

6.6 Ceramics As Blood Contacting Devices

Bioceramics are frequently used for construction of blood contacting devices, i.e., cardiac valves and cardiac assist devices in left ventricular failure. Diamond like carbon has been evaluated for prosthetic heart valves. But except for titanium nitride and aluminium nitride all other bioceramics can be safely used without causing any haemolysis.²⁸

7 Conclusions

The review focuses on the bioceramics which were earlier known to be materials in oxidized state and had a few applications in orthopaedics. Bioinert ceramics were first to be discovered and were known for their hardness and stiffness. Bioactivity was then established in the

ceramics and then the consideration of stability and biocompatibility of the implant material became important.

Bioactive glasses and ceramics were first to be discovered and then hydroxyapatite showing close resemblance to bone gained importance. Considering the merits and demerits of each class of ceramic, the development of composite ceramics which combined the good qualities of all ceramics took place. Being implantable for a long time in the human body the host-implant interaction study becomes important. Any implant reaction proceeds by initial mineralization step followed by migration and differentiation of cells and finally bone growth occurs. The novel applications of the bioactive ceramics as drug carriers allows targeted drug delivery of antibiotics and viral antigens as required. However, the search for the better material composites still continues and future trends require studying the effects of the pretreatments of the implant material before implantation. Technologies for future research in bioceramics suggest cell viability techniques to evaluate cytotoxicity, chemical and physical analysis for biomechanical stability, and designing of ceramic implants and new animal models that will simulate conditions seen in diseased animals.

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