1.1. Introduction

Biomaterials improve the quality of life for an ever increasing number of people each year. The range of applications is vast and includes joint and limb replacements, artificial arteries, skin, contact lenses and dentures. While the implementation of these materials may be for medical reasons such as the replacement of diseased tissues required to extend life expectancies, other causes may include purely aesthetic pleasure ones including breast implants. This increasing demand arises from an aging population with the higher quality of life expectations. The biomaterials community is producing new and improved implant materials and techniques to meet this demand, but also to aid the treatment of younger patients where the necessary properties are even more demanding. The first biomaterials were used by Egyptians and Romans is gold and ivory for replacements of cranial defects. Biological materials such as placenta have used since the 1900s. Celluloid was the first human-made plastic used for cranial defects a polymethyl methacrylate (PMMA) was one of the first polymers accepted since World War II. The Williams Dictionary of Biomaterials (Williams 1999) defined biocompatibility as 'the ability of a material to perform with an appropriate host response in a specific situation.'

In the past years, the aim of developing biomaterials was to create much strong and chemically inert biomaterial for the augmentation of mechanical strength of the bones or others physiological parts. The first skeletal repairing materials is metals, which were considered purely as bio-inert. The plenty of successful applications in orthopedics are carried out with metallic implants annually. However, no material implanted in living tissues is entirely inert: all materials elicit a response from the host tissue. Although

inert metal implants can provide high strength, corrosion resistance, relative movement, [Cao et al. 1996]. A bioactive material has been defined as a material that undergoes specific surface reactions leading to the formation of a hydroxyl carbonate apatite (HCA) layer which is responsible for the creation of a firm bond with tissues, when implanted into the body [Kokubo et al. 1991]. The ability of a bioactive material to form an HCA layer when immersed in body fluid is often taken as an indication of its bioactivity [Kokubo et al. 1990].

1.2. Aim and objectives of the work

To improve our understanding, in vitro bioactivity and physicomechanical properties of HA, TiO_2, ZrO_2, Nb_2O_5, Fe_2O_3, CoO reinforced 45S5 Bioglass based biocomposite.

The following specific objectives were developed to achieve the aim:

- Development of a 45S5 bioactive glass [Composition wt. % 45 SiO_2-24.5 Na_2O-24.5 CaO-6 P_2O_5].
- Development of hydroxyapatite (HA) by sol-gel technique.
- Preparation of biocomposite pellets by powder metallurgy method.
- Characterization of biocomposite samples like DTA/TGA/DSC, XRD, FTIR, pH measurement, SEM, EDX, atomic force microscopy (AFM).
- Density and mechanical property analysis of biocomposite like hardness, compressive strength, elasticity, etc.

1.3. Thesis structure

The overall thesis has divided into eight chapters. **Chapter 1** consists of literature survey regarding the studies on bioactivity, physical and mechanical properties of

biocomposites provide an introduction to the work, highlighting the aim, the resulting objectives and illustrates how the overall manuscript has organized.

Chapter 2 starts with a brief overview about processing material methods and characterization of biocomposite like melting of bioglass, production of hydroxyapatite, preparation of biocomposite, physical structure, mechanical properties.

Chapter 3 presents the current state of the art on BC(1-4) composites. It initiates with an introduction to the existing clinical approaches, followed by the recent progress on biomaterials used for bone tissue substitution. Specifically, it focuses on the use of bioactive glasses and the possibility to modify their compositions by adding specific and functional hydroxyapatite agents. Furthermore, a relevant literature review on biocomposite fabrication methodology has presented, along with an in-depth description of powder metallurgy techniques to frame the scope of the work.

Chapter 4 reports the rationale for the design and development of four novel BG/HA/TiO_2 biocomposites formulations for bone tissue repair and regeneration. The addition of hydroxyapatite to pure bioglass increased its biological properties but limits its strength. Hydroxyapatite is the best option among bioactive material due to its chemical and crystallographic structure being similar to that of bone mineral. This material has been successfully used as a bone substitute and for reconstitution in both orthopedic and dental fields. However, one of its primary restrictions on clinical use as a load-bearing implant is its poor mechanical properties. A good combination of the bioactivity of hydroxyapatite and the mechanical properties of titanium is considered to be a promising approach to fabricating more suitable biomedical materials for load-bearing applications [M. Jarcho et al. 2005; M. Jarcho et al. 1981].

Chapter 5 deals with the methodology adopted for reinforcement of HA, ZrO_2 in 45S5 bioglass. Bioinert ceramics, such as zirconia (ZrO_2) show no interaction with the surrounding and living tissue. However, bioactive ceramics such as calcium phosphates are forming bonds with living hard and soft tissue. It has found that zirconia (ZrO_2) possess high thermal and mechanical strength. For this reason, ZrO_2 has widely used as a biomaterial for hip prosthesis, tooth crowns, and dental implants.

Chapter 6 is reported the main achievements of BGHAFeCo(1-4) biocomposite resulting from the experimental work, carried out on the processing and characterization of the synthesized biocomposite powders and dense bioceramic pellets. Iron ions are expected to exist in Fe^{3+} and Fe^{2+} valance states in this biocomposite. Fe^{3+} ions participate in the glass network in both tetrahedral and octahedral condition, whereas Fe^{2+} join in octahedral condition and act as modifiers. Co also helps protect our cells from being damaged by certain chemicals. Co along with vitamin B12 is essential for keeping blood vessels and skin elastic and flexible.

Chapter 7 the niobium (Nb) is a non-toxic element used in implants due to its excellent corrosion resistance, good biological compatibility in soft and hard tissues. Addition of HA, TiO_2, and Nb_2O_5 in bioglass concluded an increase in bioactivity.

In **Chapter 8** summary and future developments of thesis resulting from the experimental work is presented.

Bioactive glasses were invented by [Hench et al. 2006] which helped in interfacial bonding with the surrounding or the damaged tissue regarded as the second generation bio-materials. Bioactive glasses and related materials have continued to receive immense attention for application as a scaffold in bone regeneration [J.R. Jones et al.

2013]. Some of the promising materials currently used include 45S5 bioglass®, wollastonite, various forms of bioglasses and bioceramics. These materials can undergo surface reaction in the presence of physiological fluids to form biologically active apatite layer, which has close similarity in composition and structure to the mineral phase of bone. The most successful silicate-based glass is the soda-lime 45S5 bioglass® [L.L. Hench et al. 1998], having the composition: 45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5 by weight. 45S5 bioglass® has regarded as the gold standard in regenerative bone repair due to its ability to stimulate angiogenic properties, i.e., increased secretion of the vascular endothelial growth factor (VEGF) and the VEGF gene expression in vitro, as well as enhancement of the vascularization in vivo [A. Gorustovich et al. 2010]. Additionally, 45S5 bioglass® possesses excellent bioactivity, biocompatibility, degradability, and shows a strong chemical bonding with the neighboring tissues in vivo[P. Ducheyne et al. 1987].

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is one of the best-known phosphates in the biologically active phosphate ceramic family by its similarity to natural bone mineral. Synthetic and organically harvested hydroxyapatite finds a variety of biological applications and elicits the formation of an apatite layer at the interface with bone tissue [R. Xinet al. 2005;G. Goller et al. 2003; F. N. Oktaret al. 2002]. Applications include bone repair in prosthetics and dental applications [M. Akao et al. 1981].

Nevertheless, due to the poor mechanical properties of bulk HA ceramics, such materials cannot be used as implant devices for load-bearing applications [F. J. Garcıa-Sanz et al. 1997]. Numerous techniques have investigated in attempts to improve the mechanical properties for particular applications or implant configurations, by the formation of HA composites reinforced with polymers, ceramics, etc. Such composites

aim to retain their useful bioactive properties while providing more suitable mechanical properties for particular applications.

On the other hand, the bioactivity of HA and its reactivity with bone can improve the addition of appropriate amounts of TiO_2 and bioactive glasses, thus obtaining BG-HA-TiO_2 based biocomposites. The loss of an organ or tissue due to cancer, disease or trauma is a critical problem in human health care. A challenging promising approach to address such issue is to create biological or hybrid replacement for implantation into the body itself, as proposed in the framework of the emerging tissue engineering [R.M. Nerem et al. 1991; L.G. Griffith et al. 2002; R. Lanza et al. 2007; R. Langer et al. 1993].

It had found that zirconia (ZrO_2) possess high mechanical strength and very low toxicity [V. Sollazzo et al. 2008; T. Albrektsson et al. 1985]. For this reason (ZrO_2) is widely used as a biomaterial for hip prosthesis [J.L. Masonis et al. 2004; A.H. DeAza et al. 2001], tooth crowns [Y. Kong et al. 1998] and dental implants [R.J. Kohal et al. 2010] and it had formed as a new bone restoring material in the future. Sintered zirconia (ZrO_2) has very high mechanical strength than a cortical bone therefore new class zirconia is used as a new bone restoring material [S. Atilgan et al. 2010; H. Nisitani et al. 1994].

Iron ions are expected to exist in Fe^{3+} and Fe^{2+} valence states in these glasses. Fe^{3+} ions participate in the glass networking in both tetrahedral and octahedral coordination, whereas Fe^{2+} join in octahedral condition and act as modifiers [V. Vercamer et al. 2015; G. Nagarjuna et al. 2009]. The simultaneous presence of iron ions in divalent and trivalent oxidation states with different coordination will have a strong behavior on the

bioactivity of the base glass. New approaches for the preparation of magnetic bone substitutes have been described, like bioactive (Fe^{+2}/Fe^{+3}) doped hydroxyapatite (Fe-HA) with superparamagnetic like properties as well as hydroxyapatite-based scaffolds with magnetic properties attained by dip-coating in aqueous ferrofluids containing iron oxide nanoparticles [T. Kokubo et al. 2006; A.Tampieri et al. 2011; N. Bock et al. 2010]. The aim of attracting and taking up in vivo growth factors, stem cells or other bio-agents is to bound to magnetic particles via magnetic driving, but they are not intended for the hyperthermic treatment of bone tumors.

The niobium (Nb) is a non-toxic element (Dsouki et al. 2014) used in implants due to its excellent corrosion resistance, good biological compatibility in soft and hard tissues (Matsuno et al. 2001; Eisenbarth et al. 2006). A small barrier type oxide layer (niobium pentoxide) tightly covers the entire metal surface due to biocompatibility and corrosion resistance (Mazur et al. 2015; Sowa et al. 2013). Niobium is a transition metal and has the atomic number 41. This metal is widely used to enhance mechanical properties in the development of metal alloys (Ficarro et al. 2008). Niobium pentoxide (Nb_2O_5) has shown bioactive properties, like hydroxyapatite crystal growth when comes in contact with human saliva and has been used as an anti-allergic coating in endoprostheses with favorable results (Karlinsey et al. 2006).

1.4. Biomaterials

Any material of natural or synthetic origin that comes in contact with tissue, blood or biological fluids and intended for use in prosthetic, diagnostic, therapeutic or storage application without adversely affecting the living organism and its components. American National Institute of Health that describes biomaterial as ‘any substance or

combination of substances other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual'.

Biomaterials have classified into three distinct categories based on the reaction of the tissue to the biomaterial: 1. Biotolerant Materials: which are separated from the bone tissue by a layer of fibrous tissue. 2. Bioactive materials: which have the property of establishing chemical bonds with bone tissue, known as osseointegration. The collagen and mineral phase of the adjacent bone is deposited directly on the implant surface. 3. Bioinert Materials: in this class, it is possible, under certain conditions to have direct contact with the adjacent bone tissue. No chemical reactions shall occur between the implant and the tissue.

Biomaterials, either permanent or biodegradable, naturally occurring or synthetic, preformed or injectable, provide cell anchorage sites, mechanical stability, structural guidance within an in vivo environment to the interface respond to physiological and biological changes and to remodel the ECM in order to integrate with the surrounding native tissue [T. Gorski et al. 2004].

Recognition of an active interface between biomaterials and biological systems led to several significant basic ideas about biocompatibility. These ideas persist and comprise the essence of biocompatibility. The first idea is that the interactions at the material-tissue interface occur a response from the body and the body obtains a reply from the biomaterial. All elements will be changed at some level by their introduction into a biological environment either via corrosion, chemical modification, deposition of

substance, degradation or another mechanism. Responses lead to a second idea: that the material-tissue interface is dynamic. As the material and biological tissue are modified by each other, the changes themselves may suppose other changes. Thus, the interface is not static but is changing over its lifetime. Furthermore, the human buccal conditions are always changing by aging, developing systemic or local diseases by adopting new activities, eating differently, etc. any equilibrium established at a material-tissue interface is subject to perturbation. The third idea is that reactions at the material-tissue interface are a function of the tissue where the interface has created. The fourth idea about biological-tissue interfaces recognizes the nearly obvious. Biomaterials are foreign bodies, and foreign body responses characterize biological responses to these materials. Finally, the most recent idea about biocompatibility is that it is possible to customize interactions at the material-tissue interface. These materials are used to make devices to replace damaged or diseased body parts in human and animal bodies.

Biomaterials in the form of implants (sutures, bone plates, joint replacements, etc.) and medical devices (pacemakers, artificial hearts, blood tubes, etc.) are widely used to replace and restore the function of traumatized or degenerated tissues or organs and thus improve the quality of life of the patients. Human body parts implant by using biomaterials is in practice from last seven decades. Rapid growth in research activities over the years in the field of biomedical science have developed the biomedical products such as dental implants, craniofacial plates, screws, parts of artificial hearts, pacemakers, clips, valves, balloon catheters, medical devices and equipments, bone fixation devices, dental materials, medical radiation shielding products, prosthetic and orthodontic devices, tools of machining metallic biomaterials.

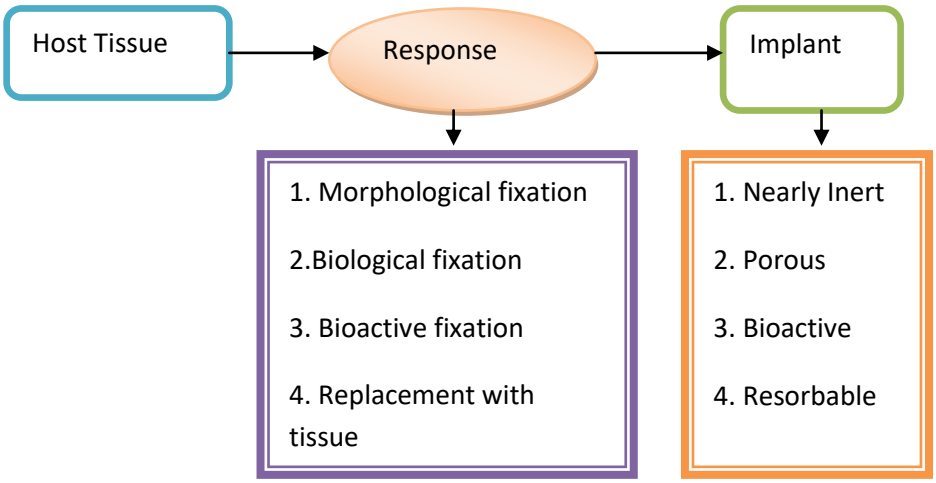

Figure 1.1: Tissue attachment of Biomaterials.

The materials that are used to build biomedical devices such as orthopedic, dental, bone cement, etc. It has broadly classified into metallic materials, ceramics, polymers, and composites. Metallic materials within these four categories are widely used due to their high tensile strength, high yield strength, fatigue strength, toughness, and excellent biocompatibility despite some shortcomings such as the release of metallic ions and wear debris. Metals have extensively used in a variety of applications in the medical field for internal support and biological tissue replacements, such as joint replacements, dental roots, orthopedic fixation, and stents.

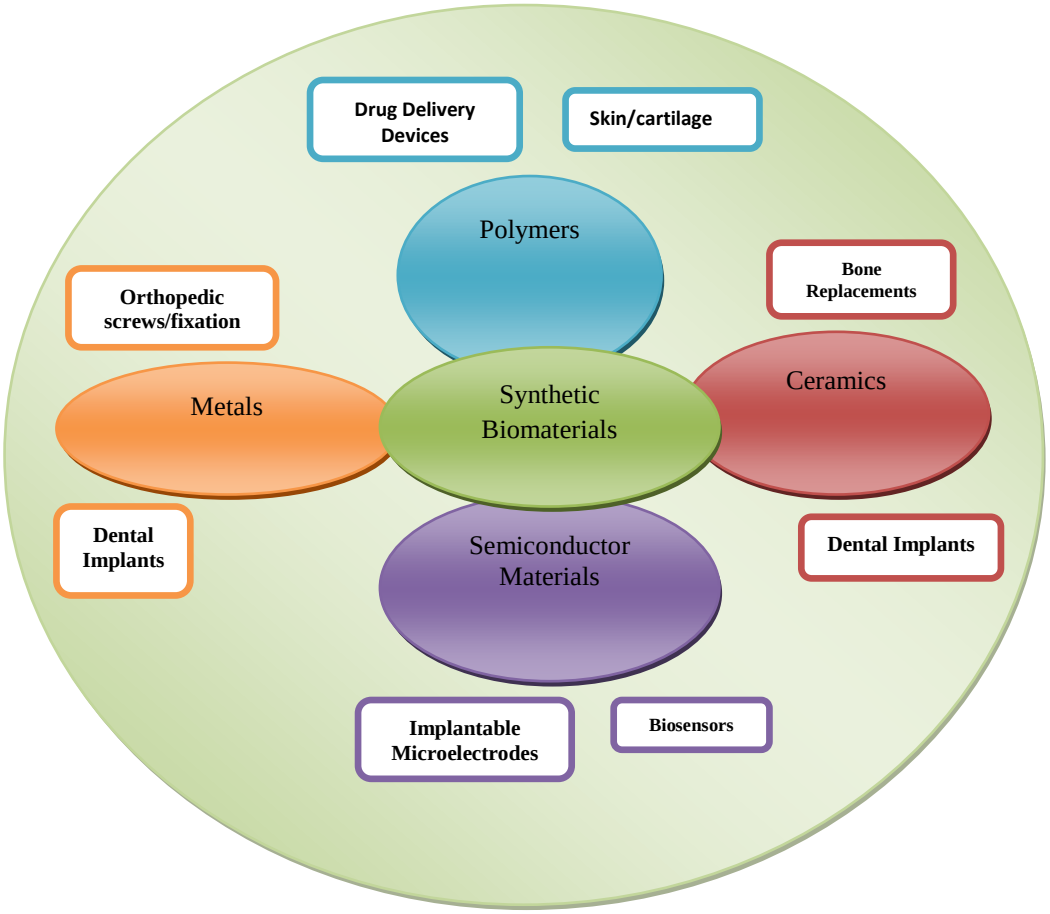

Figure 1.2: Medical field biomaterial.

Metals and alloys biomaterials such as stainless steel (316L), Co-Cr alloys, Ti6Al4V, Au-Ag-Cu-Pd alloys, Amalgam (AgSnCuZnHg), Ni-Ti, Titanium; Advantages: high strength, fatigue resistance, wear resistance, Easy fabrication, Easy to sterilize, Shape memory; Disadvantages: High elastic modulus, Corrosion, Metal ion sensitivity, toxicity. Ceramics biomaterials such as Alumina, Zirconia (partially stabilized), Silicate glass, Calcium phosphate (apatite), Calcium carbonate, Alumina, Hydroxyapatite. Its advantages are high compression strength, wear & corrosion resistance can be highly polished, Bioactive/inert. And its disadvantages is high modulus (mismatched with bone), low strength in tension, low fracture toughness, difficult to fabricate. Polymer

biomaterials are such as PMMA, PVC, PLA/PGA, PE, PP, PA, PTFE, PET, PUR, Silicones. Its advantages are easy to make complicated items, physical & mechanical properties, Surface modification, immobilize cell. And its disadvantages is leachable compounds, absorb water & proteins, surface contamination, wear & breakdown, biodegradation, difficult to sterilize.

Applications of biomaterials such as skeletal system is joint replacement (Hip, knee), bone plate, bone cement, artificial tendon and ligament, dental implant; Cardiovascular system is blood vessel prosthesis, Heart valve, Catheter; Organs is artificial heart, skin repair template, artificial kidney, heart, lung machine; Senses is cochlear replacement, intraocular lens, contact lens, corneal bandage. Biomaterials is titanium, stainless steel, Co-Cr alloy, PMMA, Hydroxylapatite, Teflon, Dacron – titanium, Alumina, Calcium phosphate – Dacron, Teflon, Polyurethane – Reprocessed tissue, Stainless steel, Carbon – Silicone rubber, Teflon, Polyurethane – Polyurethane – Silicone-collage composite – Cellulose, Polyacrylonitrile – Silicone rubber – Platinum electrodes – PMMA, Silicone rubber, hydrogel – Silicone-acrylate.

Implant-tissue interaction is: (1) If the material is toxic, the surrounding tissue dies; (2) If the material is nontoxic and biologically inactive (almost inert), fibrous tissue of variable thickness forms; (3) If the material is nontoxic and biologically active (bioactive), an interfacial bond forms; (4) If the material is nontoxic and dissolves, the surrounding tissue replaces it. General criterion for biomaterial selection is (1) Mechanical and chemicals properties (2) No undesirable biological effects-carcinogenic, toxic, allergenic or immunogenic (3) Possible to process, fabricate and sterilize with good reproducibility (4) Acceptable cost/benefit ratio. Cell/tissue reaction

to implant is (1) Soft tissue (2) Hard tissue (3) Blood cells. There are various biological levels (Atomic scale, Molecular scale, Cellular level, Tissue Organ, System, Organism).

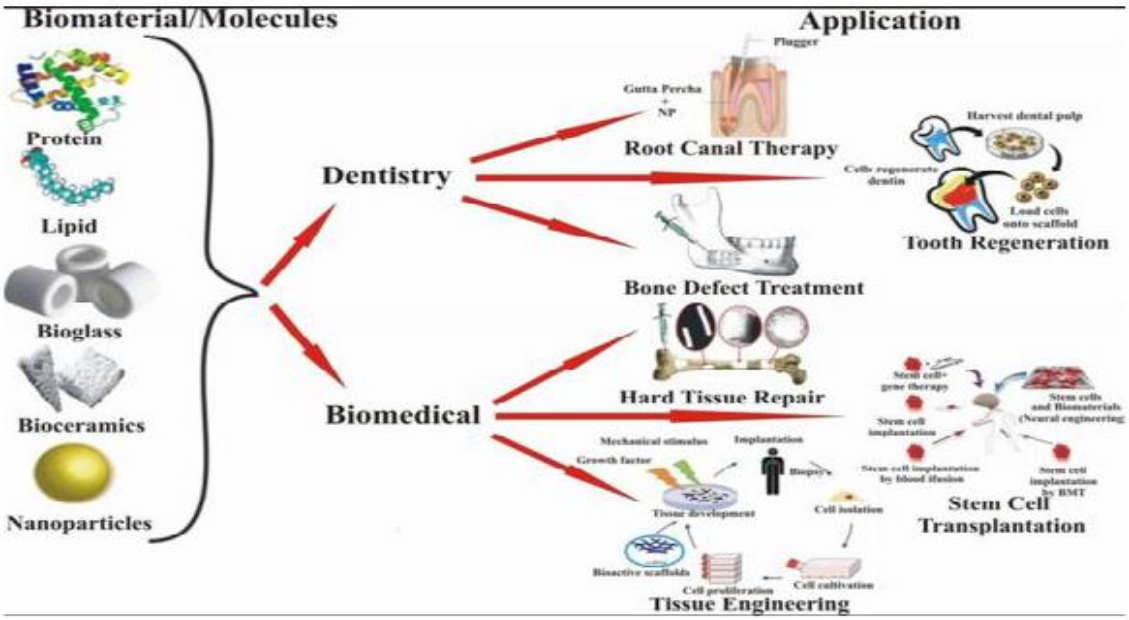

Figure 1.3: Biomaterial tissue attachment application [M. Sharma et al. 2013].

1.4.1. Biomaterials for Bone Tissue Engineering Scaffolds

Several qualities required for a useful scaffold material, although no single material meets all these criteria. The basic requirements of a scaffold material are high cell/tissue biocompatibility, non-toxicity, capability of promoting cell proliferation and differentiation and sufficient mechanical properties (Jones et al., 2013; Leong et al., 2003). Scaffold materials can be natural, synthetic, semi-synthetic, and hybrid (Causa et al., 2007). Natural materials include proteins such as collagen, fibrin, saccharides such as alginates and inorganic natural or modified natural materials such as coralline hydroxyapatite. Natural materials have many advantages concerning its structural and mechanical compatibility with tissue. Synthetic materials have been extensively exploited because they are often easier to fabricate into structures with a designed

internal architecture. Synthetic materials include synthetic organic materials (polymers) and synthetic inorganic materials (ceramics, glasses, and glass-ceramics) (Causa et al., 2007; Hutmacher, 2001). Tissue response is the primary concern for selecting the appropriate scaffold material. Therefore, scaffold biomaterials have classified into three categories according to the nature of their interaction with the surrounding tissue. These are bioinert, bioactive and biodegradable or bioresorbable (Hench, 1991). Other terms have been used to describe the biological properties of materials used in bone tissue engineering (Albrektsson and Johansson 2001; Stevens 2008).

Table 1.1: The biological properties of materials used in bone tissue engineering [M.M. Stevens 2008].

Term	**Definition**
Osteoinductive	Materials capable of promoting the differentiation of progenitor cells from the surrounding tissue and stimulating the osteogenesis process.
Osteoconductive	Materials allowing the bone cells to adhere, proliferate and form extracellular matrix on its surface or down into pores and channels.
Osteointegration	Materials bonded with surrounding bone without growth fibrous tissue at the bone implant interface.

Various materials have been used to produce scaffolds for bone tissue engineering including ceramics, bioactive glass, natural and synthetic biodegradable polymers, and composite materials. Metals and alloys can be used to fabricate scaffolds for load-bearing defects, e.g., titanium and stainless steel as non-biodegradable scaffolds. In

these cases, the scaffold will not be replaced by the host tissue or by magnesium alloys as a biocompatible, osteoconductive and degradable scaffold (Staiger et al., 2006). Polymer-based scaffolds biodegradable polymers such as collagen, fibrin, chitosan, and starch have obtained from natural sources. The main advantages of these materials are their design flexibility, low immunogenic potential, excellent biocompatibility, osteoconductive properties, and an unlimited source in the case of starch and chitosan (Salgado et al., 2004; Schieker et al., 2006). However, the low mechanical strength and high degradation rate of natural polymers has led to their use as composites or requires their chemical modification by cross-linking to improve properties and reduce their degradation rate.

On the other hand, these changes may cause cytotoxic effects and may provoke a severe immune response or harbor microbes or viruses (Karageorgiou and Kaplan et al. 2005). Synthetic biodegradable polymers can be produced under controlled conditions and therefore exhibit predictable and reproducible mechanical and physical properties such as tensile strength, elastic modulus, and degradation rate. Another advantage is the control of material impurities (Yang et al. 2002).

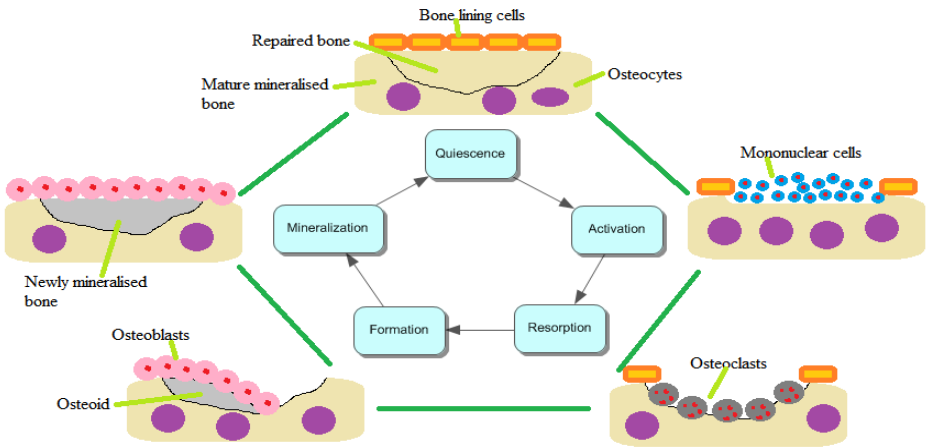

Figure 1.4: Bone remodelling cycle under normal conditions [Marie-Eve Marquis et al. 2009].

1.4.2. Essential features of biomaterials

(a) Biocompatibility:

Biocompatibility has defined as the ability of a material to perform with an appropriate host response in a specific application. It is the first significant criterion to inspect while selecting a biomaterial. The metallic implant tends to corrode in the environment which leads to deteriorating the implant and breakdown of the implant. Due to which adverse effects on the nearby tissues and organs will occur. It is to be careful that the developed biomaterial should be compatible with the human body and may not generate any unwanted harmful effects. Biocompatibility is a function of several factors B=f (X_1, X_2.....X_n) Where X: material, design, application, etc.

(b) Mechanical properties: The implant material should exhibit the desirable mechanical properties to extend the service period by preventing the chances of revision surgery. The mechanical properties include low modulus with high strength to avoid loosening. The modulus of elasticity of biomaterials should be equivalent to that of bone which varies from 4 to 30 GPa. It will prevent the chances of stress shielding.

(c) Long fatigue life: The material should exhibit a long fatigue life. The fatigue failure of implants has observed for hip prostheses.

(d) High corrosion resistance: A biomaterial implanted in a human body with a low corrosion resistance can discharge metal ions into the body will produce toxic reactions. Therefore the implant material with high corrosion resistance should be selected. The metal implant is prone to corrosion during its services due to the corrosion medium of the implantation subjected to cyclic loading. Types of corrosion that frequently found in implant applications are fretting, pitting and fatigue.

(e) High wear resistance: The material should have a high wear resistance and low friction coefficient. It is the fact that an increase in the friction coefficient or a decrease in the wear resistance can cause the implant to lose when sliding against body tissues. Moreover, the wear remains generated can cause inflammation that is destructive to the bone supporting the implant.

(f) Osseointegration: It has first defined as 'a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant.' Currently, an implant has considered as osseointegrated when there is no relative progressive movement between the implant and the bone which it has direct contact. From the study of Branemark research work, titanium implants could become permanently integrated within the bone. It means that the living bone could grow with the titanium oxide layer of the implant that have not separated without fracture.

(g) Non-toxic: The biomaterial should be non-toxic so that it can satisfy its purpose without adversely affecting the biological system of the human tissues and organs. Thus the material should be neither genotoxic (which can alter the DNA of the genome) nor cytotoxic (causes damage to individual cells).

(h) Cost of the Biomaterial: The final consideration for choosing a metal for a medical implant is cost. Some metals cost much more than others as a raw material, processing and machining expenses can vary considerably depending on their application.

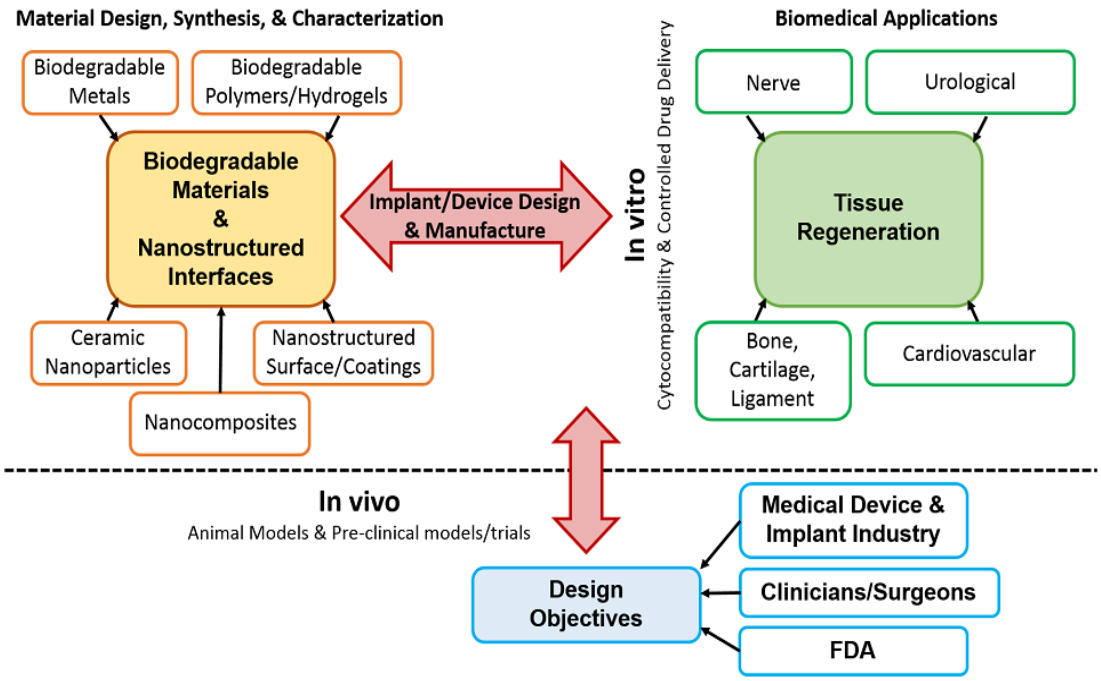

Figure 1.5: Biodegradable materials and tissue regeneration interface for in-vivo, in-vitro application [H. Liu Research Group].

1.5. Bioactive materials

A material is said to be bioactive if it provides an appropriate biological response and results in the formation of a bond between material and tissue. Bioactive ceramic is a general term covering bioactive glasses, glass-ceramics and hydroxyapatite. They exhibit a positive reaction at the interface between the host tissue and the implant in the biological environment resulting in bonding each with varying ability according to its type. Hench introduced an index to measure the level of bioactivity referred to as the rate of development of a bond between the implant and surrounding tissue.

$$\text{Bioactivity Index } IB = 100/t0.5bb \qquad (1.1)$$

Where (t0.5bb) is the time taken for more than 50% of the interface to bond bone. According to the bioactivity index, bioactive materials can classify into two types as listed below: Bioactive materials class A: materials exhibiting an IB value greater than

8, they are considered as osteogenetic and osteoconductive materials and bond to both soft and hard tissue, e.g., the bioactive glass 45S5 (Hench et al. 2013); Bioactive materials class B: materials with an IB less than eight but greater than zero, they are considered only as osteoconductive materials, e.g. synthetic hydroxyapatite (HA) which has chemical similarity to bone, good biocompatibility and tricalcium phosphate (β-TCP) which forms a bond to bone in vivo but not to soft tissue (Hench and Wilson et al. 1993).

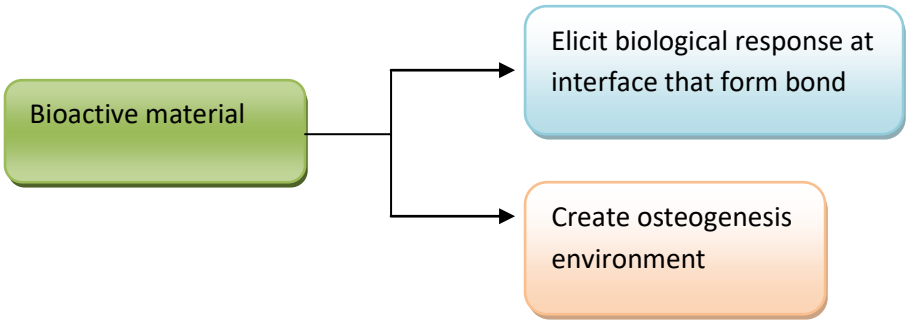

Figure 1.6: Bioactive material response.

1.6. Biocompatibility

The Williams Dictionary of Biomaterials updated its original definition of biocompatibility '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 to that specific situation and optimizing the clinically relevant performance of that therapy'.

The biocompatibility is inherently linked to contact between a technical system and a biological one. It has considered that a biomaterial is compatible to the extent that it can replace a function within a biological system without harmful effects on the natural

environment in which it works. The great variety of biomaterials are different approaches as well as formulations of biocompatibility phenomenon. There is a widely accepted formulation in the literature that the biocompatibility is (Williams, 1987) the ability of a material to work under a specific medical device, producing a corresponding reaction in the host body.

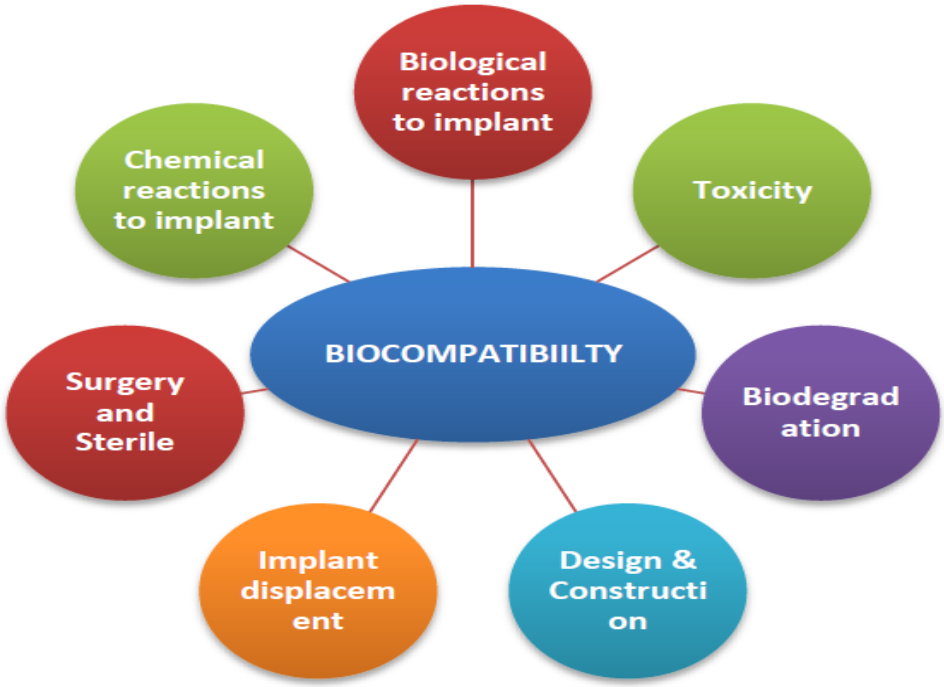

Figure 1.7: Factors influencing the biocompatibility.

Biocompatibility of dental materials depends upon: (1) Biocompatibility interaction between body & material; (2) Placement of material has created an dynamic interface. Interface activity depends on (a) location of material (b) its duration in the body (c) its properties (d) health of the host. Requirements for dental material (1) Should not be harmful to pulp & soft tissues. (2) Should not contain toxic diffusible substances. (3) Should not produce allergic responses. (4) Should not be carcinogenic.

1.7. Restorative biomaterials

Restorative biomaterials are designed to recover the shape, and the function of the teeth for fillings as well as materials for the preparation of cavities. The latter has used to protect the pulp tissue to create adhesion between the tooth surface and the restorative material. Dental substances should not be toxic, irritating or corrosive and should be easy to use. The biomaterials used in dentistry may be metals (silver amalgam, titanium, and gold), ceramics (feldspar, alumina, zirconia, silica reinforced porcelain) and composites. There are only three main divisions to the spectrum of dental ceramics (1) predominantly glassy materials (2) particle-filled glasses (3) polycrystalline ceramics.

1.8. Bioinert materials

Bioinert refers to a material that retains its structure in the body after implantation and does not induce any immunologic host reactions. Bioinert ceramics are nearly biologically inert or have no chemical interaction with biological systems. Fibroblasts form fine, non-adherent fibrous tissue capsules of varying thickness around the material because the body tries to isolate itself from the foreign implant (Hench et al.1993). Alumina (Al_2O_3) and zirconia (ZrO_2) were the first successful ceramics used in medical applications. They exhibit stability in human body fluids used to repair hard tissue in non-porous form. The only alumina among the bioinert ceramics has been used in the porous structure to repair bone tissue. It must have high purity (≥99.6%), high density (≥3 g/cm^3), fine-grained (< 7 μm in grain size) to exhibit good flexural strength and high compressive strength (Hench et al. 1991). Zirconia ceramics have higher fracture toughness values than alumina, but there are some concerns about the application of zirconia ceramics in the orthopedic field.

1.9. Bioceramics materials

The class of ceramics used for repair and replacement of diseased and damaged parts of the musculoskeletal system are referred to as bioceramics.

Areas of Bioceramics

- Glasses
- Diagnostic devices
- Thermometers
- Tissue culture vessels

} Health Sector

- Filling materials
- Gold porcelain coating
- Prosthetic parts

} Dental

Table 1.2: Application of ceramics as implant [N.R. Patel et al.2012].

Types of Materials	Applications
Alumina	Artificial total joint replacement, acetabular and femoral components, vertebrae spacers and extensors, orthodontic anchors, dental implant for tooth fixation
Zirconia	Replacement for hips, knees, teeth, tendons and ligaments, repair for periodontal disease, bone fillers after tumor surgery
Pyrolytic carbon	Prosthetic heart valves, End osseous tooth replacement implants, permanently implanted artificial limbs
Bioglass-ceramics	Dental implants, middle ear implants, heart valves, artificial total joint replacement, bone plates, screws, wires, intramedullary nails, spinal fusion, tooth replacement implants
Calcium phosphates	Skin treatments, dental implants, jawbone reconstruction, orthopedics, facial surgery, ear, nose and throat repair, dental implant

Table 1.3: Types of tissue attachment to biomaterials.

Type of implant	Type of attachment	Example
Nearly inert	Mechanical interlock (morphological fixation)	Metals, Alumina, Zirconia, Polyethylene (PE)
Porous	Ingrowth of tissue into pores (biological fixation)	Hydroxyapatite (HA), HA coated porous metals
Resorbable	Replacement with tissues	Tricalcium phosphate, Polylactic acid (PLA)
Bioactive	Interfacial bonding with tissues (Bioactive fixation)	Bioactive glasses, HA, Bioactive glass-ceramics

1.10. Preparation of SBF

Kokubo and his colleagues developed simulated body fluid that has an inorganic ion concentration similar to those of human body fluid to reproduce in vitro formation of apatite on bioactive materials (Kokubo et al. 2006). The SBF solution had prepared by dissolving reagent grade NaCl, KCl, $NaHCO_3$, $MgCl_2.6H_2O$, $CaCl_2$, and KH_2PO_4 into the double distilled water. It was buffered at pH-7.4 with TRIS (tris-hydroxymethyl aminomethane) and 1N HCl at 37˚C as compared to the human blood plasma (WBC) (A. Agarwal et al.,1997).

1.11. Bioactive glass

Bioactive glasses were first developed by Hench et al.1969 and represent a group of reactive materials that can bond to mineralized bone tissue in the physiological environment. Bioactive glasses have widely used in the biomedical area. Early applications of bioactive glasses were in the form of solid pieces for small bone replacement in middle ear surgery. Later, several applications of bioactive glasses have been proposed, including the dental field. Recently, bioactive glasses have widely studied for potential use in tissue engineering and regenerative medicine. A range of bioactive glasses with attractive properties like biocompatibility, bioactivity and synthesized by newer methods. Various investigations have been undertaken to obtain bioactive glasses in different forms such as bulk, powder, composites, and porous scaffolds.

Bioactive glasses are amorphous silica-based materials that are biocompatible, osteoproductive, osteoconductive and osteoinductive. The reaction process between the

glass and physiological fluids results in the formation of a crystallized hydroxycarbonate apatite (HCA) layer at the glass/bone interface. This HCA layer is similar in composition, structure to the inorganic component of bone mineral and a strong bond can form without fibrous tissue around it (Vallet-Regi et al. 2006). The bioactivity and osteogenesis ability of bioactive glass depends on the reaction rate and HCA layer formation at the glass/bone interface. Bioactive glasses are considered to be biodegradable materials. However, their degradation rate is dependent on the glass composition and the specific surface area which are influenced by the particle size or morphology when it is used as a scaffold (Jones et al. 2013). Base component in most bioactive glass and ceramics (traditional) are SiO_2, Na_2O, CaO and P_2O_5.

The earliest bioactive glass-ceramic for clinical use was developed by Bromer in 1977 [Bromer et al. 1977] and named Ceravital. This designation includes a wide range of glass - ceramic compositions. Some of them are KG Cera [composition (weight %) 46.2 SiO_2 - 25.5 $Ca(PO_2)_2$ - 20.2 CaO - 4.8 Na_2O - 2.9 MgO - 0.4 K_2O], Mina13 [composition (weight %) 46 SiO_2 - 16 $Ca(PO_2)_2$ - 33 CaO - 5 MgO], KGy213[composition (weight %) 38 SiO_2 - 13.5 $Ca(PO_2)_2$ - 31 CaO - 4 Na_2O - 7 Al_2O_3 - 5.5 Ta_2O_5 - 1 TiO_2] and M8/1 [composition weight % 50 SiO_2 - 7.1 $Ca(PO_2)_2$ - 5 Na_2O -1.5 Al_2O_3 - 4 B_2O_3 - 2.4 $Al(PO_3)_3$ - 20 SrO - 6 La_2O_3 - 4 Gd_2O_3]. This bioactive glass ceramics consists of apatite crystals and glassy phases. One of the bioactive glass ceramics of more clinical success, be probably the denominated A/W [composition (weight %) 34 SiO_2 - 44.7 CaO - 4.6 MgO - 6.2 P_2O_5 - 0.5 CaF_2], which is constituted by two crystalline phases: oxyfluorapatite $Ca_{10}(PO_4)_6(OF2)$ and wollastonita ($CaSiO_3$) and a residual vitreous phase. This was originally developed by Kokubo [Kokubo et al. 1986] and is commercially available under the trade name Cerabone A/W. In 1983,

[Holand et al 1985], developed a new series of bioactive glass-ceramics, which they called Bioverit I [composition (weight %) (29.9-50) SiO_2 - (6-28) MgO - (13-28) CaO - (5.5 - 9.5) Na_2O/K_2O - (0-19.5) Al_2O_3- (2.5 - 7) F - (8-18) P_2O_5 additions TiO_2].

Bioactive glasses are bioceramics that are solid, nonporous and hard materials which consist of the main component silicon dioxide (or silicate) and three other essential components: sodium dioxide, calcium oxide, and phosphorous. By varying all of these components, different forms of bioactive glasses have made [M. Brink et al. 1997]. Bioactive glasses have been investigated for decades and have shown good results in bone regeneration. In all these years several types of bioactive glasses are developed: the conventional silicate glass (45S5 bioactive glass or Bioglass®), glass ceramics (S53P4 bioactive glass or BonAlive®) and borate-based glass (19-93B3 bioactive glass). The biocompatibility of bioactive glasses generally depends on the silicate part of the glass and reaches an optimum graft-bone bonding when the glass contains 45–52% silicate [RF Brown et al. 2008]. The process of graft-bone bonding of bioactive glasses starts with the release of soluble ions after which a silica gel layer has formed on the bioactive glass surface.

The original bioglass (45S5) composition is as follows: 45% silica (SiO_2), 24.5% calcium oxide (CaO), 24.5% sodium oxide (Na_2O) and 6% phosphorous pentoxide (P_2O_5) in weight percentage. Bioglass material is composed of minerals that occur naturally in the body (SiO_2, Ca, Na_2O, H and P) and the molecular proportions of the calcium and phosphorous oxides are similar to those in the bones. The surface of a bioglass implant, when subjected to an aqueous solution or body fluids converts to a silica-CaO/P_2O_5-rich gel layer that subsequently mineralizes into hydroxycarbonate in a

matter of hours. More the dissolution, better the bone tissue growth. The backbone of the bioactive glass structure is the SiO_4 tetrahedral network which displays short to medium-range 3D order. According to Zachariasen [P. Ducheyne et al. 1999] network formers such as Si can form a network with bridging (BO) and non-bridging oxygens (NBO) while alkali and alkaline earth oxides do not have network forming capability and hence act as network modifiers by replacing BO by NBO. As these ions reduce the network connectivity, they can have a profound effect on the levels of material bioactivity [J. Wilson et al. 1981]. The general structure of bioactive glass has displayed in Figure 1.8.

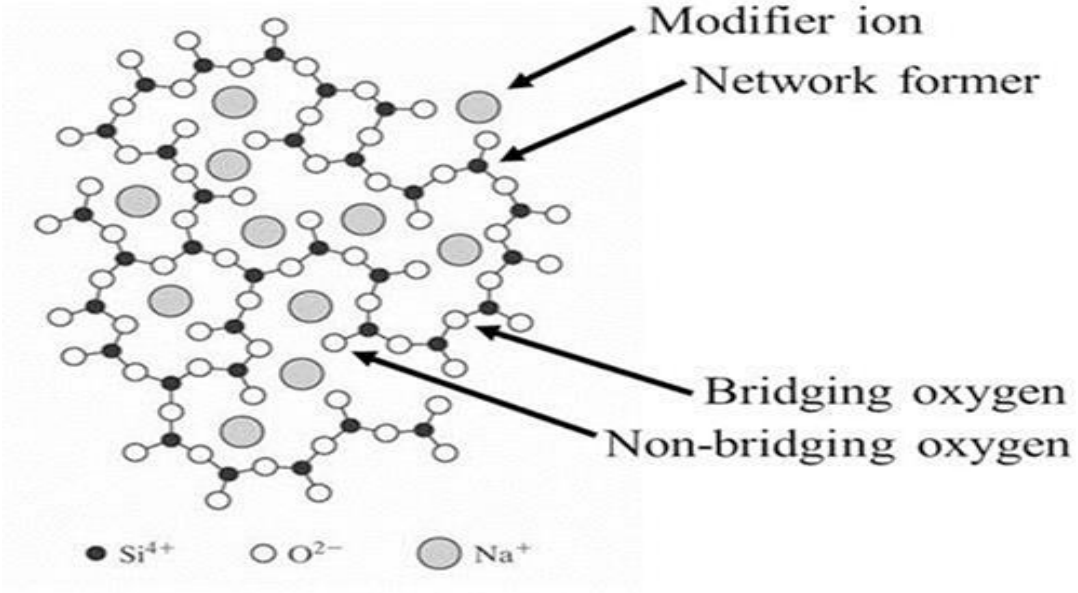

Figure 1.8: Two-dimensional general structure of bioactive glass [S.K. Nandi et al. 2016].

The mechanism of bioactivity and bone bonding of 45S5 glass have widely studied [LL. Hench et al. 1998; W. Huang et al. 2006]. The bonding of 45S5 glass to bone has attributed to the formation of a carbonate substituted hydroxyapatite like (HCA) layer

on the glass surface in contact with the body fluid. This HCA layer is similar to the mineral constituent of bone, and it bonds firmly with living bone and tissue.

Stage 1: Rapid ion exchange reactions between the glass network modifiers (Na^+ and Ca^{2+}) with H^+ (or H_3O^+) ions from the solution, leads to hydrolysis of the silica groups and the creation of silanol (Si−OH) groups on the glass surface: e.g.

$$Si - O - Na^+ + H^+ \rightarrow Si - OH + Na^+(aq) \qquad (1.2)$$

The pH of the solution increases due to the consumption of H^+ ions.

Stage 2: The increase in pH (or OH^- concentration) leads to attack of the SiO_2 glass network, and the dissolution of silica, in the form of silicic acid $Si(OH)_4$ into the solution, and the continued formation of Si−OH groups on the glass surface:

$$Si - O - Si + H_2O \rightarrow Si - OH + OH - Si \qquad (1.3)$$

While the solubility of silica is low, the products of 45S5 glass and glass ceramic dissolution in aqueous solutions have shown an increase in Si concentration [LL. Hench et al. 2002] indicating that dissolution of silica is an important mechanism. However, other mechanisms could also contribute to the increase in Si concentration.

Stage 3: Condensation and polymerization of an amorphous SiO_2-rich layer (typically 1–2 μm thick) on the surface of the glass depleted in Na^+ and Ca^{2+}.

Stage 4: Further dissolution of the glass, coupled with migration of Ca^{2+}, $(PO_4)^{3-}$ ions from the glass through the SiO_2-rich layer to the solution, leading to the formation of an amorphous calcium phosphate (ACP) layer on the surface of the SiO_2-rich layer.

Stage 5: The glass continues to dissolve, as the ACP layer incorporates $(OH)^-$, $(CO_3)^{2-}$ from the solution and crystallizes as an HCA layer.

With the initial formation of an HCA layer, the biological mechanisms of bonding to bone are believed to involve adsorption of growth factors, followed by attachment proliferation and differentiation of osteoprogenitor cells. Osteoblasts (bone-forming cells) create an extracellular matrix (collagen), which mineralizes to form a nanocrystalline mineral and collagen on the surface of the glass implant while the degradation and conversion of the glass continue over time.

A complication with the use of 45S5 glass and biodegradable materials is that the local biological microenvironment can be influenced significantly by their degradation. Increases in the concentration of ions, such as Na^{+} and Ca^{2+}, and changes in the pH occur as a result of the degradation, particularly in the early stages when the degradation rate is fast. The biological effects of these changes are difficult to predict from in vitro experiments. Furthermore, the biological roles of these soluble species, toxicity, and their removal are often not clearly understood.

Bioactive glass (45S5) has been shown to enhance new bone formation in vivo [DL. Wheeler et al.1997; DL. Wheeler et al. 1998]. When implanted in the rabbit femurs, granules of 45S5 bioactive glass were found to promote more rapid bone proliferation than (synthetic) HA [H. Oonishi et al. 1999]. HA is classified as osteoconductive because it supports new bone growth along the implant at the bone-implant interface. However, 45S5 glass is considered to be osteoconductive as well as osteoinductive, because it promotes new bone growth along the bone-implant interface as well as within the implant away from the bone-implant interface.

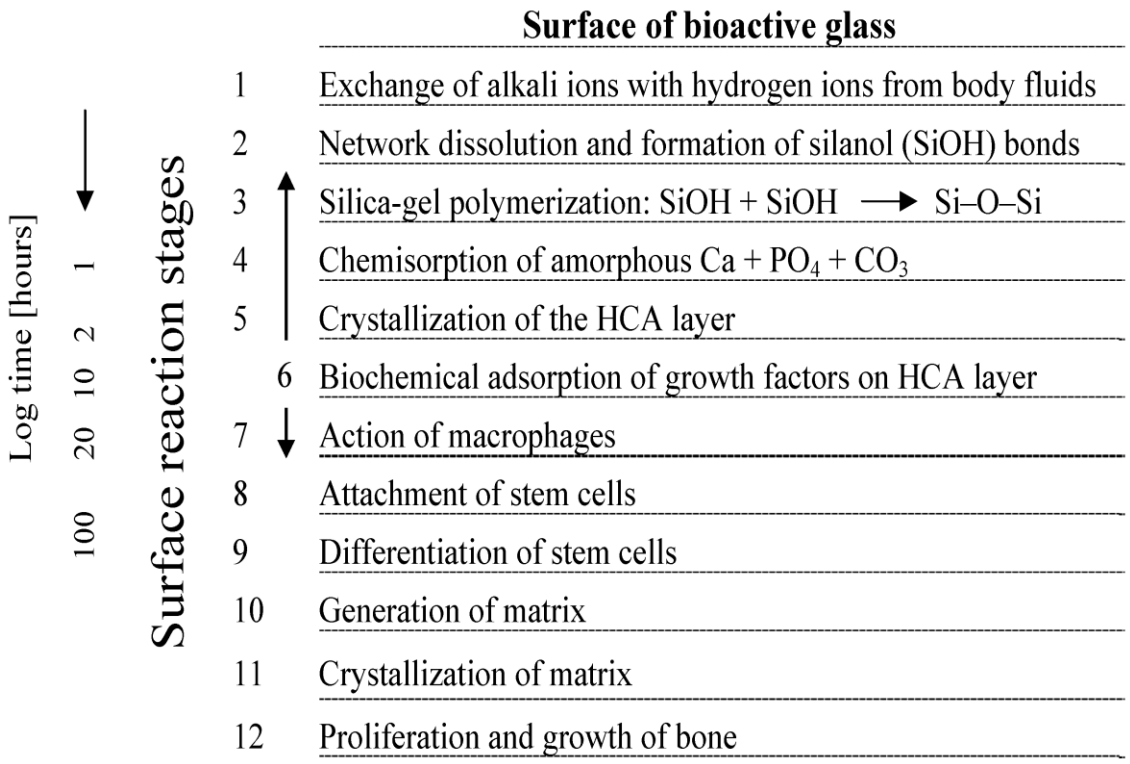

Figure 1.9: surface reaction stages [L.C. Gerhardt et al. 2010].

1.12. Hydroxyapatite

Hydroxyapatite (HA) is a calcium phosphate similar to the human hard tissues in morphology and composition. Mainly it has a hexagonal structure [SJ Kalita et al. 2007; NY. Mostafa et al. 2007] and a stoichiometric Ca/P ratio of 1.67, which is identical to bone apatite [S Teixeira et al. 2009; L. Guo et al. 2003]. An essential characteristic of hydroxyapatite is its stability when compared to other calcium phosphates. Thermodynamically, hydroxyapatite is the most stable calcium phosphate compound under physiological conditions as temperature, pH and composition of the body fluids. The production of nanomaterials has gained considerable attention for adsorption, catalysis, and optical applications, mainly when biomaterials are involved [N. Kantharia et al. 2014]. Nano-hydroxyapatite (nano-HAp) is attracting interest as a biomaterial for use in prosthetic applications due to its similarity in size, crystallography and chemical

composition with human hard tissue. Bone and teeth enamel are primarily composed of a form of this mineral.

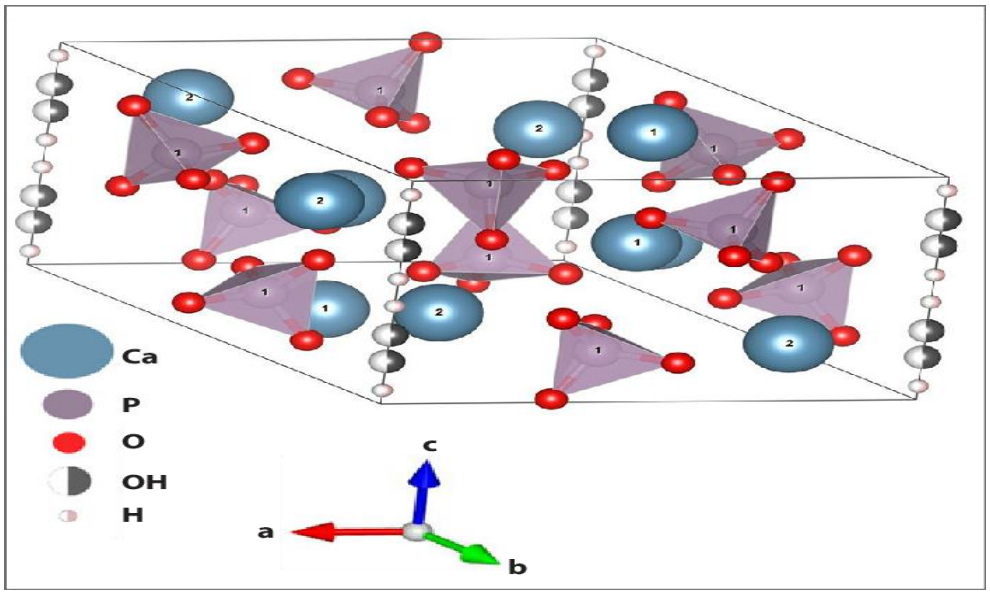

Figure 1.10: Structure of hydroxyapatite [M. Kolencik et al. 2016].

HA power (HA) is a major inorganic component of bone, has been used extensively for biomedical implant applications and bone regeneration due to its bioactive, biocompatibility, biodegradable, osteoconductive, nontoxicity and noninflammatory nature. HA is available in the market in many forms like solids blocks, micro-porous blocks and as granules. Nano-hydroxyapatite (n-HA) has proven to significant biological efficacy. nHA precipitates may have higher solubility and therefore affect the biological responses. It was able to promote the attachment and growth of human osteoblast-like cells (Huang et al., 2004). Clinical trials have shown that HA cement is both biocompatible and resistant to infection that the HA coating improves the success rate of implants. It has also been demonstrated that HA ceramics support mesenchymal stem cell (MSC) attachment, proliferation, and differentiation (Zhao et al., 2006). Nanoscaled HA with extraordinary properties such as a high surface area to volume

ratio and ultra-fine structure similar to that of biological apatite. HA significant effect on cell-biomaterial interaction has reported to the treatment of bone defects, and it could bond to living bone in implanted areas (Liuyun et al. 2008). HA has been used in bone regeneration and as a substitute of bone, teeth. Because it is a biocompatible, bioactive, non-inflammatory, non-toxic, osteoconductive and non-immunogenic material. Instability of the particulate nHA is often encountered when the particles are mixed with saline or patient's blood and hence migrate from the implanted site into surrounding tissues and causing damage to health tissue. Also HA ceramic is difficult to shape in specific forms required for bone substitution due to its hardness and brittleness. Therefore, a composites of HA and organic polymers have become a great interest to compensate the weak mechanical points of HA. Mohamed and Mostafa, (2008) reported that HA has low fracture toughness, hardness and brittleness, therefore HA cannot serve as a bulk implant material under the high physiological loading conditions traditionally associated with implants. Since the natural bone is a composite mainly consisted of nano-sized, needle-like HA crystals and collagen fibers. Bone defects that are generated by tumor resection, trauma, and congenital abnormality have clinically treated by the implantation of bioceramics or autogenous and allogenous bone grafts. Although autografting is a simplified procedure for reconstructive surgery. HA has incorporated into a wide variety of biomedical devices including dental implants, coatings on Ti-based hip implants, biodegradable scaffolds, and other types of orthopedic implants. Synthetic HA is a bioactive material that is chemically similar to biological apatite HA, has been used as a bioactive phase in the composites, coating on metal implants and granular filler for direct incorporation into human tissues (Rehman et al. 2000).

The nano-hydroxyapatite has got a variety of applications that include:

- Bone tissue engineering
- Bone void fillers for orthopaedic, traumatology, spine, maxillofacial and dental surgery.
- Orthopedic and dental implant coating
- Restoration of periodontal defects
- Edentulous ridge augmentation
- Endodontic treatment like pulp cappin
- Repair of mechanical furcation perforations and apical barrier formation
- Fillers for reinforcing restorative glass ionomer cement (GIC) and restorative composite resin
- Desensitizing agent in post teeth bleaching
- Remineralizing agent in toothpastes
- Early carious lesions treatment
- Drug and gene delivery

Titanium and stainless steel implants are often covered with hydroxyapatite coatings to trick the body and reduce the implant rejection rate. Hydroxyapatite has used in instances where there are bone voids or defects. This process is carried out through powders, blocks or beads of the material in the affected areas of bone. Due to its bioactivity, it encourages the bone to grow and restores the defect. This process can be an alternative to allogeneic and xenogenic bone grafts. It typically results in healing times shorter than those observed if hydroxyapatite had not used.

1.13. Bioactive Composites

The term “composite” usually reserves for those materials in which the distinct phases are separated on a scale more extensive than the biomaterial applications. (1) Dental

filling composites; (2) reinforced methyl methacrylate bone cement and ultra-high-molecular-weight polyethylene; (3) orthopedic implants with porous surfaces. It is known that a single material type does not always offer the mechanical and chemical properties desired for a particular application. Sometimes it is possible to combine two or more materials as a composite microstructure to achieve the desired properties. For bone tissue engineering, the requirements of a successful scaffold may not be entirely fulfilled by using single component biomaterials. Attempts have been made to develop polymer-bioceramic composite scaffolds that approximately mimic the natural bone structure. In these the biodegradable polymers (either natural or synthetic) will be reinforced by biocompatible inorganic phases (HA, TCP, bioactive glass) that can improve the mechanical properties (strength and toughness), control scaffold degradability and enhance the osteoconductive properties of the resulting composite material (Wang et al. 2006; Hutmacher et al. 2007). The development of strong biocomposite materials requires an appropriate selection of biomaterials, optimizing the loading volume, particle size, and shape of the inorganic phase to create effective bonding across the composite's interface. There are two principal ways for making bioceramic polymer composite scaffolds. Both can be used to fulfill a specific clinical need (Wang et al. 2006): 1- Incorporating bioceramic particles or fibers into a polymer base scaffold as a dispersed second phase through a variety of techniques; 2- Coating a polymer scaffold with a thin layer of bioceramic. Biocomposite scaffolds is used for bone tissue engineering to combine the advantages of both materials from which they are composed and also alleviates some of their drawbacks. For polymer-ceramic composites, the bonding between organic and inorganic phases is controlled by the addition of surfactants and chemical modification to increase interaction with the

polymer chains. The stiffness of the composite is directly proportional to the ceramic particle loading, but a dramatic increase in the number of interfaces present may give rise to more natural pathways along which cracks can propagate (Chen et al. 2008). Also, the composite material should exhibit good dispersion of ceramic particles not only into the polymer matrix, but should also be exposed on the material surface to improve osteoconductivity (Hutmacher et al. 2007). The acidic products from the degradation of bioactive polymers can be buffered by the primary degradation products of calcium phosphate or bioactive glasses, thus preventing the formation of an unfavorable environment for cells due to low pH values (Chen et al.2008).

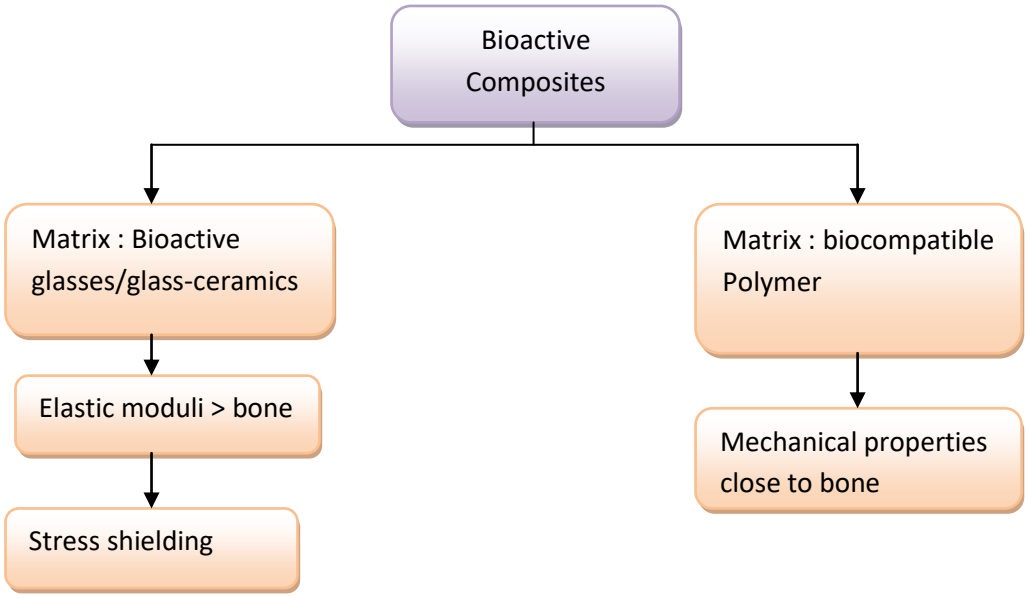

Figure 1.11: Bioactive composites classification.

The earliest bioceramic composites were designed to mimic the mechanical properties of the natural components of bone by replacing natural apatite with a synthetic HA and collagen with polyethylene (PE). The HA-PE composite has been used to replace the bones of the middle ear (Shirtliff et al.2003; Kikuchi et al.1999) fabricated a composite

polymer ceramic from TCP with Polylactic acid (PLA) to combine the osteoconductivity of ß-TCP and the degradability of PLA. A resorbable composite scaffold can be used for bone regeneration. It works by the degraded carrier systems delivering bioactive particles to a specific site within the body (Shirtliff et al., 2003).

Table 1.4: Application of Composite as implants used in human body [N.R. Patel et al. 2012].

Applications	**Types of materials**
Dentistry	CF/C, SiC/C,CF/Epoxy, GF/Polyester, GF/PC, GF/PP, GF/Nylon, GF/PMMA,UHMWPE/PMMA, CF/PMMA, GF/PMMA, KF/PMMA, Silica/BIS-GMA
Vascular Grafts	Cells/PTFE, Cells/PET, PET/Collagen, PET/Gelation, PU/PU-PELA
Joint replacements	PET/PHEMA, KF/PMA, KF/PE, CF/PTFE, CF/PLLA, GF/PU, PET/PU, PTFE/PU, CF/PTFE, CF/C, CF/UHMWPE,UHMWPE/UHMWPE, CF/Epoxy, CF/PS, CF/PEEK, CF/UHMWPE, CF/PE,
Bone cement	Bone particles/PMMA, Titanium/PMMA, UHMWPE/PMMA, GF/PMMA, CF/PMMA, Bio-Glass/BisGMA
Bone Replacement Materials	HA/PHB, HA/PEG-PHB, CF/PTFE, PET/PU, HA/HDPE, HA/PE, BioGlass/PE, Bio-Glass/PHB, Bio-Glass/PS, HA/PLA
Spine Cage, Plate, Rods, Screws, Disc, Finger Joint, Intramedullary Nails, Abdominal wall Prosthesis,	PET/PU, PET/Collagen, CF/LCP, CF/PEEK, GF/PEEK, CF/Epoxy, CF/PS, Bio-glass/PU, Bio-glass/PS, PET/SR, PET/Hydrogel, CF/UHMWPE

1.14. Bioactive coating

Bone can be considered as a natural composite of a polymer (collagen) and nanoceramic particles (nano HCA). This combination confers proper toughness as well as stiffness to the bone. Polymers are flexible but lack in mechanical strength while

inorganic materials such as ceramics are stiff and brittle. Although processing of polymers into complex shapes is easier. They are not bioactive and cannot provide osseointegration. Therefore, one promising tissue engineering approach to mimic the structure of the bone is the fabrication of biodegradable polymer/bioactive ceramic (or bioactive glass) composite materials.

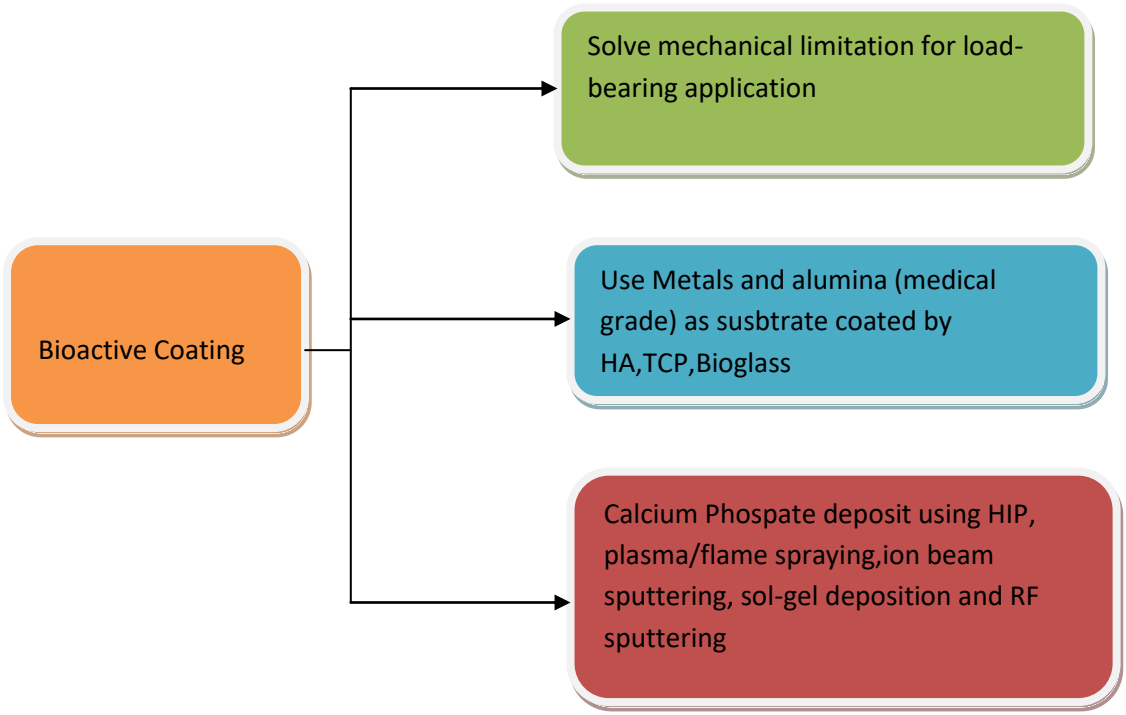

Figure 1.12: Bioactive coating.

The first advantage of this trend is an improved mechanical property of the biomedical device concerning strength, stiffness and fracture toughness. Secondly increased bioactivity and bone bonding capability of the structure due to the incorporation of bioactive ceramic or glass is expected. Moreover, the bioactive phase introduces a specific topography on the polymer surface (nano or micro roughness), which is tuned can be favorable for cell adhesion and deposition of ECM [Sk Misra et al. 2007]. Additionally, degradable polymers are resorbed by hydrolysis of the polymer chains

which shows an acidic behavior and has an autocatalytic effect on polymer degradation. Addition of a material such as bioactive glass leads to the rapid exchange of protons for alkali in the glass. Such glass dissolution buffers the surrounding medium and controls the fast degradation rate of the polymer [Li H et al. 2005]. Finally, not only polymer degradation kinetics is controlled by the higher amount of water absorption at the interfaces between the polymer and the more hydrophilic bioactive phase but also the ionic release rate of the bioactive ceramic can be controlled, resulting in better bone growth. As there is an increasing interest to add surface functionality to bioinert metallic implants, more efforts are concentrated on developing polymer/inorganic composite coatings. These coatings can enhance bioactivity, chemical stability and antimicrobial function of the implants [X Pang et al. 2005].

There are different techniques available to produce polymer matrix composite coatings. Composite CS/apatite coatings have been fabricated on Ti alloy substrates by mixing different ratios of CS and apatite powders, followed by dip coating of metal and a subsequent alkaline transformation at room temperature. In a novel approach, a silica xerogel/CS film was spin-coated on Ti discs at room temperature. These composite films displayed more hydrophilicity and improved osteoblastic proliferation compared to pure chitosan [SH Jun et al. 2010].

1.15. Significance of metals or alloys as biomaterials

Metals have played a primary role in establishing a scientific and technological development due to advances in engineering materials in the last few decades. Metallic implants have a significant economic impact in the biomaterial field. Metals are used as biomaterials due to their excellent electrical and thermal conductivity provided with

desired mechanical properties. While metals in general exhibit properties that make them appropriate for load-bearing applications, the high strength and resistance to fracture those metals with proper processing method gives reliable long-term implant performance in major load-bearing situations. Metals have different mechanical properties which make some advantageous compared with others for certain conditions.

Metallic biomaterials continue to be used for the fabrication of surgical implants that led to their selection for these devices. Metals have various applications throughout the body as implants. Electrically conductive metals such as platinum have tested as useful as electrodes in implantable cardiac pacemakers and defibrillators. In practice, a metallic implant will require a high load to cause deformation and will resist failure caused by repeated loadings. Metals are not prone to brittle fracture, therefore avoids sudden breakdown and prevents injury to a patient. Some metals are used as substitutes for hard tissue replacement such as total hip and knee joints, for fracture healing aids as bone plates, screws, spinal fixation devices, and dental implants because of their excellent mechanical properties and corrosion resistance. Some metallic alloys are used for more active roles in devices such as vascular stents, catheter guide wires, orthodontic archwires, and cochlear implants. Meanwhile, the mechanical properties of metals depend on their purity and processing method. Metals such as iron (Fe), chromium (Cr), cobalt (Co), nickel (Ni), titanium (Ti), tantalum (Ta), niobium (Nb), molybdenum (Mo), and tungsten (W) are present in a human body with a little amount. Sometimes those metallic elements in naturally occurring forms are essential in red blood cell functions (Fe) or synthesis of a vitamin 812 (Co), but cannot be tolerated in large amounts in the body. The first metal alloy explicitly developed for human use was the vanadium steel which was used to manufacture bone fracture plates and screws.

(a) Stainless Steels: During the 1960s, improved understanding of metallurgy combined with the development of superior surgical techniques, resulted in the implantation of the first total hip implant made from a stainless steel stem. The first stainless steel utilized for implant fabrication was the 18-8, which is stronger and more resistant to corrosion than the vanadium steel. Later on, stainless steels of grade 316 or 316L are frequently used as biomaterials. The 316 designation specifies that the alloy contains mostly iron, about 17% chromium, 10% nickel and small amounts of other metals. The addition of 17% chromium plays a vital role in making the metal corrosion resistant. Advantages and disadvantages of the stainless steel (SS) materials have certain benefits like high strength, ductility, toughness, ease of machining and cheaper than other metals but they are also suffering from problems such as corrosion problem, much higher modulus than bone, less bone bonding than other metals, Allergy consideration with Ni, Cr, Co and may create nickel ion sensitivity. Applications are surgical instruments like the bone plate for fracture fixation, stents, joint replacements (hip, knee), the dental implant for tooth fixation, heart valve, spinal Instruments, surgical instruments, screws, dental root implant, pacer, fracture plates, hip nails, shoulder prosthesis, etc.

(b) Cobalt based alloys: The cobalt chromium alloys generally consist of 58-70% Cobalt, 26-30% chromium and a small amount of other alloying elements like molybdenum, tungsten, iron, titanium, and nickel, etc. There are two types of cobalt chromium alloys. The castable Co-Cr-Mo alloy and the Co-Ni-Cr-Mo alloy which is usually wrought by (hot) forging. The two essential elements of the Co-Cr alloys form a robust solution of up to 65% Co. In Co-Cr-Mo alloy molybdenum up to 6 % is used. The molybdenum is added to produce fine grains which result in higher strengths after

casting or forging. The chromium enhances corrosion resistance as well as solid solution strengthening of the alloy. The castable Co-Cr-Mo alloy has been used for many decades in dentistry and recently used in making artificial joints. Advantages and disadvantages of Co-Cr alloys have the desirable features like high strength, high fatigue resistance high wear resistance and suitable to carry high loads and ideal for long-term implantation in the human body. But these alloys are very expensive and difficulty in fabrication of medical implants as per specific standards. Another limitation of these alloys has a much higher modulus than bone. Typical applications include bone and joint replacements (hip, knee), dental implants, dental restorations, a heart valves bone plate for fracture fixation, screws, dental root implant, pacer, suture, dentistry, orthopedic prosthesis, mini plates, surgical tools, etc.

(c) Ti and Ti Alloys: Since the 1930s, the use of titanium started as a biomaterial for implant fabrication. Titanium is a superior choice for medical implant applications due to similar yield strengths as stainless steel. Titanium‘s elastic modulus is only about half that of stainless steel. It is a biomaterial with high superficial energy and after implantation, it provides a favorable body reaction that leads to the direct opposition of minerals on the bone-titanium interface and titanium osseointegration. Ti forms a stable oxide (TiO_2) layer on its surface and provides it with protection against corrosion. Furthermore, Ti and its alloys are also often praising for their mechanical properties because they are very strong but also lightweight. Titanium is mainly used in implants in two forms as commercially pure titanium (CP-Ti) and extra low interstitial Ti-6Al-4V (ELI). These materials are classified as biologically inert biomaterials. These metals do not induce allergic reactions such as has been observed with some stainless steels which have produced nickel hypersensitivity in surrounding tissues. The advantages

include high biocompatibility, low Young‘s modulus, excellent corrosion resistance, low density but having certain disadvantages as poor tribological properties. As a metal, titanium is more expensive than iron and other components of stainless steel. Bulk titanium alloys used in implants present three main problems: (a) High cost because the amount of processing energy, melting and casting difficulties (b) Higher elastic modulus compared to bone. (c) Although the inert behavior of Ti is an excellent property, its bone attachment is difficult because it does not react with the human tissues. Applications bone are a joint replacement, fracture fixation, dental implants, pacemaker encapsulation, suture, parts for orthodontic surgery, bone fixation devices like nails, screws and plates, artificial heart valves and surgical instruments, etc. For permanent implant applications the alloy has a possible toxic effect resulting from released vanadium and aluminum.

(d) Zr-Nb Alloy: Developed initially for nuclear industry applications. Zirconium is a highly reactive metal. When it is annealed in an oxygen-containing atmosphere at 500˚C develops a relatively thick (5 μm) monoclinic ZrO_2 layer over the alloy substrate and form a dense cohesive surface oxide layer (ZrO_2) spontaneously on exposure to an oxygen-containing environment. ZrO_2 is very hard and can be used to build good wear resistant surface considering sufficient layer thickness. It also results in a corrosion protection layer. Zr-Nb alloy is used for making orthopedic components that are primarily intended for compressive loading and resisting wear (such as femoral hip implant and knee implant components).

(e) Ni-Ti Alloys: The use of Ni-Ti for medical purposes was started since 1970s. The titanium-nickel alloys have exceptional properties that could be very useful in surgical applications. When applied in certain surgical implants, Ni-Ti is expected to provide

radically new functional capabilities, improved performance and a possibility of using modestly invasive techniques. The use of Ni-Ti as a biomaterial is fascinating because of its superelasticity and shape memory effect and excellent damping properties, which are entirely new properties compared to the conventional metal alloys. Low Young‘s modulus Ni cause allergy because of the high nickel content of Ni-Ti, it is theoretically possible that nickel may dissolve from the material due to corrosion and cause unfavorable effects. The biocompatibility of Ni-Ti alloys must be considered before it can be safely used as an implant material. These alloys are used to develop the bone plates, stents, and orthodontic wires. Orthodontic wires formed from a Ni-Ti-based alloy are useful because of the wide range of working‘ that these wires provide during force application for tooth repositioning.

1.16. Dental Alloys

The metals and alloys for dental implant is used in practice from an ancient period. From research finding it is observed in archaeological records of China and Egypt before the Common Era. These countries had utilized stone and ivory in earliest dental implants. Research study reveals that metal implant devices of gold, lead, stainless steel cobalt alloys, iridium, and tantalum were developed in the early 20th century. Implant designs are traceable to early Egyptians and South Central American cultures and have developed the present implant designs that are now experiencing explosive popularity. In recent dentistry field, metals or alloys like Titanium, cast Ti components, Cast Ti-based alloys, Ti-6AI- 4V, CP- Ti, Ti-Cu-Ni, Ti-V, Ti-Cu, Ti-Pd and Ti-Co alloys, Co-Cr-Mo based alloy, Fe-Cr-Ni based alloys etc., are either in used in practice or in the experimental stage of development. These metals or alloys used in dentistry for the following purposes (a) Direct fillings in teeth (i.e., dental amalgams). (b) Fabricating

crowns and bridges (noble metal and base metal alloys). (c) Partial denture frameworks (base metal alloys). (d) Orthodontic wires and brackets (stainless steel, Ti alloys, and Ni-Ti alloys) and dental implants (CP -Ti and Ti-6A-l4V). Necessity of acceptable characteristics in dental implant includes sufficient strength, toughness, ease of fabrication, wear resistance, corrosion resistance, biocompatibility, tissue interface characteristics, surface properties of the implant and freedom from defects, etc. As in the orthopedic applications, the significant advantage of metal for these dental applications is the high intrinsic strength and fracture resistance of this class of materials. A number of the metals and alloys already described finding application in dentistry. Dental implant materials with requirements very similar to materials used for orthopedic joint replacement implants are made almost exclusively from Ti and Ti-6Al-4V. Orthodontic wires and brackets are made of stainless steel (types 302, 303, 304 and 305), Co-Cr-Ni-Mo alloys (Elgiloy), β-Ti, and Ni-Ti alloys (because of their low elastic moduli, high strengths and consequently large working range, a desirable characteristic for this application).

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