SYNTHESIS AND CHARACTERIZATION OF CARBONATED HYDROXYAPATITE AS BIOCERAMIC MATERIAL

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SYNTHESIS AND CHARACTERIZATION OF CARBONATED HYDROXYAPATITE AS BIOCERAMIC MATERIAL

by

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LIST OF ABBREVIATION

BET : Brunauer, Emmet and Teller

CHA : Carbonated Hydroxyapatite

DTS : Diametral Tensile Strength

FE-SEM : Field Emission Scanning Electron Microscope

FTIR : Fourier Transform Infra-Red

FWHM : Full Width at Half Maximum

HA : Hydroxyapatite

ICDD : International Centre for Diffraction Data

MPa : Megapascal

nm : Nanometer

SBF : Simulated Body Fluid

TEM : Transmission Electron Microscope

TG/DSC : Thermogravimetry/Differential Scanning Calorimetry

TTCP : Tetra-calcium Phosphate

XRD : X-ray Diffraction

XRF : X-ray Fluorescence

β-TCP : Beta Tri-Calcium Phosphate

ABSTRAK

(SINTESIS DAN PENCIRIAN HIDROKSIAPATIT BERKARBONAT SEBAGAI BAHAN BIO-SERAMIK)

Dalam kajian ini, hidroksiapatit berkarbonat (CHA) disintesis menggunakan dua kaedah sintesis, iaitu melalui kaedah pemendakan dan pengemulsian nano. Kandungan karbonat di dalam larutan dipelbagaikan dengan nisbah CO_3^{2-}/PO_4^{3-} iaitu 1, 3, 5 dan 7, manakala pH dan nisbah Ca/P adalah tetap dengan masing-masing 11 dan 1.67. Kaedah penurasan vakum dan pengeringan digunakan dalam proses sintesis untuk menghasilkan serbuk CHA. Rawatan haba pada suhu berbeza, iaitu 600, 700, 800, dan 900^o, dilakukan ke atas serbuk bagi menganalisa kestabilan haba. CHA pukal disediakan melalui kaedah penekanan, dengan diikuti pengkarbonatan bagi menghasilkan produk seramik daripada serbuk untuk terus permohonan. Proses penekanan dan masa pengkarbonatan dipelbagaikan semasa penyediaan CHA pukal.

Kesemua serbuk yang disintesis menghasilkan CHA jenis B, yang mana jenis ini sesuai untuk digunakan sebagai pengganti tulang asli, dengan saiz nanometer pada lingkungan 20-35 nm. Merujuk kepada keputusan yang diperoleh, didapati kandungan karbonat memberi pengaruh kepada sifat serbuk CHA. Dengan nisbah CO_3^{2-}/PO_4^{3-} yang tinggi, iaitu dengan nisbah 7, telah menyebabkan fasa kedua kalsit ($CaCO_3$) terbentuk. Serbuk dengan kandungan karbonat yang tinggi juga menghasilkan kestabilan terma yang rendah semasa rawatan haba, yang mendorong pembentukan fasa $CaCO_3$ dan CaO. Sebaliknya, serbuk CHA dengan nisbah CO_3^{2-}/PO_4^{3-} adalah 1 menghasilkan fasa tunggal CHA dengan nisbah Ca/P yang menghampiri tulang asli. Di samping itu, serbuk CHA dengan komposisi ini juga menghasilkan kestabilan terma yang tinggi. Serbuk CHA dengan nisbah CO_3^{2-}/PO_4^{3-} yang rendah menunjukkan tiada apa-apa bukti pembentukan fasa sekunder semasa rawatan haba walaupun ada sesetengah kumpulan karbonat yang berpindah ke kawasan A semasa rawatan haba. Proses penekanan semasa membentuk CHA pukal juga memainkan peranan penting bagi ciri-ciri mekanikal. CHA pukal yang telah disediakan melalui penekanan sebesar 8 MPa dan pengkarbonatan selama 72 jam, telah menunjukkan nilai DTS yang optimum pada 1.68 MPa. Pembentukan lapisan apatit juga didapati berlaku di dalam CHA pukal selepas perendaman dalam larutan SBF selama 14 hari. Ini menunjukkan bahawa CHA yang disintesis dalam kajian ini telah menunjukkan kebioserasian yang baik dengan kekuatan yang mencukupi dan ini menjadikan bahan ini sesuai untuk diaplikasikan sebagai pengganti tulang dalam kawasan tiada galas beban.

ABSTRACT

Carbonated hydroxyapatite (CHA) was synthesised from two synthesis routes, which were the precipitation method and nano-emulsion method. The carbonate content in the solution was varied with CO_3^{2-}/PO_4^{3-} ratio of 1, 3, 5 and 7, while pH and Ca/P ratio were constant at 11 and 1.67 respectively. Vacuum filtration and drying was used in the synthesis process to obtain the CHA powder. Heat treatment at different temperatures, which were 600, 700, 800 and 900^{o}C, in flowing CO_2 gas were performed to the powder to analyse the thermal stability. Moreover, bulk CHA was prepared by pressing method, followed by carbonation to produce the ceramic part from the powder for further application. The molding pressure and carbonation time were varied during the preparation of bulk CHA.

All the synthesised powder was found to produce B-type CHA, which is the preferred substitution type in biological bone, in nanometer size of the range 20-35 nm. Based on the results obtained, the carbonate content was found to influence the properties of the CHA powder. With high CO_3^{2-}/PO_4^{3-} ratio of 7, it was found that the secondary phase of calcite had formed. The powder with high carbonate content also had low thermal stability during heat treatment, which leads to formation of $CaCO_3$ and CaO phases. On the other hand, CHA powder with CO_3^{2-}/PO_4^{3-} ratio of 1 had produced single phase CHA with the Ca/P ratio close to biological bone. It also has high thermal stability, reaching 900^{o}C. CHA powder with this composition, having low CO_3^{2-}/PO_4^{3-} ratio, showed no evident of secondary face formation during heat treatment although some of the carbonate group was found to move to A-sites during the heat treatment. The compaction pressure of bulk CHA also played important role in the mechanical properties. Bulk CHA that was prepared with molding pressure of 8 MPa and 72 hours of carbonation showed optimum DTS value at 1.68 MPa. The formation of apatite layer occurred in the bulk CHA after soaking in SBF solution for 14 days. This indicated that the CHA synthesised in this study has a good biocompatibility with sufficient strength to be applied as bone substitute in non-load bearing areas.

CHAPTER I

INTRODUCTION

1.1 Background and Problem Statement

The role of hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$, in biomedical application is well known. Hydroxyapatite has a long history of being used as a bioceramic material in bone grafting, bone tissue engineering and drug delivery system (Suchanek et. al., 2002). This is possible due to its properties of biocompatibility, bioactivity, osteoconductivity and non-toxicity. Furthermore, the function of hydroxyapatite in this biomedical application is largely determined by its similarity in chemical structure with biological apatite, which comprises the mineral phases of calcified tissues in the enamel, dentine and bone (Murugan and Ramakrishna, 2006).

As a mineral substance in the biological bone, HA is approximately 70% by weight and 50% by volume (Shackelford, 1999). However, biological apatite does differ from pure synthesised hydroxyapatite, in terms of structure, composition, crystallinity, solubility, biological reactivity and other physical and mechanical properties. It has been reported that biological apatite is usually calcium deficient with low crystallinity and always carbonated substituted. Carbonate is the major secondary ions, by weights, in the biological apatite besides the Ca^{2+} and PO_4^{2-}. The amount of carbonate is about 3-8wt% of the hard tissues of the human body (Barinov et. al., 2006). Hence, lately, biological apatite is referred to as carbonate apatite.

Synthetic carbonated hydroxyapatite (CHA) is reported to be a better model for biological apatites than pure Hydroxyapatite. Carbonate ions can substitute, either in the hydroxyl groups (A-type) or the phosphate groups (B-type). These two types of substitutions can also occur simultaneously, resulting in mixed AB-type substitutions (Lafon et. al, 2008). Typically, the carbonate content in the mineral bone is dependent on the age. The value of A/B type ratio in the carbonated hydroxyapatite is reported to increase with increase of human age. A-type carbonated hydroxyapatite is mostly found in the old tissue, while B-type is found in the young tissue. B-type CHA is the most abundant species in human bone (Landi et. al., 2004).

CHA has been reported to have better biological activity than pure hydroxyapatite. HA is the least soluble and the most stable material among the calcium phosphates and thus is undesirable characteristic because HA may impede the rate of bone regeneration upon implantation. Incorporation of carbonate into HA caused an increased in solubility, decrease in crystallinity, change in the crystal morphology and better biological activity (Porter et. al, 2005). CHA appears to be an excellent material for bioresorbable bone substitutes. The carbonate in the B-site, synthesised by precipitation method, has been found to reduce size of the precipitates and durability of the tooth enamel and bones against weak acids. Increasing the carbonate content in the apatite structure was also found to reduce the sintering temperature as well as the decomposition temperature at which HA decomposes to tricalcium oxide and calcium oxide (Sampath-Kumar et. al., 2000).

Various synthesis routes have been explored to produce nano-sized CHA. These methods mainly include chemical precipitation, hydrothermal synthesis, and mechano-chemical. A-type CHA is commonly prepared by exposing hydroxyapatite at high temperature under flow of carbon dioxide, while B-type CHA is generally synthesised using wet method from precipitation reaction in aqueous media with controlled parameters (pH, temperature, reagent concentrations) (Lafon et. al., 2008). Since the synthesis method influences the properties of CHA, it is of great importance to develop the synthesis method for CHA initial powder with suitable characteristic, i.e chemical composition, morphology and particle size.

Carbonated hydroxyapatite is formed into a dense or porous bioceramics to be applied as bone substitute. CHA bioceramic is applied in non load-bearing areas due to its low mechanical reliability. To obtain high strength ceramic parts, sintering is often performed at a certain temperature. However, sintering of CHA would cause the decomposition of carbonate and also the formation of secondary phases. Carbonate substitution in the apatite is caused by lattice defects and this would depress the thermal stability. The thermal stability of the CHA can be controlled by varying the carbonate content, heating rate and calcination atmosphere (He et. al., 2007a). Though some studies have been made to produce CHA powder and ceramic, the production of bulk CHA with varying and controlled amounts of carbonate ions in the apatite structure has never been totally investigated and is still difficult to achieve.

In the current research work, different synthesis methods were conducted to produce pure B-type carbonated hydroxyapatite with suitable chemical composition, morphology and particle size. The effects of the carbonate content and heat treatment atmosphere are also investigated to assess the thermal stability of synthesised CHA powder. In this study, bulk CHA was then prepared with an alternative method without exposing to any heat treatment process. This research is focused to produce carbonated hydroxyapatite with suitable chemical, physical, mechanical and biological properties that can be applied in the biomedical application.

1.2 Objective of the Research

The aim of this research is to produce carbonated hydroxyapatite biomaterial with adequate strength, good physical properties and biocompatibility. With this main objective, the following studies were conducted:

1. Synthesis of CHA powder by two synthesis methods, i.e. precipitation and nano-emulsion routes.
2. Characterization of the physical and chemical properties as well as the thermal stability of as-synthesised CHA powder.
3. Preparation of bulk CHA by carbonation method and characterizing the physical and mechanical properties.
4. Investigation of the bioactivity of bulk CHA using simulated body fluid (SBF) solution.

1.3 Project Overview

In this study, two methods were selected to synthesis carbonated hydroxyapatite. These were the precipitation and nanoemulsion methods. These techniques were selected due to the simple process, availability of the equipments and also easily adjustable parameters with potentially good results. The amount of carbonate addition was varied in order to study the formation of carbonate in carbonated hydroxyapatite, while pH and temperature were maintained at constant value. The CHA bulk was prepared by uniaxial pressing method and followed by carbonation. Various parameters were investigated in preparing the bulk CHA. The compaction pressure was varied using several different loads. The time of carbonation was also studied. Thermal stability of the powder was also analyzed in this study by varying the heat treatment temperature of the as-synthesised powder under CO_2 atmosphere.

The phase of the as-synthesised powder was examined using X-ray diffraction. The presence of carbonate ions was confirmed using Fourier Transformed Infra-Red (FTIR) Spectroscopy. The ratio of Ca/P in the powder was measured by XRF. Field Emission Scanning Electron Microscope and Transmission Electron Microscope was used to characterize the morphology of the as-synthesised powder, the heat treated powder and the fracture surface of bulk samples. The density and the porosity of the bulk CHA samples were measured, and the mechanical properties of the bulk CHA were determined by using Diametral Tensile Strength (DTS) test. The bioactivity of the bulk CHA was also investigated by in vitro test in the SBF solution. The formation of hydroxyapatite on the surface bulk

CHA was analyzed by SEM method. The general flow chart in this study is shown in Figure 1.1.

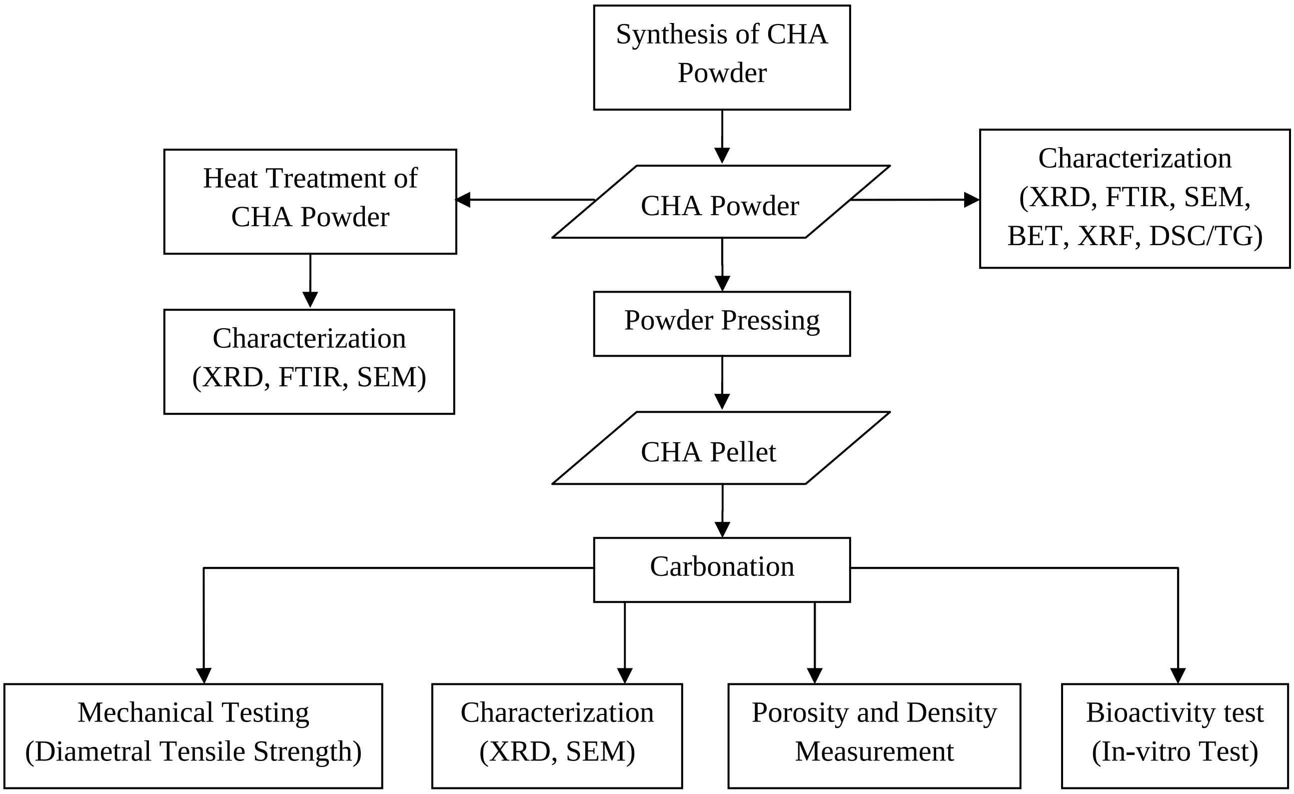

Figure 1.1 General flow chart of the research

CHAPTER II

LITERATURE REVIEW

2.1 Introduction

The use of bone substitutes in human surgery has dramatically increased over the last few decades. These materials has been used to guide and expand the bone healing tissue, to become integrated within it and then subjected to the same remodelling process as the actual bone (Frayssinet et. al, 1998). Autograft, which is graft transplanted from part of the patient's body to another part, is designated as the "golden standard" of all bone substitution materials. However, the available amount of proper bones substitution is generally limited and the implantation requires a second operation which is very painful (Neumann and Epple, 2006). Therefore, there is high clinical demand for synthetic bone substitution materials. Schwartz et. al. (1999a) reported that they had used biphasic calcium phosphate ceramic, consisting of 65% hydroxyapatite and 35% β-TCP, since 1996 for bone defect filling in any orthopaedic or trauma operation where autograft use was not possible or even wanted. Currently the worldwide biomaterials market is valued at close to US$24,000M. Orthopedic and dental applications represent approximately 55% of the total biomaterials market (Ben-Nissan, 2004).

In recent years, synthetic hydroxyapatite has been extensively used as the synthetic bone substitution materials due to its excellent biocompatibility and its similar characteristics with biological bone. However, although the chemical structure of hydroxyapatite is similar with the biological bone, in reality biological bone contains several other ions which is absent in the pure synthetic hydroxyapatite. Carbonate is one of the major ions that substitute apatite structure in the biological bone (Tadic et. al., 2002). Consequently, a number of studies have been focussed on the production of synthetic carbonate substituted hydroxyapatite (CHA) ceramics for bone substitute.

This review discusses an overview of biomaterial definitions. The topic on bioceramic material, as a part of biomaterials, will be explained in more details with its classifications and applications. The overview of bone structure and its properties will be described as well. As CHA is calcium phosphate based bioceramics, the properties of this bioceramic are presented in this chapter. This is followed by the review of the synthesis of CHA powder.

2.2 Natural Human Bone

Bone may be simply described as a biocomposite of organic and mineral phases. It is a complex mineralized living tissue that shows a certain degree of strength and rigid structure while maintaining some degree of elasticity (Currey, 2008). The organic phase of bone mostly consists of collagen and minor amounts of important non-collageneous proteins. Bone mineral is an impure version of hydroxyapatite, essentially a carbonate substituted apatite. In particular, there is 3-8% of carbonate replacing the phosphate groups with other minor constituents such as magnesium, sodium, and fluoride. It is sometimes referred to as carbonate substituted hydroxyapatite (LeGeros et. al., 2006). Bone also contains bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts) and various osteoinductive growth factors and molecules. In most bones, the weight proportions of major components are 60-70% of mineral substances, 20-30% of collagen and other organic components, and the remaining is water (Weiner and Zaslansky, 2004). The composition of human bone is shown in Table 2.1.

Table 2.1 Composition of human bone (Hench and Wilson, 1993)

Constituent	Bone (wt %)
Calcium, Ca^{2+}	24.5
Phosphorus, P	11.5
Sodium, Na^{+}	0.7
Potassium, K^{+}	0.03
Magnesium, Mg^{2+}	0.55
Carbonate, CO_3^{2-}	5.8
Fluoride, F^{-}	0.02
Chloride. Cl^{-}	0.10
Total inorganic	65.0
Total organic	25.0
Absorbed H_2O	9.7

Most bioceramic implants are in contact with bone. Therefore, it is important to know the various types of bone in the body. There are two types of bones that are most concerned in the use of bioceramics. They are the cancellous bone and the cortical bone (Hench and Wilson, 1993). Figure 2.1 shows the structure of a long bone, consisting of the cortical and the cancellous bone.

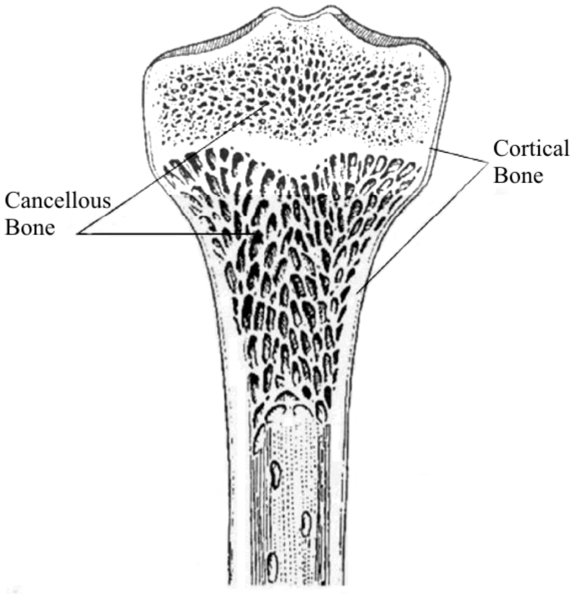

Figure 2.1 Longitudinal section of a human femur (Meyers et. al., 2008)

2.2.1 Cortical Bone

Cortical or the compact bone is a dense bone consisting of parallel cylindrical units and found in the shafts of long bones (Currey, 1998). As explained before, the main constituents are mineral hydroxyapatite, the fibrous protein, collagen and water. There is some non-collagenous organic material. The mineral is variant of hydroxyapatite, which is hydrated calcium phosphate: $Ca_{10}(PO_4)_6(OH)_2$. The crystals are impure, particularly with about 3-8% of carbonate replacing the phosphate groups, making the mineral technically a carbonate apatite. Various other substitutions can also take place (Bhat, 2005).

The mineral, hydroxyapatite with carbonate substitution, has plate-like morphology with small crystal size about 4 nm x 50 nm x 50 nm. The density of cortical bone is about 1.99 g/cm^3 and has range of values for the mechanical properties (Currey, 1998). Table 2.2 gives the general mechanical properties of cortical bone.

Table 2.2 Mechanical properties of cortical bone (Currey, 1998)

Mode	Orientation	σ_u (MPa)	σ_y (MPa)	e
Tension	Longitudinal	133	114	0.031
	Tangential	52	n/a	0.007
Compression	Longitudinal	205	n/a	n/a
	Tangential	130	n/a	n/a

2.2.2 Cancellous Bone

Cancellous bone, also known as trabecullar or spongy bone, is less dense than the cortical bone. It occurs across the ends of the long bones and is like a honeycomb in cross section. It is composed of short struts of bone material called trabeculae. The volume fraction of cancellous bone typically ranges from 0.60 for dense cancellous bone to 0.05 for porous trabecular bone (Hench and Wilson, 1993).

Cancellous bone has a relatively uniform composition that is similar to cortical bone tissue but is slightly less mineralized and slightly more hydrated than cortical tissue (Bhat, 2005). Being a heterogeneous open cell porous solid, cancellous bone has anisotropic mechanical properties that depend on the porosity of the specimen as well as the architectural arrangement of the individual trabeculae. Cancellous bone is linearly elastic until yielding at approximately 1-2%. After yielding, it can maintain a relatively large deformation. Typically the modulus of human cancellous bone is in the range 0.010-2 GPa. Strength which is linearly and strongly correlated with modulus is typically in the range 0.1-30 MPa (Keaveny, 1998). Table 2.3 shows the mechanical properties of cancellous bone.

Table 2.3 Mechanical properties of cancellous bone (Keaveny, 1998)

Property	Cancellous Bone
Compressive Strength (MPa)	2-12
Flexural Strength (MPa)	10-30
Tensile strength (MPa)	0.1-20.0
Strain to failure	5-7
Young's Modulus (GPa)	0.1-2.0
Fracture Toughness, K_{IC} ($MPa.m^{1/2}$)	N.A.

2.3 Bone Grafting

The value of bone transplantation is increasing over the years. Transplant bone surgery is done at least ten times more often than any other transplantable organ. Thus, bone grafting or bone substitute has become critical in orthopaedic surgery (Sutherland and Bostrom, 2003).

Bone graft can be defined as an implanted or transplanted tissue from another part of the body or any synthetic material to reconstruct bone defect. Bone grafts should have a good local and systemic compatibility, the capability of being substituted by bone and of completely filling any defect (Schnettler et. al., 2004). Bone graft source can be adopted from another part of human body (autograft and allograft), animal (xenograft), or synthetic biomaterial.

2.3.1 Autogenous Bone Grafting

The most compatible source of bone graft tissue is offered by humans themselves. Autogenous bone grafting is a method where the bone is transplanted from part of a patient’s body to another. This bone grafting provides all three elements for generating and maintaining bone tissue, which are osteogenic progenitor cells, osteoinductive growth factors and osteoconductive matrices. The autogenous bone graft is considered as the “golden standard” of bone grafting (Schieker et. al., 2006).

However, it has been pointed out that bone autograft has several drawbacks, including invading a healthy site to collect the required bone. The amount of collectable bone is limited and the collected bone is also limited in its form. Moreover, this method requires secondary operation procedure which is costly, time consuming and sometimes causes additional trauma (Ishikawa et. al., 2003).

2.3.2 Allogeneic Bone Grafting

Allogeneic bone grafting is also a method that replaces the bone tissue with the tissue from humans themselves. The difference with the autograft is that the tissue source is not from the same individual. This type of grafting is not restricted by harvest availability as found in autogenous grafting (Sutherland and Bostrom, 2003).

In practice, fresh allografts are rarely used because of immune response and the risk of transmission of disease. Allogeneic bone grafting carries the potential risk of transmitting tumour cells and a variety of bacterial and viral infections including those that cause AIDS or hepatitis on patients. Additionally, blood group-incompatible bone transplantation can cause the development of antibodies within ABO systems (Schnettler et. al., 2004).

2.3.3 Xenogeneic Bone Grafting

Xenograft is another type of bone grafting whereby the bone graft is transferred from other mammalian species (Neumann, 2006). Bovine graft, e.g kiel bone, is a typical example of xenogeneic bone graft. Similar with allograft, xenograft is generally associated with potential infections. This graft tends to be less effective than allograft despite antigenicity treatment. Antigenicity means the ability of a substance to trigger the immune response in a particular organism. Generally, the graft must be impregnated with the host marrow. However, it elicits an acute antigenic response with a high failure rate (Tancred et. al, 1998).

2.3.4 Alternative Synthetic Materials

As there is limited availability of autogenous graft and high risk of infections in allogeneic and xenogeneic grafts, bone substitutes of synthetic materials are now considered useful alternatives. In the last decade, technological research has moved towards the synthesis of new substituting materials mimicking natural bone tissue (Tampieri et. al., 2005). These synthetic materials have to fit the basic criteria of bone implants which are:

1. Compatible with the physiological environment, and
2. Its mechanical properties should be closely matched with the tissue being replaced.

The synthetic bone substitutes are safe and proven as an alternative to other bone graft. They provide a suitable environment for the body to repair or produce its own bone, either replacing the bone graft substitute over time with the original bone, or combining with the bone graft substitute to form a strong repaired bone (Tadic, 2004).

2.4 Biomaterials

The term biomaterials can be interpreted in many ways. Black (1992) defined biomaterials as a nonviable material used in a medical device, intended to interact with biological systems. Williams (1992) defined it as a material intended to interface with the biological systems to evaluate, treat, or replace any tissue, organ, or function of the body. As a simple definition, biomaterials can be defined as a synthetic material used to replace part of a living system or to function as intimate contact with living tissues (Park and Bronzino, 2003).

In reality, biomaterial applications had begun as far back as ancient Egypt and Phoenicia, where loose teeth were bound together with gold wires for tying artificial ones to neighbouring teeth (Park et. al., 2000). From as early as 19th century, artificial materials and devices have been developed to a point where they can replace various components of the human body. In the early 1900s bone plates were successfully implemented to stabilize bone fractures and to accelerate their healing (Ben-Nissan, 2004)

The success of biomaterials in the body depends on factors such as the material properties, design and biocompatibility of the material used. Biocompatibility involves the acceptance of an artificial implant by the surrounding tissues and the body as whole (Park and Bronzino, 2003). The compatibility characteristics which may be important in the function of an implant device made of biomaterials include adequate mechanical properties such as strength, stiffness and fatigue and biological characteristics of the material (Schwartz et. al., 1999b).

Biomaterials can be broadly categorized under the four categories: metal, polymer, ceramic, and composite. Each material has their own benefits. Metallic biomaterials have mechanical reliability that other class of biomaterials could not succeed. Ceramic biomaterials have excellent biocompatibility while implanted in the body. On the other hand, polymer biomaterials are easy to manufacture to produce various shapes with reasonable cost and desired mechanical and physical properties. Composite biomaterials offer a variety of advantages in compare to homogeneous materials (Lakes, 2003). The advantages and disadvantages of each category of biomaterials are briefly explained in Table 2.4.

Table 2.4 Class of materials used as biomaterials (Park and Lakes, 2007)

Materials	Advantages	Disadvantages	Examples
Polymers (nylon, silicone, rubber, polyester, etc)	Resilient, easy to fabricate	Not strong, deforms with time, may degrade	Sutures, blood vessels, other soft tissues, hip socket
Metals (Ti and its alloys, Co-Cr alloys, Au, Ag, stainless steel, etc)	Strong, tough, ductile	May corrode, dense, difficult to make	Joint replacements, dental root implants, bone plates and screws
Ceramics (alumina, zirconia, calcium phosphates including hydroxyapatite, carbon)	Very bio-compatible	Brittle, not resilient, weak in tension	Dental and orthopaedic implants
Composites (carbon-carbon, wire- or fiber- reinforced bone cement)	Strong, tailor-made	Difficult to make	Bone cement, dental resin

2.5 Bioceramics

Kingery et. al. (1976) defined ceramic as the art and science of making and using solid articles that have their essential component as inorganic and non metallic materials. In recent years, ceramics are used to replace various part of the body, especially for bone substitute. Ceramics used in medical and dental practices for the human body are classified as bioceramics (Bilotte, 2003).

In general, bioceramics show better biocompatibility with tissue response compared to polymer or metal biomaterials (Bilotte, 2003). Based on their excellent biocompatibility, they are used as implants within bones, joints and teeth in the form of bulk materials of specific shape. They are also used as coatings on a substrate or in conjunction with metallic core structures for prosthesis (Desai et. al., 2008). In other situations, bioceramics are used as reinforcing components in a composite, combining the characteristics of both into a new material with enhanced mechanical and biochemical properties. Ceramic structures can also be modified with varying porosity for bonding with the natural bones (Hench and Wilson, 1993).

In order to be classified as a bioceramic, the ceramic materials have to exceed the properties listed in Table 2.5.

Table 2.5 Desired properties of implantable bioceramics (Bilotte, 2003)

1. Non-toxic
2. Non carcinogenic
3. Non allergic
4. Non-inflammatory
5. Biocompaticle
6. Biofunctional for its lifetime in the host

However, despite the excellent biocompatibility of bioceramics, the problems that occur in conventional ceramics are also exist in bioceramics. Primary drawbacks of bioceramics are their brittleness, low strength and inferior workability. Consequently, bioceramics are very sensitive to notches or microcracks because they do not deform plastically (Bilotte, 2003).

2.5.1 Classification of Bioceramics

In general, bioceramics can be described according to the tissues response in three terms. These are bioinert, bioactive and bioresorbable. Table 2.6 summarized the implant-tissue response of each type of bioceramics.

Table 2.6 Consequences of implant tissue interactions (Hench and Wilson, 1993)

Implant-tissue Reaction	Consequence	Example
Bioinert	Tissue forms a non-adherent fibrous capsule around the implant	Alumina (Al_2O_3), Zirconia (ZrO_2) and Carbon
Bioactive	Tissue forms an interfacial bond with the implant	Hydroxyapatite, Bio-glass, A-W glass
Bioresorable	Tissue replace implant	β-tricalcium phosphate, carbonated hydroxyapatite, calcium carbonate

The relative chemical activity of different types of bioceramics is compared in Figure. 2.2. As showed in Table 2.6 and shown in the Figure. 2.2, bioinert implant does not form a bond with the bone. In the case of bioactive ceramic, a bond forms across the implant-tissue interface. On the other hand, resorbable bioceramic actually dissolve in the body and is replaced by the surrounding tissue (Carter and Norton, 2007).

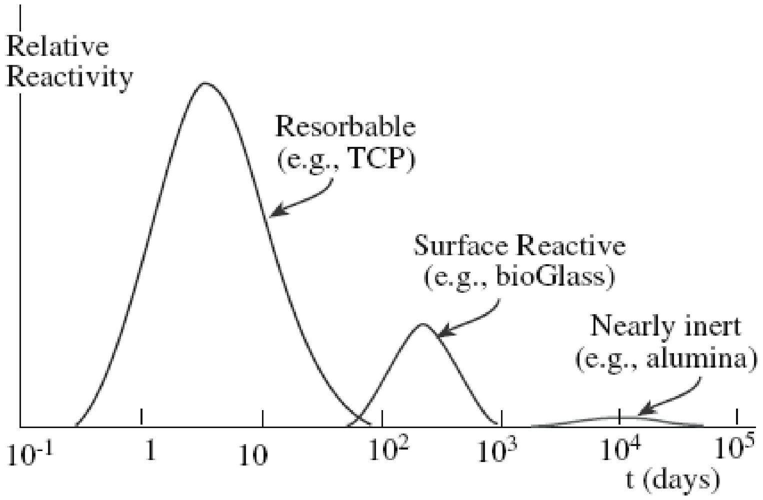

Figure 2.2 Relative reactivity of different type of bioceramics (Carter and Norton, 2007)

2.5.1.1 Bioinert Ceramics

The term bioinert refer to any material that has minimal interaction with its surrounding tissues once placed within human body. This type of bioceramic shows little chemical reactivity, even after long term of exposure to the physiological condition and therefore shows minimal interfacial bonds with the living tissues (Bhat, 2005). Bioinert ceramics are relatively stable in a human body and do not show harmful response or bioactivity. They resist corrosion and wear and have all the properties listed in Table 2.6. Generally, fibrous capsules are developed around bioinert implants at their interface. The thickness of the capsules depends on the tissue compatibility of the bioinert material. Materials with excellent tissue compatibility allow thinner fibrous capsules. Thus, its biofunctionality relies on tissue integration through the implants (Ben-Nissan, 2004).

Single oxide ceramic, alumina (Al_2O_3) and Zirconia (ZrO_2), as well as carbon are typical examples of bioinert ceramic. They allow the formation of thin fibrous capsules in the interface and do not form a bonding to bone. Bioinert ceramics are usually applied as bone plates, bone screws, artificial joints, artificial heart valves and femoral-head component (Bilotte, 2003; Li and Hastings, 1998).

2.5.1.2 Bioactive Ceramics

A bioactive material is a material that obtains a specific biological response at the interface of the material, which would result in the formation of a bond between the tissues and the material. A bioactive ceramic undergoes chemical reactions in the body, but only at its surface (Bilotte, 2003). Upon implantation, surface-reactive ceramics form strong bonds with the closest tissue. The surface reactive implants respond to local pH changes by releasing Ca^{2+}, Na^+ and K^+ ions and lead to bonding of tissues at the interfaces (Hench and Wilson, 1993). The ion exchange reaction between the bioactive implant and the surrounding body fluids, in some cases, results in the formation of a biogically active carbonated apatite (CHA) layer on the implant that is a mimic to the mineral phase of bones (Ben-Nissan, 2004).

Common bioactive ceramics used in orthopaedic surgery are dense hydroxyapatite, bioglass, ceravital, and A-W glass ceramic. However, the mechanical properties of these bioactive ceramic are generally weaker than bioinert ceramics. Only A-W glass ceramic has higher mechanical strength than cortical bone. Thus they are not suitable for major load-bearing implants such as joint implants. Bioactive ceramics are most frequently used as bone defect fillers. They are supplied in the forms of block, porous material and granules (Hench and Kokubo, 1998).

2.5.1.3 Bioresorable Ceramics

Bioresorbable refers to a material that, upon placement within the human body, would start to dissolve and slowly be replaced by advancing tissues. In other words, resorbable implants are designed to degrade gradually with time and be replaced with natural tissues (Bilotte, 2003). It leads to tissue regeneration, instead of their replacement. The rate of degradation varies from one material to another. The advantage of this implant is that it will be replaced by normal, functional bone thus eliminating any long term biocompatibility problems. However, during the remodelling process, the load bearing capacity of the implant could possibly be weakened and result in mechanical failure. Therefore, the resorption rates of the material should be matched with the repair rates of body tissues (Hench and Wilson, 1993).

Plaster of Paris is one of the first resorbable bioceramic that was used as bone substitute. Examples of other resorbable ceramics are β-tricalcium phosphate, calcium carbonate, calcium sulphate and carbonate apatite. They are used as bone repair due to disease or trauma, bone defect filler and also as drug delivery devices (Bilotte, 2003).

2.5.2 Application of Bioceramics

Interest of ceramics as biomedical applications has increased over the last thirty years. Recently bioceramics have acquired a lot of attention as candidates for implant materials since they possess some highly desirable characteristics, such as biocompatibility and inertness, for some applications. Bioceramics used singularly or with additional of natural, organic, polymer, or metallic materials are amongst the most promising of all synthetic biomaterials for hard and soft tissue applications. In addition to their application as bone graft substitutes or autograft extenders, some of these bioceramics are efficient carriers for growth factors or drugs, and as scaffolds for tissue engineering (LeGeros et. al., 2006).

Generally, bioceramics are used in dense, porous or granular form (Bilotte, 2003). Dense ceramics are used where high mechanical strength is required. Porous ceramics are used for large bone defect reconstruction in non-load bearing area. On the other hand, granular ceramics are used as fillers to fill medical defects such as a hole. Bioceramics can also be used as a reinforcements or matrices in composite biomaterials and as a coating for metallic biomaterials. They are produced in a variety of forms and phases and serve many different functions in repairing the part of the body (Ishikawa et. al., 2003). Figure 2.3 summarized the applications of bioceramics in human body.

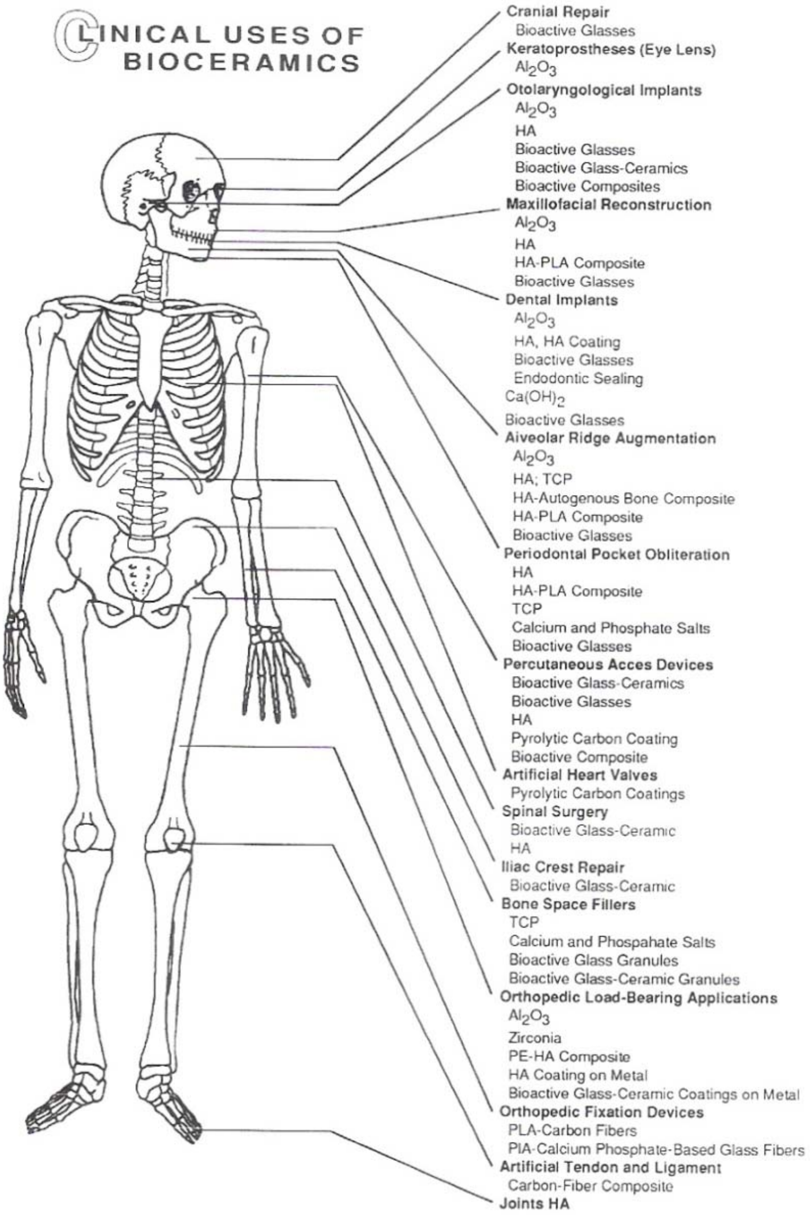

Figure 2.3 Illustration of clinical uses of bioceramics (Hench and Wilson, 1993)

2.6 Calcium-Phosphate Based Bioceramics

The dominant inorganic component of human hard tissues is apatite, which exists in several forms of calcium phosphate. The calcium phosphate compounds are abundant in nature and living systems. Carbonated hydroxyapatite (CHA) of varying crystallinity and concentration of minor elements constitute the mineral phase of