SYNTHESIS OF CARBONATE-SUBSTITUTED HYDROXYAPATITE BY A MECHANICAL ACTIVATION METHOD

by

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LIST OF ABBREVIATION

BCP	: Biphasic calcium phosphates
BET	: Brunauer, Emmet and Teller
BPR	: Ball to powder weight ratio
Ca/P	: Calcium-to-phosphorous molar ratio
CaP	: Calcium phosphate
CHA_p	: Carbonate- substituted hydroxyapatite
CHN	: Carbon, hydrogen, and nitrogen
DCPD	: Dicalcium phosphate dihydrate
DTS	: Diametral Tensile Strength
FE-SEM	: Field Emission Scanning Electron Microscope
FTIR	: Fourier Transform Infra-Red
FWHM	: Full Width at Half Maximum
HA_p	: Hydroxyapatite
ICDD	: International Centre for Diffraction Data
ICP	: Inductively coupled plasma
MPa	: Megapascal
nm	: Nanometer
rpm	: revolutions per minute
S.G.	: Specific gravity
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

SINTESIS HIDROKSIAPATIT DITUKARGANTI KARBONAT MENERUSI KAEDAH PENGAKTIFAN MEKANIK

ABSTRAK

Kaedah pengaktifan mekanik telah dipilih untuk menghasilkan serbuk hidroksiapatit ditukarganti karbonat (CHA_p) dengan menggunakan $CaHPO_4.2H_2O$ dan $CaCO_3$ sebagai bahan mula. Nisbah mol kalsium-fosforus (Ca/P) bahan-bahan tindakbalas adalah 1.67. Pengempaan telah dilakukan dalam suatu bekas agat (dengan bebola agat) tertutup dengan pelbagai parameter untuk mengoptimumkan proses. Keputusan menunjukkan bahawa kecekapan proses ditentukan oleh tempoh kempa, nisbah berat bebola-serbuk (BPR), halaju kempa dan persekitaran kempa. Parameter optimum adalah tempoh kempa 24 jam, BPR sebanyak 10:1, halaju kempa 400 rpm dan kempa kering. Berasaskan parameter optimum ini, pengempaan seterusnya bahan mula pada nisbah Ca/P 1.85 dan 2.00 telah dikaji bagi menilai kesan kandungan karbonat ke atas sifat CHA_p. Kajian terma ke atas serbuk CHA_p dengan kandungan karbonat berlainan mengesahkan bahawa penukargantian ion karbonat untuk kumpulan fosfat meningkatkan kestabilan terma apatit. Padatan CHA_p juga telah dihasilkan menerusi kaedah penekanan serbuk. Ini dituruti dengan pengkarbonatan (pada suhu bilik) dan olahan haba (pada suhu tinggi) untuk menghasilkan blok bioseramik bagi kegunaan seterusnya. Hasil kajian menunjukkan bahawa padatan yang diperolehi menerusi pengkarbonatan menerusi pengkarbonatan mempamerkan kebioaktifan yang cemerlang tetapi kekuatan mekanik yang lemah. Olahan haba ke atas padatan CHA_p dengan nisbah Ca/P 1.67 didapati tidak sesuai untuk menghasilkan blok bioseramik kerana kebioaktifan didapati menurun. Oleh itu, CHA_p 1.67 boleh digunakan sebagai simen apatit contohnya, yang boleh set dan mengeras ditapak kecacatan pada suhu rendah. Padatan CHA_p 1.85 dan CHA_p 2.00 yang diolah haba menunjuknya sifat mekanik yang memadai dan kebioaktifan yang baik. Namun kekuatan mekanik ini masih tidak memadai bagi kegunaan menampung beban. CHA_p dengan Ca/P 1.85 dan 2.00 boleh melalui proses olah haba tanpa menjejaskan sifat kebioaktifan. Oleh itu, kegunaannya lebih sesuai untuk menyalut implan logam atau sebagai implan bukan struktur, contohnya “ossicles” telinga.

SYNTHESIS OF CARBONATE-SUBSTITUTED HDROXYAPATITE BY A MECHANICAL ACTIVATION METHOD

ABSTRACT

A mechanical activation method was used to produce a carbonate-substituted hydroxyapatite powder (CHA_p) using $CaHPO_4.2H_2O$ and $CaCO_3$ as starting materials. The calcium-to-phosphorous molar (Ca/P) ratio of reactants was 1.67. Milling was performed in a sealed agate vials and balls with various parameters to optimize the process. The results showed that processing efficiency was governed by milling time, ball-to-powder weight ratio (BPR), milling speed and milling environment. The optimum parameters are as follows: milling duration of 24 hours, BPR of 10:1, milling speed of 400 rpm and dry milling. Based on these optimum parameters, subsequent milling of reactants at Ca/P ratios of 1.85 and 2.00 were also investigated to evaluate the effect of carbonate content on the properties of CHA_p. Thermal behaviour of CHA_p powders with different carbonate contents depicted that the substitution of carbonate ions for phosphate group enhanced the thermal stability of apatite. Bulk CHA_p was prepared by a pressing method, followed by carbonation (at room temperature) and heat treatment (at elevated temperature) to produce a bioceramic block from the powder for further application. Based on the results obtained, bulks prepared by the carbonation method showed excellent bioactivity but insufficient mechanical strength. For bulk CHA_p with initial Ca/P 1.67, heat treatment above 700^oC was not preferable for fabrication of bioceramic parts because the bioactivity was reduced. Thus, CHA_p 1.67 could be used as apatite cement, for example, which could be set and harden at the bone defect at low temperature. Heat-treated bulk CHA_p 1.85 and CHA_p 2.00 showed adequate mechanical properties and good bioactivity. However, their mechanical strength was still insufficient for load-bearing applications. CHA_p with initial Ca/P 1.85 and 2.00 could undergo heat treatment without reducing the bioactivity properties and thus their application would be more appropriate for coating metallic implants or as non-structural implants, i.e. ossicles in the ear.

CHAPTER I

INTRODUCTION

1.1 Background and Problem Statement

Large bone defects still represent a major problem in orthopaedics. Dental and orthopaedic treatments require sufficient bone and therefore interest in bone regeneration is increasing. Bone mineral is calcium phosphate based with a structural similarity to hydroxyapatite (HA_p). Synthetic HA_p with a stoichiometric composition $Ca_{10}(PO_4)_6OH)_2$ has been widely used as bone graft substitute because of its biocompatibility, bioactivity and osteoconductivity (LeGeros *et al*, 2006). However, stoichiometric HA_p has a limited ability to form an interface with, and to stimulate the development of, new bone tissue. Stoichiometric HA_p also does not degrade significantly but rather remains as a permanent fixture susceptible to long-term failure (Ishikawa, 2003).

LeGeros (1994) suggested that carbonate-substituted hydroxyapatite (CHA_p) is superior to pure HA_p for bioresorbable implants. Bone apatite with a carbonate content is of 4 – 8 wt% (Vallet-Regi and Gonzalez, 2004) and the calcium-to-phosphorous molar (Ca/P) ratio is 1.7-2.6 (LeGeros *et al*, 1993) has better bioactivity and osteoconductivity. The presence of carbonate in the apatite lattice is known to increase chemical reactivity and would probably contribute to the facilitate resorption in bony tissue (Vallet-Regi and Gonzalez, 2004). Two carbonate-substituted hydroxyapatites differ in the mode of substitution in the stoichiometric hydroxyapatite as described by LeGeros (1969) as A-type (CO_3 for OH) or B-type (CO_3 for PO_4).

Associated with its biological importance, CHA_p has been widely studied recently. A key target of biomaterials research therefore is the preparation of a synthetic CHA_p bone-substitute ceramic that mimics the chemical composition of hard tissue. The preparation of carbonate-substituted hydroxyapatite ceramics must be easy and reproducible for it to achieve commercial exploitation and result in a new range of biomedical implants materials. Several studies were used to produce CHA_p and these were classified into two groups such as the wet and dry processes according to the processing method. The drawback of a wet process lies in the composition of the resulting product which is greatly affected by even a slight difference in the reaction conditions (Silva *et al*, 2004). Moreover, in a wet process, the operations require accurate pH adjustment and reaction temperature control of solutions. Calcination and drying steps are involved in a wet process after synthesis to eliminate moisture and the presence of synthesis residues such as nitrous species. Thus, the handling of material and the operation of the apparatus become complicated so they cause poor reproducibility and high processing cost.

Mechanical activation method is an alternative route to produce CHA_p during which a solid-state reaction is activated by mechanical force. If the mechanochemical method involves only a solid state reaction, it should be clearly distinguished from the mechanical-hydrothermal synthesis (wet mechanochemical method) which incorporates an aqueous phase in the system. Besides, although it is categorized as a dry synthesis, this method should be differentiated from solid state reaction. The chemical reaction in a solid state reaction is induced by thermal process at high temperature, whereas for mechanosynthesis, the chemical reaction is induced by the mechanical force (Aaron, 2005). The powder obtained by dry

mechanosynthesis can be used directly, without filtering and drying stages, to prepare bioceramics. In constrast to the wet processes, it has a lot of well-known inherent advantages because of being both an economical and technically simple approach to perform mass productivity, and the tremendous flexibility to generate nanocrystalline powders (Suryanarayana, 2004; Coreno *et al*, 2005 and El Briak-BenAbdeslam, 2008).

Heat treatments are used to prepare dense and porous bioceramics or to coat metallic implants by plasma spraying. Heat treatment of CHA_p results not only in carbonate loss but also in the formation of secondary phases so a crucial consideration when sintering CHA_p is the thermal stability of the phases. So far, previous studies reported that the thermal stability of CHA_p varies and depends on the carbonate content, the substitution type, heating rate and the heat treatment atmosphere (Bigi *et al*, 1997; Merry *et al*, 1998; Barralet *et al*, 2000 and Slosarczyk et al, 2005). Generally, the CHA_p must be thermally stable such that it will not decompose to undesirable secondary phases upon heat treatment. Also, during heat treatment, the CHA_p must not loose the carbonate that has been substituted into the HA_p structure in order to retain the bioactivity property of CHA_p.

In this research, the possibility of using the mechanical activation technique to prepare pure CHA_p is studied. The preparation of bulk CHA_p was carried out by a pressing method, followed by both carbonation and heat treatment methods. Carbonation method differs from heat treatment method in creating the interlock between particles without supplying thermal energy. In carbonation method, bulk

CHA_p was prepared at room temperature so it could prevent the loss of carbonate content. Thus, bulk CHA_p obtained by carbonation method could keep the excellent bioactivity as well as the increase in mechanical properties. On the other hand, in the heat treatment method, the high temperature could provide the strong interlocking between particles so that bulk CHA_p could increase the mechanical strength. However, high temperatures make bulk CHA_p reduce its bioactivity by the decrease in carbonate content. For this reason, it is important to find a temperature at which CHA_p still retain good bioactivity. In this study, the heat-treated temperatures for bulk CHA_p were selected from the evaluation of thermal stability of CHA_p powder. In general, the final target is to find an optimum method to produce CHA_p for biomedical applications which has appropriate mechanical, physical, chemical as well as bioactivity properties.

1.2 Objectives of the Research

This study is focused on the preparation of CHA_p with high performance properties which can be applied in biomedical materials technology. Therefore, the main objectives are:

1. To synthesize CHA_p which mimics the chemical composition of the natural hard tissue by a mechanical activation method.
2. To investigate the physical and chemical properties as well as the thermal stability of as-milled CHA_p powder.
3. To evaluate mechanical, physical, chemical as well as bioactivity properties (using stimulated body fluid (SBF)) of bulk CHA_p derived from carbonation and heat treatment methods.

1.3 Project Overview

In general, the mechanical activation technique is used to synthesize CHA_p from dicalcium phosphate dihydrate DCPD ($CaHPO_4.2H_2O$) and calcium carbonate ($CaCO_3$). This technique is selected due to the simple process and low production cost. The calcium-to-phosphorous molar (Ca/P) ratio of the reactants is deliberately calculated as being equal to the stoichiometric value of 1.67. Various milling parameters were investigated in preparing the CHA_p powder. Based on the optimum milling parameters, the amount of calcium carbonate was varied according to Ca/P ratios of 1.85 and 2.00 in order to evaluate the effect of carbonate content on the formation and properties of CHA_p. The thermal stability of the CHA_p powders was investigated by varying the heat treatment temperature under CO_2 atmosphere in a tube furnace. The purpose of using CO_2 atmosphere is to retain the carbonate content in the CHA_p at elevated temperatures.

Subsequently, CHA_p powders were used to prepare bulk CHA_p by pressing method, followed by carbonation and heat treatment methods. The CHA_p green bodies were prepared by unaxial pressing. Various pressures and carbonation times were investigated in the carbonation method. The optimum pressure selected from the carbonation method was used to press the pellets for the heat treatment method so as to compare the mechanical, physical and bioactivity properties of the two methods. Heat treatment of CHA_p pellets was done under CO_2 atmosphere in the range of temperatures at which the carbonate content still remained without signs of decomposition. In summary, the scope of the research is presented in Figure 1.1:

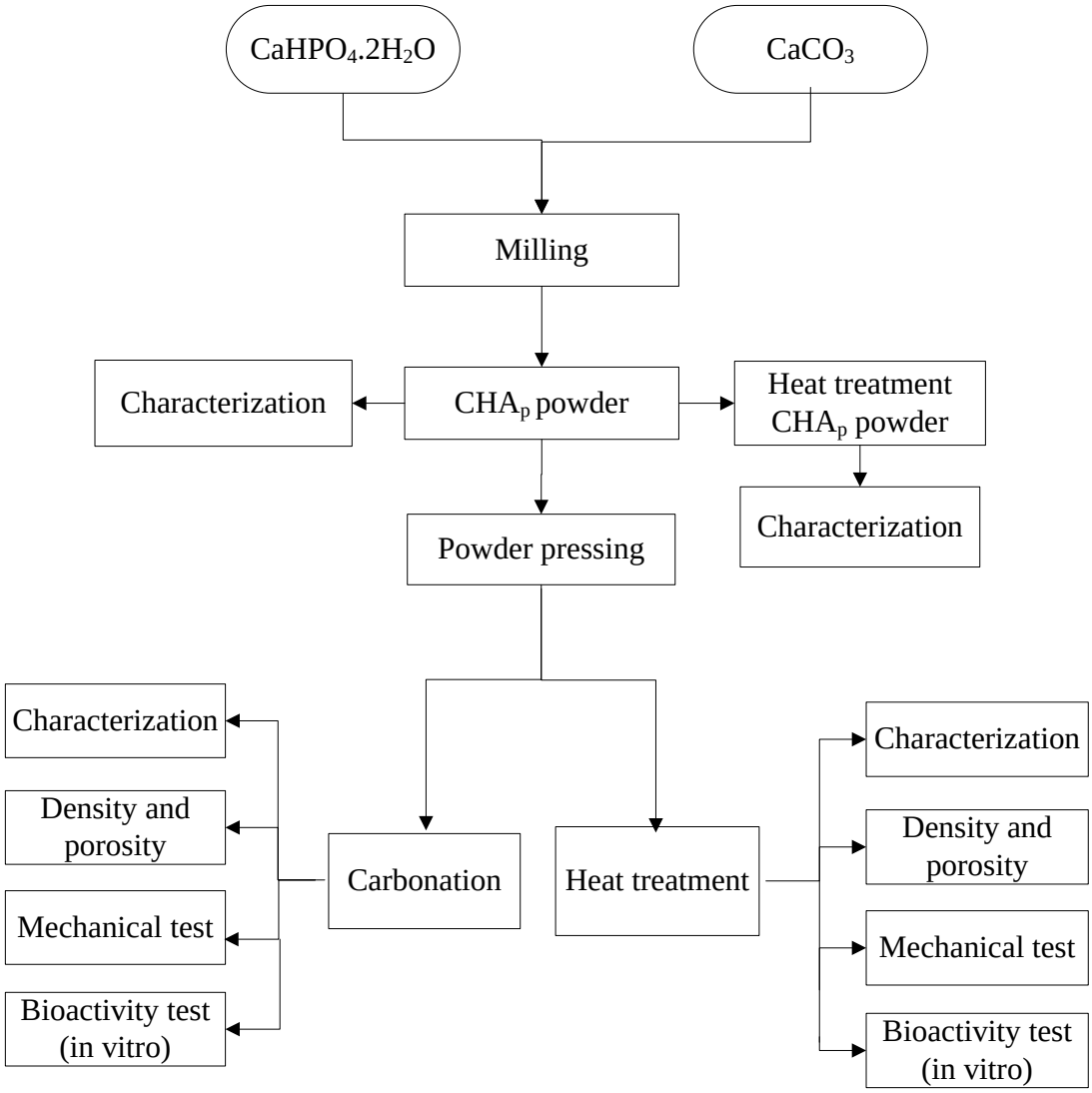


Figure 1.1 Flow chart of the scope of the research.

CHAPTER II

LITERATURE REVIEW

2.1 Introduction

The development of new advanced materials for bone tissue repair is one of the main challenges in current developed societies. Large defects and some bone fracture need a longer recovery period and sometimes refuse to heal during the body's natural bone-healing processes. Bone is especially vulnerable to fracture in older people because of a loss of bone density and strength with age. For instance around 40% women older than 50 years will suffer an osteoporotic fracture (Vallet-Regi, 2006). Dental and orthopaedic treatments require sufficient bone and therefore interest in bone regeneration is increasing. So far, bone implantation materials have 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 over the last few decades (Bhat, 2005).

Hydroxyapatite (HA_p) has been intensely studied in recent years and is the most important inorganic constituent of biological hard tissues due to its excellent biocompatibility (Hench and Wilson, 1993). However, human bone mineral differs in composition from stoichometric HA_p because it contains additional ions, of which carbonate is the most abundant specie. Introduction of carbonate ions in the HA_p would increase its dissolution rate in solution and could enhance its osteointegration rate (LeGeros, 1994). Thus, carbonate-substituted hydroxyapatite (CHA_p) is a prospective material for bone healing and represents one of the most remarkable accomplishments of biomaterial research.

The goal of this review is to provide an overview of structure and properties of bone tissue. Subsequently, biomaterials are defined and classified in general. Bioceramic materials which are a part of biomaterials will be also discussed particularly in this review. The review then described more detail about calcium phostphate materials especially hydroxyapatite and carbonate-substituted hydroxyapatite (CHA_p). The final part of this review addresses some methods used to synthesis CHA_p to amplify how the synthesis method, processing step and fabrication technique has been utilized in solid-state technology.

2.2 Bone tissue

Natural bone has long been the object of biomimetic study because of its characteristic structure and excellent biomechanical properties. It is important to understand this complex structure in detail in order to comprehend how the complex process of bone healing occurs when bone fractures heal. Furthermore, it is only by understanding the biomechanical and biological properties of bone we can understand what type of bone grafts or bone substitutes could be best used to reconstruct large defects of normal bone. The best grafts and bone substitutes are naturally those with biomechanical and biological properties most closely resembling those of normal bone.

Bone is a complex living tissue which has an elegant structure at a range of different hierarchical scales. It is basically a composite which is formed by an organic matrix with inorganic nanocrystals of apatite phase. The extracellular matrix is composed of 50 vol% (or 70 wt%) of inorganic apatite in the form of small, nanometer-sized crystallites, and 50 vol% (or 30 wt%) of organic collagen fibres that

are fabricated into a three-dimensional structure (Kobuko *et al*, 2003), as shown in Figure 2.1.

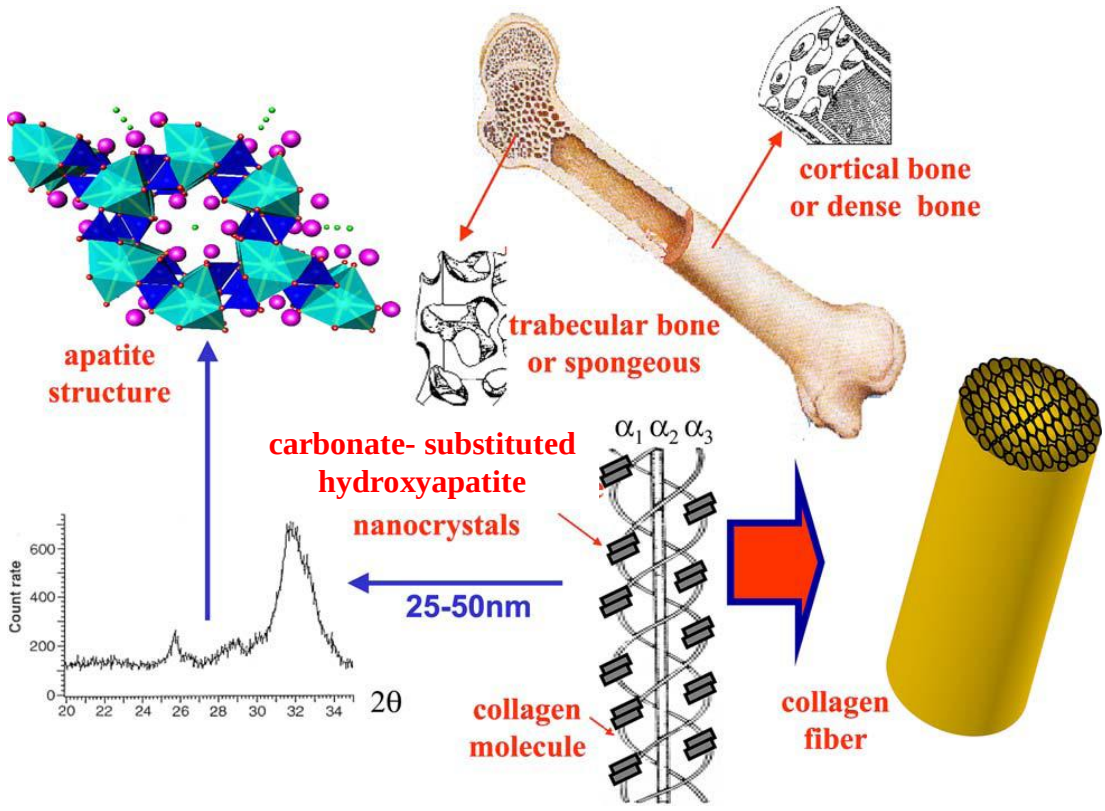


Figure 2.1 Cortical or compact bone and trabecular or spongy bone. Arrangement of carbonate- substituted hydroxyapatite and collagen in the formation of hard tissues. (Vallet-Regi and Gonzalez, 2004)

Biological apatite is identified as an impure HA_p. Besides the main ions Ca^{2+}, PO_4^{3-} and OH^-, the composition of biological apatites always includes CO_3^{2-} and also a series of minority ions, usually including Mg^{2-}, Na^-, K^-, Cl^-, F^- . The composition of apatites in human enamel, dentin and bone is shown in Table 2.1 (LeGeros, 1994). The carbonate hydroxyapatite of bones ranges between 4% and 8% in carbonate content, which increases with age while the hydrogen phosphate ion decreases. The crystals are nanometer sized, with an average length of 50 nm, 25 nm in width and

thicknesses of just 2–5 nm, scattered in the organic matrix (as shown in Figure 2.1). This mineral component gives rise to the compressive strength of bone (Vallet-Regi and Gonzalez, 2004). Bone also contains bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts) and various osteoinductive growth factors and molecules (LeGeros, 2006).

Table 2.1 Composition of of apatites in human enamel, dentin and bone. (LeGeros, 1994).

	Composition (% wt)		
	Enamel	Dentin	Bone
Calcium, Ca^{2+}	36.5	35.1	34.8
Phosphorous, P	17.7	16.9	15.2
Sodium, Na^{+}	0.5	0.6	0.9
Magnesium, Mg^{2+}	0.44	1.23	0.72
Potassium, K^{+}	0.08	0.05	0.03
Carbonate, CO_3^{2-}	3.5	5.6	7.4
Flouride, F^{-}	0.01	0.06	0.03
Chloride, Cl^{-}	0.30	0.01	0.13
Pyrophosphate, $P_3O_7^{4-}$	0.022	0.1	0.07
Total inorganic (mineral)	97	70	65
Total organic	1.5	20	25
Absorbed H_2O	1.5	10	10

Bone is a rather unique tissue with many functions such as providing the cells in the marrow that differentiates into blood cells, acting as a calcium reservoir, providing mechanical support for soft tissues and serving as an anchor for the muscles that generate motion (Nather *et al*, 2005). There are two types of bone that are of most concern in the use of bioceramics. They are compact or cortical bone and cancellous or trabecular (also known as spongy) bone (Carter and Norton 2007) as shown in Figure 2.2.

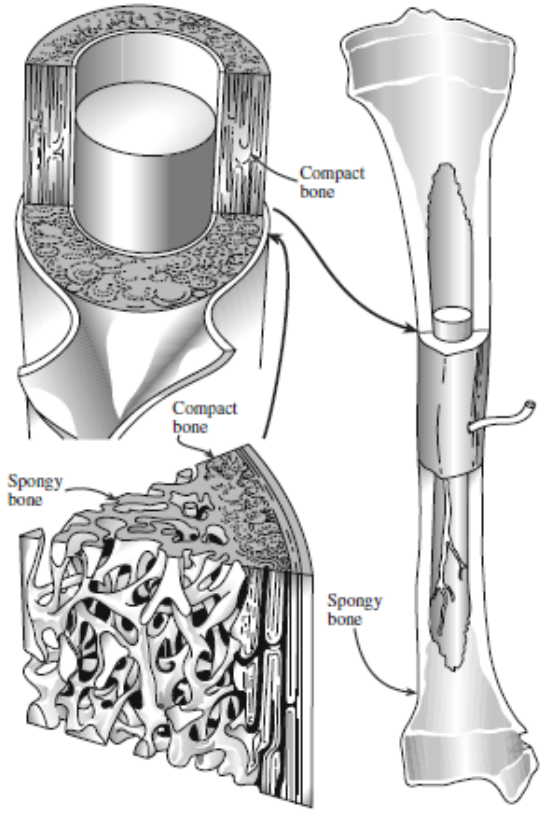


Figure 2.2 Longitudinal section showing the structure of long bone. (Carter and Norton 2007).

Cortical (compact) bone refers to the dense hard, calcified bone that forms the hard outer "shell" of a bone that surrounds the marrow cavity (Safadi, 2009). Cancellous bone, also called trabecular or spongy bone is less dense than the cortical bone. It consists primarily of lamellar bone, arranged in packets that make up an

interconnected irregular array of plates and rods, called trabeculae, the pore of which is filled with a gel-like tissue known as bone marrow (Keaveny, 1998) (Figure 2.3). The mechanical properties of trabecular bone are highly dependent on its density. Due to its lower density, cancellous bone has a lower modulus of elasticity and higher strain to failure than cortical bone (Hench and Wilson, 1993). Table 2.2 gives the general mechanical properties of cortical bone and cancellous bone.

Table 2.2 Mechanical properties of cortical bone and cancellous bone. (Hench and Wilson, 1993)

Property	Cortical bone	Cancellous bone
Compressive strength (MPa)	100-230	2-12
Flexural, Tensile strength (MPa)	50-150	10-20
Strain to failure	1-3	5-7
Young's (Tensile) Modulus (GPa)	7-30	0.5-.005

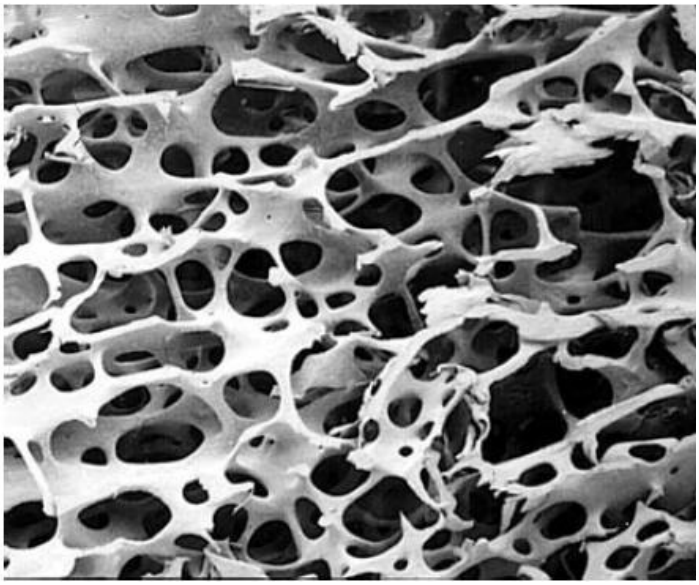


Figure 2.3 Cancellous bone. Both the bone and the pores (filled in life with marrow fat) are interconnected (Currey, 2008)

2.3 Bone graft

Skeletal defects have been replaced by bone grafts for more than 300 years. Bone grafting became an accepted technique in the early part of the 20th century and nowadays, an estimated 1.5 million bone grafting operations are performed annually in the United States. These operations include a multitude of procedures such as spinal fusion, internal fixation of fractures, treatment of bone defects and others (Carlisle, 2005). The most common method involves placing a bone graft, which can be derived from the patient (autograft), from a registered bone bank (allograft), from other mammalian species (xenograft) or synthetic biomaterial into the defect site (LeGeros, 2006).

Autograft refers to bone taken from one anatomic site and transplanted to another site in the same individual. Autograft remains the gold standard in bone transplantation. It contains hydroxyapatite and collagen as an osteoconductive scaffold while stromal cells have osteogenic potential (Long and Ibrahim, 2005). Although autogenous bone represents the most common graft substance used in bone surgery, there are limitations such as donor site morbidity, limited donor bone supply, anatomical and structural problems, and elevated levels of resorption during healing (Parikh, 2002).

Allograft bone is another alternative to autograft. The difference with autograft is the tissue source is not from the same individual. Allograft bone is freeze-dried mineralized or demineralized bone matrix processed from cadaver (LeGeros, 2006). Allografts may be cancellous, cortical, or a combination of each. Though they are attractive sources, there are several problems encountered in using

them, including the risk of disease transmission (the small risk of HIV, hepatitis B, hepatitis C and syphilis transmission), immunogenicity, loss of biologic and mechanical properties secondary to its processing, increased cost, and non-availability world-wide due to financial and religious concerns (Parikh, 2002). Moreover, allografts are primarily osteoconductive with minimal osteoinductive potential, but because the donor cells are eradicated during tissue processing, this material is not considered to be osteogenic. Allografts are prepared either by freezing or lyophilization (ie, freeze-drying) in order to decrease their antigenicity and permit storage for extended periods of time (Whang and Wang, 2003).

Xenograft is bone graft whereby the bone is transferred from other mammalian species. Xenograft has the same inherent problems as allografts, and being from a different species, it may cause even more pronounced immunological problems. Human allograft materials are considered more effective and more widely available compared to xenografts at present. Xenografts tend to be less effective than allografts despite antigenicity treatment. Antigenicity means the ability of a substance to trigger an 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 (Boneva *et al, 2001*).

Generally, bone grafting currently mainly relies on the use of natural materials often bone from another operation. One of the biggest problems with these types of procedure is the limited availability of the natural material and consequently there is a need for alternative sources of bone graft material. There is a need for the development of chemically synthesised materials with reproducible structures and

chemical composition to ensure adequate supply and reproducibility (Best *et al*, 2008).

2.4 Biomaterial

The term biomaterials can be interpreted in many ways. The most commonly used term to describe appropriate biological requirements of a biomaterial or biomaterials used in medical device is biocompatibility. According to its legal definition as frequently referenced in the literature, a biomaterial is a nonviable material used in a medical device, intended to interact with a biological system (Williams, 1987). Park and Lakes (2007) defined biomaterial as any systemically, pharmacologically inert substance or combination of substances utilized for implantation within or incorporation with a living system to supplement or replace functions of living tissue or organs. Besides, as a simple definition, biomaterial can be defined as a synthetic material used to replace part of a living system or to function in intimate contact with living tissues (Wong and Bronzino, 2007). Thus, in general, materials that interface with biological entities and are used to create prosthesis, medical devices and replace natural body tissue are broadly called as biomaterials.

Application of biomaterials in medicine has a longer history. The earliest record of an application of metal in surgical procedures is as far back as the year 1565. However, most early medical implants were doomed to failure because important concepts relating to infection, materials, and the biological reaction to materials were not yet established. The modern implant developments, which centered on repairing long bones and joints, began at the end of nineteenth century

(Bhat, 2005). In general, biomaterials development was dominated by the characteristics of the materials intended for prostheses and medical devices from 1950 to 1975. Important in the early days was the long-term integrity of the biomaterial as well as its non-toxic nature. In the 1980's, the revolution in techniques for the study of cell and molecular biology led to their application to the investigation of interactions occurring at biomaterial interfaces. More recently, with the advent of the areas of tissue engineering and regenerative medicine, heavy emphasis has been placed on biological interactions with biomaterials (Anderson, 2006).

The selection and application of synthetic materials for surgical implants has been directly dependent upon the biocompatibility profiles of specific prosthetic devices. Biocompatibility was defined as the ability of a material to perform with an appropriate response in a specific application (Williams, 1987). The biocompatibility of biomaterials is important because implants and tissue interfacing devices can corrode in an *in vivo* environment. The corrosion of the implant can lead to loss of load-bearing strength and consequent degradation into toxic products within the tissue (Desai *et al*, 2008). Thus, it is necessary to seek for novel synthesis routes by which ideal materials can be developed with required bioactivity, porosity, microstructure, and mechanical properties.

Biomaterials can be broadly categorized under the four categories namely: polymers, metals, ceramics and composites. Table 2.3 summarizes the advantages and disadvantages of each category of biomaterials as well as several common applications of them.

Table 2.3 Class of materials used in implants (Bhat, 2005).

Materials	***Advantages***	***Disadvantages***	***Common application***
Polymers Polyolefins, Polyesters, Silicon rubber.	Low density Easy to fabricate	Low mechanical strength; Additives, oligomers may cause tissue reaction	Cardiovascular, maxillofacial, soft skeletal tissue, sutures, tissue adhesives, percutaneous devices, drainage tubes, shunts, drug delivery systems
Metals Stainless steel Cobalt-chromium, Titanium alloys.	High impact strength, High resistance to wear ductile, absortion of high strain energy.	Low biocompatibility, corrosion in physiological environment, mismatch for mechanical properties with soft connective tissues	Orthopedic load bearing and fixation devices, dental implants.
Pt, Pt-Ir alloy	High conductivity	Low mechanical strength, high cost	Neuromuscular stimulation
Ceramics Alumina, Zirconia Calcium phosphates	Good biocompatibility, inert, corrosion resistance, high tensile strength, Biodegradable	Undesirable surface properties, special techniques are need for material fabrication, Degradation not controllable	Hip and Knee prosthese, dental implants, improving biocomaplity. Temporary support, assist regeneration of natural tissues.
Composites (carbon-carbon, wire- or fiber-reinforced bone cement) (Wong and Bronzino, 2007)	Strong, tailor-made	Difficult to make	Bone cement, dental resin

The mechanical properties (e.g., strength, modulus, and fatigue limit) of metals make them desirable choices for many load-bearing biomedical prostheses applications. Metals are susceptible to degradation by corrosion, a process that can release by-products (such as ions, chemical compounds, and particulate debris) that may cause adverse biological responses. The properties of polymers depend on the composition, structure, and arrangement of their constituent macromolecules. Ceramics are attractive biomaterials because they can be either bioinert, bioactive, or biodegradable; however, they have serious drawbacks because they are brittle and have low tensile strength (Wong and Bronzino, 2007). Thus, in the present and future, election of a biomaterial for a specific application must be based on several criteria. The physicochemical properties and durability of the material, the desired function of the prosthesis, the nature of the physiological environment at the organ/tissue level, adverse effects in case of failure, as well as cost and production issues must be considered for each specific application.

2.5 Bioceramics

Ceramics, in general, can be defined as the art and science of making and using solid articles composed of inorganic and nonmetallic materials for functional applications. Ceramics are refractory, polycrystalline compounds, usually inorganic, including silicates, metallic oxides, carbides, nitrides, and various refractory hydrides and sulfides (Kingery et al, 1976). The development of designed and fabricated ceramics for the repair and reconstruction of diseased and damaged parts of a body is found to improve the quality of life of humans in recent years. Ceramics that can be used in a human body are called bioceramics (Hench and Wilson, 1993).

The ceramic material must meet or exceed the following desired properties of implantable bioceramics in order to be classified as a bioceramic: they should be nontoxic, noncarcinogenic, nonallergic, noninflammatory biocompatible and biofunctional for its lifetime in the host (Bilotte, 2007).

2.5.1 Classification of Bioceramics

The types of bioceramics are divided into three broad categories according to their chemical reactivity with the environment (i) nearly inert (ii) surface reactive (iii) completely resorbable bioceramics. For examble, alumina, zirconia and carbons are inert bioceramics. Certain glass ceramics and dense hydroxyapatites are semi-inert (bioactive), calcium sulfate (plaster of Paris) and calcium phosphates (β tricalcium phosphate, carbonated hydroxyapatite) are resorbable bioceramics (Hench, 1998). A comparison of the relative chemical activity of these different types of bioceramics is given in Figure 2.4.

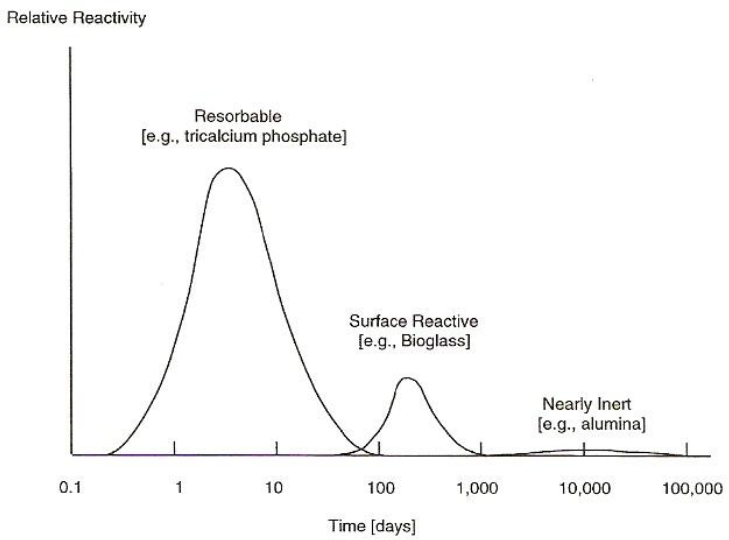


Figure 2.4 Bioceramics can be classified into three subgroups, based on their chemical reactivity in a physiological environment (Shackelford, 1999)

Relative inert bioceramics, such as alumina (Al_2O_3), show inherently low levels of reactivity which peak on the order of 10^4 days (over 250 years). Bioactive ceramics have a substantially higher level of reactivity, peaking on the order of 100 days, while resorbable bioceramics have even higher levels of reactivity peaking on the order of 10 days (Shackelford, 1999).

2.5.1.1 Almost-inert bioceramics

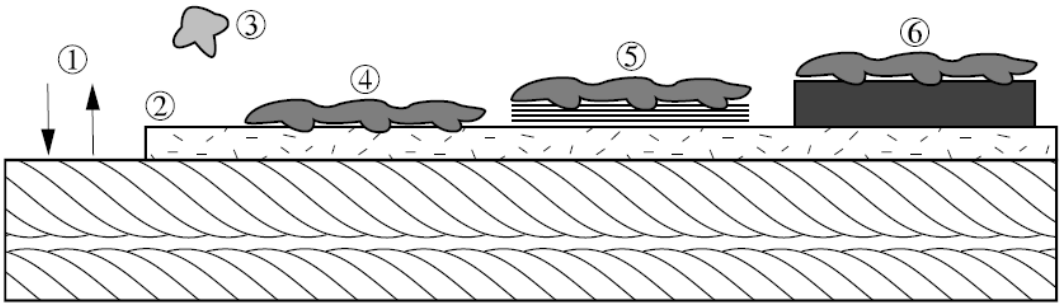
When biomaterials are almost inert and the interface is not chemically or biologically bonded, there is relative movement, and progressive development of a non-adherent fibrous capsule occurs in both soft and hard tissues. The weak interface between bioceramics and bone lead to deterioration in function of the implant or of the tissue at the interface or of both. The thickness of the non-adherent capsule relies on both the material and the extent of relative motion. Almost-inert implant which is less compatible will make interfacial movement occur so the fibrous capsule becomes thicker and the implant loosens quickly (Hench, 1998).

The most utilized bioinert ceramics are alumina, zirconia, hard porcelain, cordierite, sillimanite, etc. They offer very good bological performance associated with high mechanical load and high mechanical resistance, particularly to cyclic compressive loads. So they are utilized to make parts in which the applied compressive load is very high and parts in reciprocal movement which should run through sliding. Some carbides and nitrides are useful as is porcelain for dental applications (Krajewski and Ravaglioli, 2002). Alumina, because of the ability to be polished to a high surface finish and its excellent wear resistance, is often used for wear surfaces in joint replacement prostheses. Zirconia, known as tetragonal zirconia

polycrystals (TZP), is the material of choice currently for ball heads (Hao and Harris, 2008).

2.5.1.2 Surface reactive bioceramics

Hench and Wilson (1993) defined a bioactive material as one that elicits a specific biological response at the interface of the material, which results in the formation of a bond between tissues and the material. Bioactive ceramics directly attaches to the bone by the formation of a carbonate-substituted hydroxyapatite (CHA_p) layer on their surface when implanted (Figure 2.5) (Combes and Rey, 2007). The thickness of the reaction layer among different materials depends upon their solubility (Knabe and Ducheyne, 2008).



1. Equilibrium of the ceramic surface and the solution. Eventual release of mineral ions, adsorption of ions and/or of proteins
2. Nucleation and growth of a layer of carbonate-substituted hydroxyapatite analogous to bone mineral from supersaturated biologic fluids. This layer contains a number of bioactive proteins.
3. Cells go towards the modified surface on which these will settle and become differentiated in order to give rise to osteoblasts.
4. The osteoblasts multiply and colonize the surface of the biomaterial.
5. The cell layer synthesizes a collagenic organic matrix.
6. The organic matrix mineralizes and the new bone is deposited.

Figure 2.5 Events happening at the surface of a bioactive ceramic leading to the formation of a bone tissue (Combes and Rey, 2007)

Bioactive bioceramics are available as powders, granules, pellets and blocks (dense or porous), as cements, as composites and as coatings on orthopedic and dental implants (LeGeros, 2006). Among the bioceramics with bioactive properties, only some glass-ceramics, for instance apatite-wollastonite (A-W) glass-ceramics have evidenced a good performance in spine and hip surgery of patients with extensive lesions or bone defects due to its excellent mechanical strengths and capacity of binding to living bone (Best *et al*, 2008).

2.5.1.3 Resorbable bioceramics

Resorbable biomaterials are designed to degrade gradually over time and be replaced by the natural host tissue and the rate of degradation varies from material to material. This leads to a very thin or nonexistent interfacial thickness. Natural tissues can repair themselves and are gradually replaced throughout life by a continual turnover of cell populations. The role of resorbable bioceramics is to serve as scaffolding, permitting tissue infiltration and eventual replacement. Thus, resorbable biomaterials are based on the same principles of repair that have evolved over millions of year (Hench, 1998).

One of the first resorbable bioceramics used was Plaster of Paris. However, variable resorption rates and poor mechanical properties have prevented plaster implants from being used widely (Bhat, 2005). For a successful application of this kind of materials, the resorption rates must match the repair rates of body tissues, and the mechanical performance should also be compatible while regeneration of tissues is occurring (Hench and Wilson, 1993). Porous or particulate calcium phosphate ceramic materials, such as tricalcium phosphate (TCP), are successful materials for

resorbable, hard tissue replacements when only low mechanical strength is required, such as in some repairs of the jaw or head (Carter and Norton 2007). Besides, carbonate-substituted hydroxyapaite (CHA_p) is a safe and convenient implant material which aids the regeneration of bone in defects produced by the surgical excision of benign bone tumors (Uchida, 1990).

2.5.2 Application of Bioceramics

Bioceramics are now used in a number of different applications throughout the body (Figure 2.6). The ability to bond with bone tissue is a unique property of bioceramics. This has led to their wide clinical use in both orthopedics as well as dentistry. Bioceramics are used as bone substitute materials for bone grafting and as coatings for titanium and its alloy (KoBuko, 2008). Some carbons have been used as implant for blood interfacing application such as heart valves. Due to their high specific strength as fibers and owing to their biocompatibility, ceramics are also used as reinforcing components of composite implant materials and for tensile loading applications such as tendons and ligaments (Park, 2008).

Bioceramics, particularly calcium phosphates and bioactive glasses, show excellent biocompatibility with not only hard tissues, but also with skin and muscle tissues, without any toxic effects (LeGeros, 2006). Unfortunately, their mechanical properties are relatively poor when compared with natural hard tissue. Furthermore, the bioceramics workability is not good; it is difficult for the surgeon to shape the bioceramics when necessary during the surgery (Krajewski and Ravaglioli, 2002).

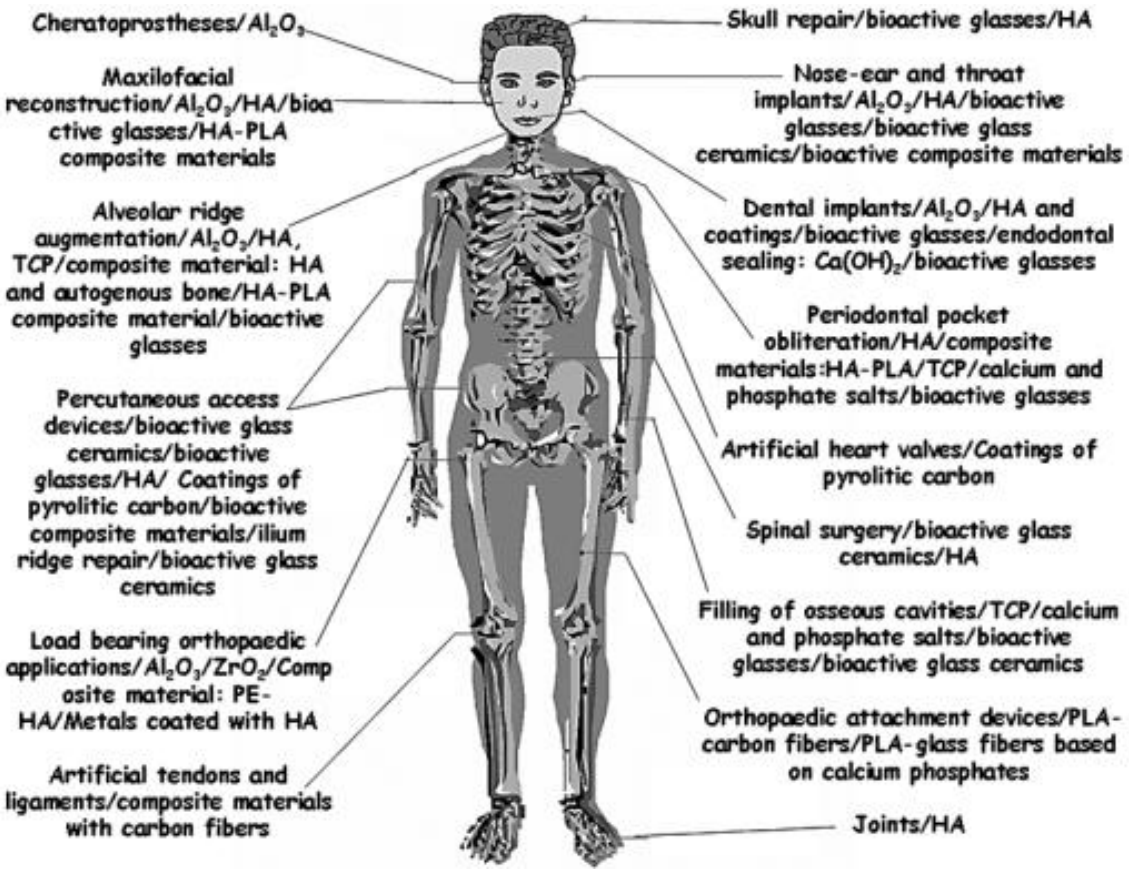


Figure 2.6 Different applications of bioceramics in a human body reconstruction (Vallet-Regi, 2006).

The poor mechanical properties of ceramic biomaterial (as shown in Table 2.4), especially in aqueous environments, limit their applications to small, unloaded and lightly-loaded implants, powders, coatings, composites and porous scaffolds for tissue engineering, and so on. Among bioceramics, alumina has the highest mechanical properties, but its tensile properties are still below those of metallic biomaterials. Additional advantageous properties of alumina are its low coefficient of friction and wear rate. As a consequence of these properties, alumina has been used as a bearing surface in joint replacements (Dee *et al*, 2002).