SYNTHESIS OF β-TCP POWDER VIA WET PRECIPITATION AND HYDROTHERMAL METHODS

PHAM TRUNG KIEN

UNIVERSITI SAINS MALAYSIA

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by

PHAM TRUNG KIEN

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TABLE OF CONTENTS

CHAPTER 3: MATERIALS AND METHODS

CHAPTER 4: RESULTS AND DISCUSSION

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

CF	:	Carbon fiber
CPC	:	Calcium phosphate ceramics
DCP	:	Dicalcium phosphate
DCPA	:	Dicalcium phosphate anhydrous
DCPD	:	Dicalcium phosphate dihydrate
DSC	:	Differential scanning calorimetry
FTIR	:	Fourier transform infrared
HA	:	Hydroxyapatite
ICP	:	Inductively coupled plasma
MCP	:	Monocalcium phosphate monohydrate
nm	:	nanometer
PEEK	:	Polyethyletheketone
PMMA	:	Polymethylmethacarylate
ppm	:	Part per million
PTFE	:	Polytetrafluoroethylene
PU	:	Polyurethane
PVC	:	Polyvinylchloride
rpm	:	Round per minute
SEM	:	Scanning electron microscope
STA	:	Simultaneous thermal analysis
TCP	:	Tricalcium phosphate
TG	:	Thermogravimetry
UHMWPE	:	Ultra High Molecular Weight Polyethylene
XRD	:	X-ray diffraction
μm	:	Micrometer

SINTESIS SERBUK β-TCP

MELALUI KAEDAH PEMENDAKAN BASAH DAN HIDROTERMA.

ABSTRAK

Matlamat kajian ini adalah untuk mensintesis β-TCP [β-$Ca_3(PO_4)_2$] menggunakan $Ca(OH)_2$ dan H_3PO_4 sebagai bahan mula. Dua pendekatan telah digunakan dalam kajian ini untuk menghasilkan β-TCP, iaitu kaedah pemendakan basah dan kaedah hidtroterma. Kajian ini telah mengesahkan bahawa kesan kelajuan pengadukan memainkan peranan yang lebih penting berbanding tempoh pengadukan. Keadaan optimum untuk menghasilkan serbuk β-TCP fasa tunggal adalah : (1) kelajuan pengadukan : 200rpm ; (2) tempoh pengadukan: 2 jam ; (3) suhu kalsin : 900^oC dengan tempoh rendam 1 jam. Lebih penting, kajian ini telah membuktikan bahawa fasa dalam serbuk sebelum kalsin untuk mendapatkan β-TCP fasa tunggal adalah campuran fasa monetit [$CaHPO_4$] dan hidrosiapatit [$Ca_{10}(PO_4)_6(OH)_2$].

Berdasarkan kajian pemendakan, kaedah hidroterma telah digunakan untuk mensintesis β-TCP menggunakan $Ca(OH)_2$ dan H_3PO_4 sebagai bahan mula. Analisis XRD menunjukkan serbuk yang dihasilkan mempunyai fasa campuran brushite [$CaHPO_4.2H_2O$] dan HA berbanding dengan fasa campuran monetit dan HA dari kaedah pemendakan. Serbuk kemudian dikalsin pada suhu 900^oC selama 1 jam. XRD mengesahkan bahawa serbuk β-TCP fasa tunggal telah berjaya dihasilkan.

Namun, ketumpatan β-TCP yang diperolehi daripada kaedah pemendakan adalah 3.1g/cm^3, (hampir sama dengan nilai β-TCP komersil (ρ=3.17g/cm^3)) manakala kaedah hidroterma menghasilkan serbuk yang mempunyai ketumpatan lebih tinggi (iaitu sekitar 3.7 g/cm^3). Ini dipercayai berpunca daripada pemampatan (sebelum kalsin) dan seterusnya pensinteran (selepas kalsin) serbuk kepada butir-butir bersaiz seragam sewaktu sintesis. Tambahan pula, serbuk β-TCP yang disintesis menggunakan kedua-dua kaedah didapati telah menepati keperluan Piawaian implan pembedahan ASTM F1088-04a dengan kandungan toksik yang sangat rendah.

SYNTHESIS OF β-TCP POWDER

VIA WET PRECIPITATION AND HYDROTHERMAL METHODS.

ABSTRACT

The purpose of this study is to synthesize β-TCP [β-$Ca_3(PO_4)_2$] using $Ca(OH)_2$ and H_3PO_4 as the starting material. Two approaches were used in this work to produce β-TCP, namely a precipitation method and a hydrothermal method. This research work reveals that the effect of stirring speed plays significant role than that of stirring duration. The optimum conditions to produced a single-phase β-TCP are: (1) stirring speed of 200 rpm; (2) stirring duration of 2 hours; (3) calcination temperature of 900^oC for 1 hour soaking time. Since β-TCP cannot be directly precipitated from aqueous solution, it was found that the most optimum precursor phase(s) in the as-prepared powder to produce β-TCP after calcination is a mixture phase of monetite [$CaHPO_4$] and hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$].

Based on the precipitation study, a hydrothermal method was used to synthesize β-TCP using $Ca(OH)_2$ and H_3PO_4 as the starting materials in a high-pressure reactor. XRD study shows that the as-prepared powder is a mixture phase of brushite [$CaHPO_4.2H_2O$] and HA instead of monetite and HA as found in the precipitation method. The powder was then calcined at 900^oC for 1 hour and it was found that a single-phase β-TCP was also successfully produced.

The density of β-TCP obtained by the precipitation method is around 3.1g/cm^3 (almost similar to a commercial β-TCP (ρ=3.17g/cm^3)) whilst the hydrothermal method produced powders of higher density (density around 3.7 g/cm^3). This is attributed to the packing and sintering of the powder into uniformly-sized grains during synthesis. In addition, the β-TCP powders synthesized using both methods satisfy the requirements of the Standard for surgical implant, via ASTM F1088-04a with a very low level of toxic elements.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Biomaterials are the emerging fields that are growing rapidly to fulfill the demand in medicine and dentistry. Over the past few decades, new biomaterials for bone replacement, total hip prosthesis and dental implants have been synthesized and commercialized for various needs. Currently, thousands of these materials can be found easily in the market. The market for orthopedic biomaterials over the world is worth over US$25 billion in 2006 and with a growth rate of more than 5% a year (refer Table 1.1). The market for orthopedic biomaterials is expected to increase each year due to the need for better solution for injuries, diseases and ageing population all over the world.

Table 1. 1: Prediction of market share of orthopedic biomaterials over the world in five years from 2007 to 2011 (Driscoll, 2006).

Year	Worldwide sales (US$ Billions)	Growth (%)
2006	25.764	
2007	27.122	5.3
2008	28.562	5.3
2009	30.989	8.5
2010	31.708	2.5
2011	33.425	5.4
Average growth rate (%)		**5.4**

However, none of orthopedic biomaterials provides a perfect solution for guiding bone healing, because there always remain the questions about mechanical stability, long term in-vivo biocompatibility and biodegradability, the

study on orthopedic biomaterials increases every year (Tadic and Beckmann, 2004).

1.2 Problem statement

The orthopedic biomaterials market consists primarily of bone graft substitutes, bone growth factors, degradable tissue fixation and tissue technologies for cartilage regeneration. Generally, orthopedic prostheses should offer a functional life of at least 20 years to match the life span of most patients. This presents a considerable problem for most orthopedic biomaterial (Batchelor and Chandrasekaran, 2004).

In Malaysia, orthopedic biomaterial researches especially on bone graft and degradable materials are still in the infancy stage. Up to now, Malaysia has spent more than RM20 million each year to buy synthetic bone graft from foreign countries such as Switzerland, Germany and the United States. Therefore, the Malaysian government intends to produce bone graft of it own with the supporting research from Universiti Sains Malaysia (USM), Malaysian Institute for Nuclear Technology Research (MINT), Universiti Kebangsaan Malaysia (UKM) and International Islamic University Malaysia (IIUM). (Material Medical Malaysian website, 2006).

Due to the high demands for bone substitutes, many researches have been conducted to produce synthetic bone substitutes in large quantities as reported by Jinawath *et al*., (2002), Saeri *et al*.,(2003), Kondo *et al*., (2005), Murugan *et al*., (2006) and Horch *et al*., (2006). Synthetic bone graft materials such as ceramics, polymers and metals were introduced as an alternative to the traditional bone substitute. Among these materials, calcium phosphate ceramics

such as hydroxyapatite (HA) and β-Tricalcium phosphate (β-TCP) are the most suitable materials with excellent biological properties. There are not so many researches up to date that have been done on the synthesis of β-TCP. Most of the researches focused on synthesis of HA powders or biphasic HA/β-TCP powder such as Zhang *et al*., (2001), Anee *et al*., (2003), Liu *et al*., (2003), Murugan and Ramakrishna (2003) and Cheng *et al*., (2006). However, the interest on β-TCP increases in recent years due to the high competition in producing bone graft in the market share of orthopedic biomaterial. Generally β-TCP was prepared by a solid-state reaction and a wet chemical reaction. The solid state reaction was reported by Lee *et al*., (2007), Choi and Kumta (2007), and Yoshida *et al*., (2007) whilst the wet chemical reaction was carried out by Koc (2004), Vallet-Regi *et al*., (2004), Zou *et al*., (2005) and Kwon *et al*., (2006) (all of these methods will be discussed later in chapter 2). These synthesized β-TCP powders were not stable in term of thermal properties whereby they were converted to α-TCP at temperature above 1125^{o}C.

The present research modified the study of Cheang and Khor (1995), Saeri *et al*., (2003), Afshar *et al*., (2003) and Nagai and Nishimura, (1980) to synthesize β-TCP. According to Saeri *et al*., (2003) and Afshar *et al*., (2003), HA can be synthesized by using the system of $Ca(OH)_2$ and H_3PO_4 with a Ca/P ratio of 1.67. This reaction was expected to be developed towards an industrial-scale method to produce HA with the correct stoichiometric composition, according to the Equation (1.1):

$$10Ca(OH)_2 + 6H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18H_2O \qquad (1.1)$$

The advantages of this reaction are:

- The reaction involves no foreign elements
- The only by-product of the reaction is water

In the present research work, a wet chemical reaction such as the precipitation method and also the hydrothermal method were carried out to prepare β-TCP. Instead of using a Ca/P ratio of 1.67, a modification was attempted whereby $Ca(OH)_2$ and H_3PO_4 were use as starting materials with a Ca/P ratio of 1.5. The mechanism of phase transformation in both of these synthesis methods were fully explored.

1.3 Objectives of research

This study is focused on certain variables such as reaction parameters (stirring speed and stirring duration), calcinations variables (calcination temperature and calcination soaking duration). Therefore, the objectives of this research are:

1. To synthesize single-phase β-TCP powders by a wet precipitation method and a hydrothermal method.
2. To investigate the optimum reaction parameters (stirring speed, stirring duration) and calcination condition (calcination temperature, soaking time) to form a single phase β-TCP.
3. To study the mechanism of phase transformation of the synthesized powder upon calcination.
4. To characterize the physical properties of single phase β-TCP powder such as density and morphology.

1.4 Research scope

In general, the research is divided into two parts which will be described in more detail in chapter 3. The first part is the synthesis of β-TCP using a wet precipitation method from $Ca(OH)_2$ and H_3PO_4 starting materials with a Ca/P ratio of 1.5 The effect of reaction parameters (stirring speed, stirring duration) and calcination conditions (calcination temperature, soaking time) were studied. The characterization of the product powders were carried out using XRD, FTIR, SEM and the density of powders were observed.

The second part is the synthesis of β-TCP using a hydrothermal method from the same $Ca(OH)_2$ and H_3PO_4 staring material with a Ca/P ratio of 1.5. In this part, the effect of stirring speed and calcination condition were studied. The results of first part and second part were compared to understand the effect of each method. The full detail of each method will be described in chapter 3, however the methodology adopted in this research work can be summarized in the flow charts shown in Figure 1.1 and 1.2

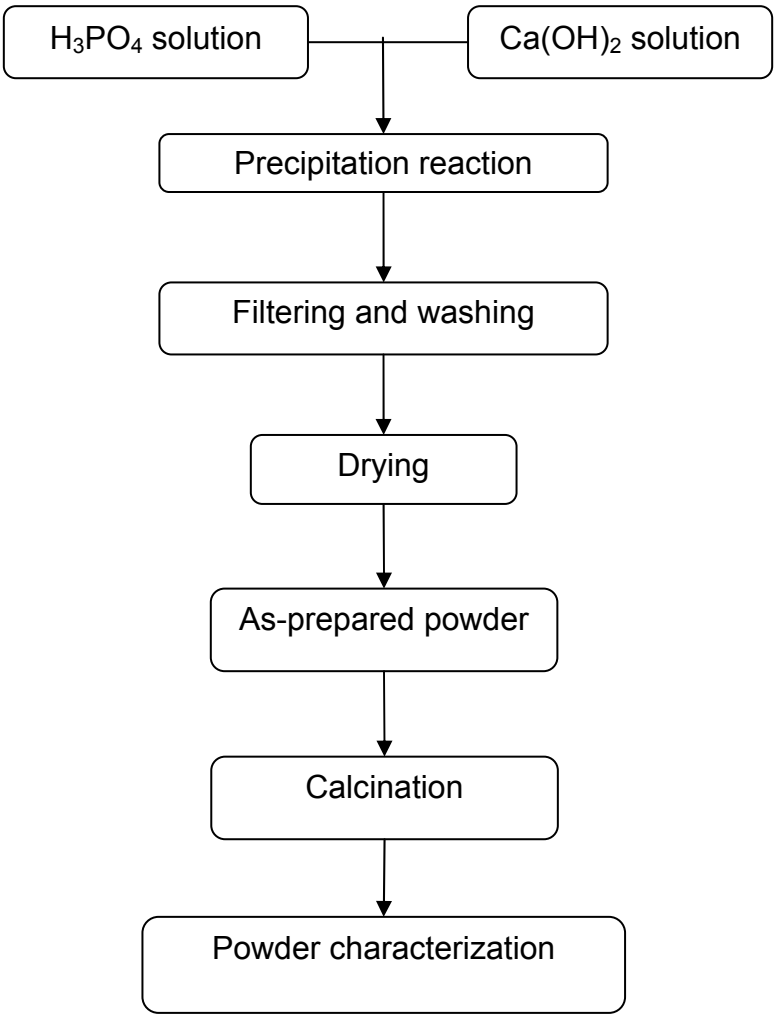

Figure 1. 1: Flow chart of the wet precipitation method (the first part).

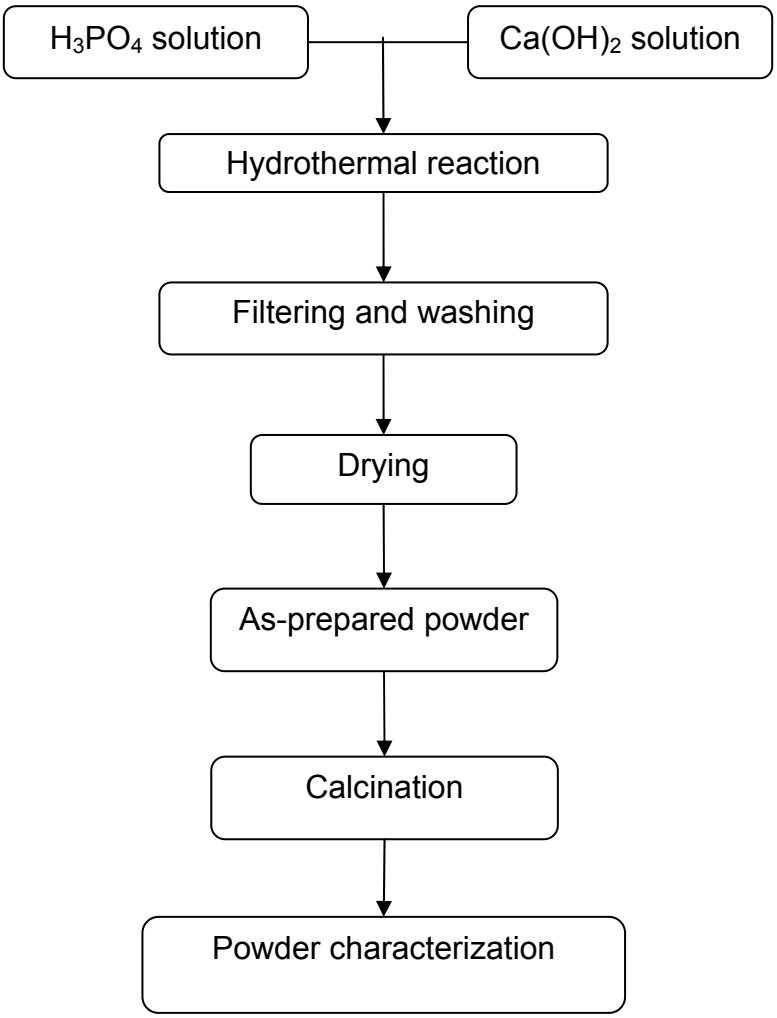

Figure 1. 2: Flow chart of the hydrothermal method (the second part).

*****Table of content**

LIST OF TABLE

LIST OF FIGURE

CHAPTER 2

LITERATURE REVIEW

2.1 Biomaterials

The term biomaterials can be interpreted in two ways; first, as biological materials such as tissue and blood; and second, as implant materials that replace the function of the biological material (Park and Lake, 1992). 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, 1988). Thus, a biomaterial must always be considered in its final fabricated and sterilized form. It was Williams, in 1988, who coined the words “biomaterial” and “biocompatibility” to indicate the biological performance of these materials. Thus, materials that are biocompatible can also be considered as biomaterials.

In 1982, the National Institute of Health Consensus Development Conference organized in America defined a biomaterial as “any substance (other than drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replace any tissue, organ, or function of the body” (The National Institute of Health Consensus Development Program: Clinical Applications of Biomaterials website, 1982).

Biomaterials can broadly be classified as biological biomaterials and synthetic biomaterials. Biological materials can be further classified into soft and hard tissue types whilst synthetic materials can be further grouped into metallic, polymeric, ceramic and composite biomaterials. Table 2.1 shows the various classifications and some examples of biomaterials.

Table 2. 1: Classification of biomaterials (Hin, 2004)

<table>
<tr><th>I. Biological materials</th><th>II. Synthetic biomedical materials</th></tr>
<tr><td>1. Soft tissue:
• Skin, tendon, pericardium, cornea, etc.</td><td>1. Polymeric:
• Ultra High Molecular Weight Polyethylene (UHMWPE), Polymethylmethacrylate (PMMA), Polyethyletherketone (PEEK), Silicone, Polyurethane (PU), Polytetrafluoroethylene (PTFE)</td></tr>
<tr><td rowspan="3">2. Hard Tissue:
• Bone, dentine, cuticle, etc</td><td>2. Metallic:
• Stainless steel, Cobalt-based alloy (Co-Cr-Mo), Titanium alloy (Ti-Al-V), Gold, Platinum</td></tr>
<tr><td>3. Ceramic:
• Alumina (Al_2O_3), Zirconia (ZrO_2), Carbon, Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], Tricalcium phosphate [$Ca_3(PO_4)_2$], Bioglass [$Na_2O(CaO)(P_2O_3)(SiO_2)$], Calcium aluminate [$Ca(Al_2O_4)$]</td></tr>
<tr><td>4. Composite:
• Carbon Fiber (CF) composite such as: CF/PEEK, CF/UHMWPE, CF/PMMA</td></tr>
</table>

Synthetic materials are currently being used for biomedical applications. Since they have different structures, they have varying properties and uses in the body. These types of synthetic biomaterials will be presented in the next section.

2.2 Types of Synthetic Biomaterials

2.2.1 Metallic biomaterials

Metals have been used almost exclusively for load-bearing implants, such as hip and knee prostheses, fracture fixation wires, pins, screws, and plates (Dee *et al*., 2002). Metals have also been used as parts of the artificial heart valves, e.g. such as vascular stents and pacemaker leads. Although pure metals are sometimes used, alloys (metal containing two or more elements) frequently provide improvement in material properties, such as strength and corrosion resistance. Three alloy systems dominate biomedical metals: 316L stainless steel, cobalt-chromium-molybdenum alloy, and pure titanium and titanium alloy. The main consideration in selecting metals and alloys for biomedical application are biocompatibility, appropriate mechanical properties, corrosion resistance and reasonable cost.

The mechanical properties of materials are of great importance when designing load-bearing orthopedic and dental implants. The mechanical properties of a biomaterial can best be described by its modulus of elasticity, tensile strength, elongation to failure and fracture toughness. Some mechanical properties of metallic biomaterials are listed in Table 2.2. With a few exceptions, the high ultimate tensile and fatigue strength of metals, compared to ceramic and polymers make them the materials of Choi and Kumtace for implants that carry mechanical loads.

The elastic moduli of the metals listed in Table 2.2 are at least seven times greater than that of natural bone. This mismatch of mechanical properties can cause “stress shielding”, a condition characterized by bone resorption (loss of bone) in the vicinity of implants. This clinical complication arises because the

preferential distribution of mechanical loading through the metallic prosthesis deprives bone.

Table 2. 2: Selected properties of metallic biomaterials (Dee *et al*., 2002)

Materials	**Young's modulus, E [GPa]**	**Yield strength, σ_y [MPa]**	**Tensile strength, σ_{UTS} [MPa]**	**Fatigue limit, σ_{end} [MPa]**
Stainless steel	190	221-1,213	586-1,351	241-820
Co-Cr alloys	210-253	448-1,606	655-1,896	207-950
Titanium	110	485	760	300
Ti-6Al-4V	116	896-1,034	965-1,103	620
Natural bone	**15-30**	**30-70**	**70-150**	**-**

2.2.2 Ceramic and glass biomaterials

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. Typically, ceramics are fabricated by synthesizing powders, followed by shaping and consolidation processes, which enable the fabrication of objects of different shapes and sizes. Ceramics are refractory, inorganic compounds made of metals and nonmetals such as O, N, C, S. Exceptions to this general category include diamond, graphite, carbon nanotubes, and pyrolized carbons (Kingery *et al*., 1976).

In recent years, ceramics and composites can also be used to augment or replace various parts of the body, particularly the bone. Ceramics that can be used for the body are called bioceramics. Their relative inertness to body fluids, high compressive strength, and pleasing aesthetic appearance have led to the use of ceramics in dentistry as dental crown. 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.

Unlike metals and polymers, ceramics do not shear plastically due to the ionic nature of the bonding and a minimum number of slips systems. Thus ceramics are non ductile and are responsible for almost zero creep at room temperature. Ceramics are susceptible to notches and cracks (micro-cracks) since they do not undergo plastic deformation. Ceramics fracture elastically on initiation of cracks. At the crack tip, stress could be many times larger than the stress in the material away from the tip, leading to stress concentration weakening in the material (Billotte, 2000).

In general, ceramics are hard: diamond is the hardest, with a hardness index of 10 on the Moh's scale followed by alumina (Al_2O_3, hardness 9) and quartz (SiO_2, hardness 8). Other characteristics are: high melting temperatures and low conductivity of electricity and heat.

The desired properties of bioceramics are:

- Non toxic
- Non-carcinogenic
- Non-inflammatory
- Biocompatible
- Biofunctional for its lifetime in the host

Ceramics used in fabricating implants can be classified as biodegradable or resorbable (non-inert); bioactive or surface reactive (semi-inert) and

nondegradable (relatively inert). Al_2O_3, ZrO_2, Si_3N_4 and carbons are inert bioceramics. Certain glass-ceramics and dense hydroxyapatite (HA) are semi-inert (bioreactive) and calcium phosphates are degradable ceramics. Some Ca-phosphates also contain alumina (AlCaP) which can be biodegradable.

Ceramics and glasses are also used as components of hip implants, dental implants, middle ear implants and heart valves. Overall, however, these biomaterials have been used less extensively than either metals or polymers. Some ceramics that have been used for biomedical application are listed in Table 2.3.

Table 2. 3: Ceramics used in biomedical application (Dee *et al*., 2002).

Ceramics	**Chemical formula**	**Remarks**
Alumina	Al_2O_3	Bio-inert
Zirconia	ZrO_2	Bio-inert
Pyrolytic carbon		Bio-inert
Bioglass	$Na_2O.CaO.P_2O_3$-SiO_2	Bioactive
Hydroxyapatite (sintered at high temperature)	$Ca_{10}(PO_4)_6(OH)_2$	Bioactive
Hydroxyapatite (sintered at low temperature)	$Ca_{10}(PO_4)_6(OH)_2$	Biodegradable
Tricalcium phosphate	$Ca_3(PO_4)_2$	Biodegradable

The fundamental principle in classifying ceramic biomaterials is based on chemical reactivity with the physiological environment (Figure 2.1). Relative inert bioceramic, such as structural Al_2O_3, tend to exhibit inherently low levels of reactivity which peak on the order of 10^4 day (over 250 years). Bioactive ceramic, such as bioglass have a substantially higher level of reactivity peaking on the order of 100 days. Resorbable or degradable bioceramics, such as

tricalcium phosphate, have even higher levels of reactivity peaking on the order of 10 days. This broad spectrum of chemical behavior has led to a corresponding range of engineering design materials (Hench, 1991).

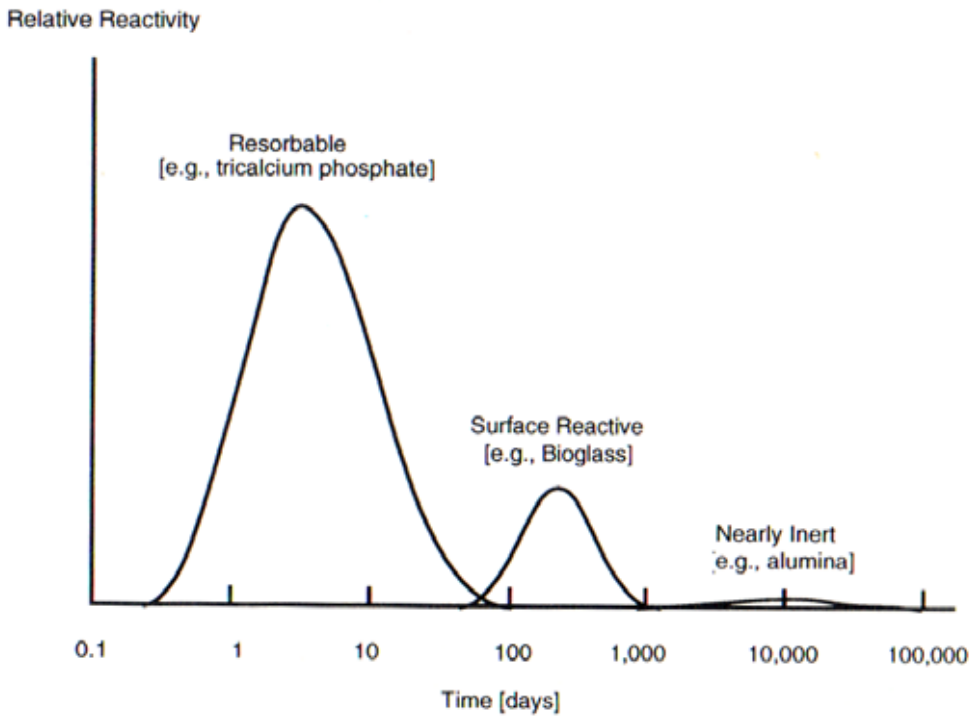

Figure 2.1: Bioactivity spectrum for various bioceramic implants. (Hench, 1991).

The major drawbacks to the use of ceramics and glasses as implants are their brittleness and poor tensile strength properties (see Table 2.4). Although they can have outstanding strength when loaded in compression, ceramics and glasses fail at low stresses when loaded in tension or bending. Among biomedical ceramics, 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.

Table 2. 4: Mechanical properties of ceramic biomaterial (Dee *et al*., 2002).

Materials	**Young's modulus , E [GPa]**	**Compressive strength, σ_{UCS} [MPa]**	**Tensile strength, σ_{UTS} [MPa]**
Alumina	380	4500	350
Bioglass-ceramic	22	500	56-83
Calcium phosphate	40-117	510-896	69-193
Pyrolytic carbon	18-28	517	280-560

The mechanical properties of calcium phosphates and bioactive glasses make them unsuitable as load-bearing implants. Clinically, hydroxyapatite has been used as a filler for bone defects and as implant in load-free anatomic sites (for example, nasal septal bone and middle ear). In addition, hydroxyapatite has been used as a coating on metallic orthopedic and dental implants to promote their fixation in bone. In these cases, the underlying metal carries the load, whereas the surrounding bone strongly bonds to hydroxyapatite.

2.2.3 Polymeric biomaterials

Polymers are the most widely used materials in biomedical applications. They are the materials of Choi and Kumtace for cardiovascular devices as well as for replacement and augmentation of various soft tissues. Polymers are also used in drug delivery system, in diagnostic aids, and as a scaffolding material for tissue engineering applications. Example of current applications include vascular graft, heart valves, artificial hearts, breast implants, contact lenses, intraocular lenses, components of extracorporeal oxygenators, dialyzers and plasmapheresis units, coating for pharmaceutical tablets and capsules, sutures,

adhesives and blood substitutes. Examples of polymers and their uses are given in Table 2.5.

Table 2. 5: Examples of biomedical application of polymers (Dee *et al*., 2002).

Applications	**Polymers**
Cardiovascular implants	Polyethylene; polyvinylchloride (PVC); polyester; silicone rubber; polyethylene terephthalate; polytetraflouroethylene
Orthopedic implant	Ultra high molecular weight polyethylene (UHMWPE); polymethyl methacrylate (PMMA)
Drug release	Polylactide-co-glycolide
Tissue engineering	Polylactic acid; polyglycolic acid; poly lactide-co-glycolide

The mechanical properties of polymers depend on several factors, including the composition and structure of the macromolecular chains and their molecular weights. Table 2.6 lists some mechanical properties of selected polymeric biomaterials. Compared with metals and ceramics, polymers have much lower strengths and moduli but they can be deformed to a greater extent before failure. Consequently, polymers are generally not used in biomedical applications that bear loads (such as body weight). Ultra high molecular weight polyethylene (UHMWPE) is an exception, as it is used as a bearing surface in hip and knee replacements. The mechanical properties of polymers, however, are sufficient for numerous biomedical application (some of which are listed in Table 2.5).

Table 2. 6: Mechanical properties of biomedical polymers (Dee *et al*., 2002).

Polymer	Tensile strength, σ_{UTS} [MPa]	Young's Modulus, E [GPa]	Elongation %
Polymethyl methacrylate (PMMA)	30	2.2	1.4
Nylon 6/6	76	2.8	90
Polyethylene terephthalate	53	2.14	300
Polylactic acid	28-50	1.2-3	2-6
Polypropylene	28-36	1.1-1.55	400-900
Polytetrafluoroethylene	17-28	0.5	120-350
Silicone rubber	2.8	Up to 10	160
Ultra high molecular weight polyethylene (UHMWPE)	≥ 35	4-12	≥ 300

2.3 Calcium phosphate ceramics (CPC)

2.3.1 General properties of calcium phosphate ceramics:

As mentioned in the section 2.2.2, β-TCP can be classified to the calcium phosphate group. Thus, calcium phosphate will be focused in this section. There are several forms of calcium phosphate. They typically form a family of compounds called "apatites". The name "apatite" was derived from "apataw", the Greek word to deceive, since it was confused with several other similar looking minerals until chemical analysis conducted proved that calcium phosphate composition is similar to enamel, dentin and bone (see Table 2.7).

There are several types of calcium phosphate, such as tricalcium phosphate (TCP), hydroxyapatite (HA), dicalciumphosphate dihydrate (DCPD or brushite), dicalcium phosphate anhydrous (DCPA or monetite). They exist in different forms and phases depending on temperature, partial pressure of waters and the presence of impurities (Hench, 1998). Different phases are used

in different applications depending upon whether a degradable or a bioactive material is desired (Billotte, 2000). Table 2.8 summarized various phases of calcium phosphate currently used in the biomedical industry. Table 2.9 presents solubility of different phases of calcium phosphate in aqueous solution.

Table 2. 7: Comparison between enamel, dentin, bone and synthetic apatite (Lacout, 1992).

Element %	Enamel	Dentine	Bone	Synthetic apatite
Calcium	36.1	35.0	35.5	39.0
Phosphorous	17.3	17.1	17.1	18.5
Carbon dioxide	3.0	4.0	4.4	-
Magnesium	0.5	1.2	0.9	-
Sodium	0.2	0.2	1.1	-
Potassium	0.3	0.07	0.1	-
Chlorine	0.3	0.03	0.1	-
Fluorine	0.016	0.017	0.015	-
Sulphur	0.1	0.2	0.6	-
Zinc	0.016	0.018	-	-
Silicon	0.003	-	0.04	-
Ca/P atomic ratio	1.62	1.59	1.61	1.667
Crystallinity	good	poor	poor	good

The mechanical properties of synthetic calcium phosphates vary considerably (Table 2.10). The wide range in the properties of polycrystalline calcium phosphates are due to the variations in their structure and manufacturing processes. Depending on the final firing condition, calcium phosphate can be hydroxyapatite or β-TCP. In many instances, both types of structures exist in the final product (Park and Lakes, 1992).

Table 2. 8: Various phases of calcium phosphate ceramics (Guelcher and Hollinger and Hollinger, 2006).

Phases	Chemical formulae	Mineral name	Ca/P ratio
Hydroxyapatite (HA)	$Ca_{10}(PO_4)_6(OH)_2$	Apatite	1.67
α-Tricalcium phosphate (α-TCP)	$Ca_3(PO_4)_2$	Whitlockite	1.5
β-Tricalcium phosphate (β-TCP)	$Ca_3(PO_4)_2$	Whitlockite	1.5
Dicalcium phosphate dihydrate (DCPD)	$CaHPO_4.2H_2O$	Brushite	1.0
Dicalcium phosphate anhydrous (DCPA)	$CaHPO_4$	Monetite	1.0

Table 2. 9: Solubility of different calcium phosphates (Schdmidt, 1993).

Phases	Solubility	
	In water [g/l]	In 0.1 Ml HCl
HA	Insoluble	Soluble
β-TCP	0.02	Soluble
Brushite	0.3	Soluble
Monetite	0.2	Soluble

Table 2. 10: Physical properties of calcium phosphates (Park and Lakes, 1992)

Property	Value
Elastic modulus (GPa)	4.0 – 117
Compressive strength (MPa)	294
Bending strength (MPa)	147
Hardness (Vickers)	3.43
Poisson's ratio	0.27
Density (theoretical, g/cm^3)	3.16 – 3.2

In addition, calcium phosphates are widely used in food and pharmaceutical products, for instance as a calcium source in mineral tablets, baking powders, cheese and meat products or as abrasive agents in toothpaste. They are also used as tablets fillers/binders because of their good binding properties, excellent flowability, low costs, chemical purity and relatively few incompatibilities with pharmaceutical drugs. Table 2.11 shows the commercially available calcium suitable for direct tablet. All these substances are also available as fine powders for wet granulation, and food industry.

Table 2. 11: Calcium phosphates used for direct tablet (Schmidt and Herzog and Herzog, 1993)

Formula	Trade names	Manufacturer
$CaHPO_4.2H_2O$ (Brushite)	Bekapress D2. Dentphos L5. Di-Cafos. Di-Tab. Emcompress Dihydrate.	BK Ladenburd, Ladenburg, FRG. BK Landenburg. Chemische Fabrik Budenheim, Budenheim, FRG. Rhone-Poulenc, New York, USA. E. Mendell Co., New York, USA.
$CaHPO_4$ (Monetite)	A-Tab. Di-Cafos A. Di-Cafos AN. Emcompress Anhydrous.	Rhone-Poulenc. Chemische Fabrik Budenheim. Chemische Fabrik Budenheim. E. Mendell Co.
$Ca_{10}(PO_4)_6(OH)_2$	Tri-Cafos S. Tri-Tab.	Chemische Fabrik Budenheim. Rhone-Poulenc.

Among these calcium phosphate ceramics, bioresorbable or biodegradable ceramics are most interesting. The concept of degradable ceramics as bone substitutes was introduced in 1969 by Hentrich. However, long before this plaster of paris was already being used as a bone substitute.

(Peltier, 1957). Degradable ceramics, as the name implies, degrade upon implantation in the host and are slowly replaced by advancing tissue (such as bone) (Guelcher and Hollinger and Hollinger, 2006). The rate of degradation varies from material to material. Most bioresorbable ceramics except for biocoral and plaster of paris are essentially variations of calcium phosphate. Example of biodegradable bioceramics include: aluminum – calcium – phosphorus oxides (AlCaP) (Mattie and Bajpai, 1988), glass fiber and their composites (Alexander et al., 1987), coral [(Guillemin et al., 1989) and (Khavari and Bajpai, 1993)]. Typical uses of biodegradable ceramics are drug delivery devices (Abrams and Bajpai, 1994) and for repair of damaged bone due to disease or trauma (Scheidler and Bajpai, 1992). A drawback of calcium phosphate ceramics is their complicated fabrication process and particularly difficult shaping. Nevertheless, calcium phosphate ceramics have gained and will keep a place in clinical practice, as an alternative for autologous bone grafting and as base material for implantable teeth.

2.3.2 Hydroxyapatie

The ideal Ca/P ratio of hydroxyapatite is 1.67 and the calculated density is 3.219g/cm^3. Substitution of OH^- ion with fluoride gives the apatite greater chemical stability due to the closer coordination of fluoride (symmetric shape), as compared to the hydroxyl (asymmetric, two atoms) by the nearest calcium. This is why fluoridation of drinking water helps in resisting caries of the teeth. (Park and Lakes, 1992).

Hard tissue such as bone, dentin, and dental enamel are natural composites which contain hydroxyapatite (or a similar mineral), as well as

protein, other organic materials and water. Enamel is the stiffest hard tissue, with an elastic modulus of 74 GPa, and containing the most mineral hydroxyapatite. Dentin (E = 21 GPa) and compact bone (E = 12 to 18 GPa) contain comparatively less mineral. The Poisson's ratio for the mineral or synthetic hydroxyapatite is about 0.27, which is close to that of bone (~ 0.3) (Park and Lakes, 1992).

2.3.3 Tricalcium phosphate (TCP)

β-TCP is the low-temperature phase in the CaO - P_2O_5 phase diagram. β-TCP transforms to α-TCP at 1125^{o}C and above this, up to 1430^{o}C, α-TCP is a stable phase. Above 1430^{o}C, the super α-TCP form becomes stable until the melting point of 1756^{o}C The ideal Ca/P ratio of β-TCP is 1.5 and the theoretical density is 3.17 g/cm^3 as reported by Guelcher and Hollinger and Hollinger (2006). Research has shown that tricalcium phosphate degrades faster than calcium phosphate, [$Ca_2P_2O_7$], which also degrades faster than hydroxyapatite (Bhat, 2006).

According to Kalita *et al*., (2007) and Guelcher and Hollinger (2006), β-TCP does not form in aqueous system under normal laboratory conditions except with the introduction of small amounts of Mg^{2+} ions. Kalita *et al*., (2007) and Billotte (2003) also agree that crystallization of various salts of calcium phosphate like hydroxyapatite and β-TCP depends on Ca/P ratio, presence of water, impurities and temperature. For instance, in a wet environment and at a lower temperature (<900^{o}C), the formation of hydroxyapatite is most likely to happen, but in a dry atmosphere and at a high temperature, β-TCP is more likely to form. Both forms are very tissue compatible and are used as bone

substitutes in a granular form or a solid block. A multi-crystalline porous form of β-TCP has been used successfully to correct periodontal defects and augment bone contours (Metsger et al., 1982). X-ray diffraction of β-TCP powder shows an average interconnected porosity of over 100μm (Lemons and Niemann, 1979).

Since TCP is a degradable temporary bone space filler material, when implanted, TCP will interact with body fluids to form hydroxyapatite as follow: (Grook, 1984).

$$4Ca_3(PO_4)_2 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 2Ca^{2+} + 2HPO_4^{2-} \qquad (2.1)$$

This reaction will decrease the pH of the local solution and further increase the solubility of TCP. Theoretically, degradable β-TCP is an ideal implant material. After implantation, TCP will degrade with time and be replaced with natural tissues. It leads to the regeneration of tissue instead of their replacement and thus solves the problem of interfacial stability. However, in clinical applications, some limitations restrict the use of degradable TCP:

Firstly, the mechanical performance of an implant must match the repair rate of body tissues. According to Legeros *et al*., (1995), Ducheyne *et al*., (1990), the order of relative solubility of α-TCP, β-TCP and HA had been suggested as α-TCP ~ β-TCP and very much greater than HA. In order to use for surgical implantation, the degradation rate of the implant must be controlled very well. To solve this problem, a composite between bioactive (semi-solubility) and bioresorbable (high solubility) was mixed together to control the

degradation rate, for instance the biphasic calcium phosphate (BCP) between hydroxyapatite and β-TCP.

Secondly, large quantities of the implant materials must be handled by the body cells and as such the constituents of a degradable implant must be metabolically acceptable. TCP implants dissolve by grain-boundary degradation. The released grains may cause a potential metabolic problem because of their size (Gross *et al*., 1988).

2.3.4 Trace element measurement of HA and β-TCP for surgical implant

The concentration of trace elements in HA and β-TCP shall be limited for surgical implant purpose (see Table 2.12). In this research work, β-TCP powders synthesized satisfy the requirement of the ASTM F1088-04a standard. The concentrations of trace elements in β-TCP powders will be discussed in Chapter 4.

Table 2. 12: Standard specification of HA and β-TCP for surgical implant (Furcola, 2005).

Standard specification of HA and β-TCP for surgical implant		
Element	Maximum concentration, [ppm]	
	HA	β-TCP
As	3	3
Cd	5	5
Hg	5	5
Pb	30	30
Standard	ASTM F1185-03	ASTM F1088-04a

2.3.5 Thermal behaviour of calcium phosphate ceramic

Schmidt and Herzog (1993) studied the thermal behavior of calcium phosphate. Four types of calcium phosphate were used for his study: (1)