Ain Shams University
Faculty of Science
Chemistry Department

Preparation, characterization and some properties of gypsum plaster / calcium phosphate composites as a bone cement

Thesis
Submitted

By
Hayam Abdel Aziz Badr Abdel Aziz
(M. Sc. in Chemistry)

For Fulfillment of the Degree of Ph. D. in Chemistry

Chemistry Department
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Prof. Dr. Ebtissam A. Saad
Professor of Inorganic Chemistry, Department of Chemistry, Faculty of Science, Ain Shams University.

Prof. Dr. Abdel Aziz Ahmed Khalil
Professor of chemistry and building materials technology, Refractories, Ceramics and Building Materials Dept., NRC.

Prof. Dr. Mahmoud Farag Mahmoud Zawrah
Professor, Chemistry of New Materials and Nanotechnology, Refractories, Ceramics and Building Materials Dept., NRC.

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Thesis Advisors **Approved**

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Professor of Inorganic Chemistry,
Dep. of Chemistry, Faculty of Science,
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Professor of chemistry and building materials technology, Refractories, Ceramics and Building Materials Dept., NRC.

Prof. Dr. Mahmoud Farag Mahmoud Zawrah
Professor, Chemistry of New Materials and Nanotechnology, Refractories, Ceramics and Building Materials Dept., NRC.

Head of Chemistry Department

Prof. Dr. Hamad Ahmed Younes Derbala

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1. Introduction

1.1. Biomaterials

Biomaterials or biomedical materials are synthetic or natural materials used to replace parts of a living system or to function in intimate contact with living tissues **[Williams, 1999]**. Very recently, a more complicated definition has been engineered to take a form which, alone or as a part of a complex system, is used to direct by control of interactions with components of living systems in human or veterinary medicine **[Williams, 2009]**. They concern the human health and economy and provide the patient with the benefits of increased longevity and improved quality of life **[Dorozhkin, 2010]**. They are needed to alleviate pain and restore function to diseased or damaged calcified tissues (bones and teeth) of the body. Moreover, Biomaterials are intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body and are now used in a number of different applications throughout the body **[Best et al, 2008 & Jandt, 2007].**

The major difference of biomaterials from other classes of materials is their ability to remain in a biological environment without damaging the surroundings and without being damaged in that process. Thus, biomaterials are solely associated with the health care domain and must have an interface with tissues or tissue components.

Biomaterials must be distinguished from biological materials because the former are the materials that are accepted by living tissues and, therefore, they might be used for tissue replacements, while the latter are the materials being produced by various biological systems (wood, cotton, bones, chitin, etc.) **(Meyers et al, 2008)**.

A surgical implant may be defined as an object comprising non-living materials introduced into the human body and designed to fulfill a specific function over a specified time span **[Williams and Raof, 1974]**. According to their required function, implants are used to substitute a diseased part of the anatomy, replace an absent part of it, help with the healing process of a tissue, correct any congenital, traumatic or pathological deformity and/ or rectify the operational mode of a vital organ.

Tissue attachment of Biomaterials are classified into four types, nearly inert, porous, bioactive and resorbable **[Hench, 1991]**. Nearly inert implant is formation of a non-adherent fibrous capsule. More chemically reactive metallic implants elicit thicker interfacial fibrous layers. Because the interface is not chemically or biologically bonded, relative movement can occur which called micromotion. This movement results in progressive development of the non-adherent fibrous capsule and eventually leads to deterioration in function of the implant or the host tissue at the interface or both. Porous biomaterials provide interfacial fixation by ingrowth of tissue into pores on the surface or throughout the implant. This attachment is called "Biological Fixation". It is capable of withstanding more complex stress states than dense nearly-inert implants which achieve only "morphological fixation" **[Hulbert et al, 1987]**. Resorbable implants are designed to degrade gradually with time and be replaced with natural host tissues. The constituents of a resorbable implant must be metabolically acceptable. Another requirement for a resorbable implant is that its resorption rate must be matched to the repair rates of body tissues **[De Groot, 1983]**. Bioactive implants offer another approach to achieve interfacial attachment. When a bioactive material is implanted in the body, a series of biophysical and biochemical reactions occur at the implant-tissue

interface. These reactions eventually result in a mechanically strong chemical interfacial bonding which is called "Bioactive Fixation" **[Hench and Ethridge, 1982 & Hench, 1988]**.

1.2. Constitution of bones

The bones or teeth of all vertebrates are natural composite materials, whereas one of the components is an inorganic solid, hydroxyapatite, which amounts to ≈ 65% of the total bone mass, with the remaining mass formed by organic matter and water. Most of this organic matter is collagen; its molecules are bound forming linear chains which are in turn arranged in fibers, giving rise to various macroscopic structures. The bones are characterized by their composition, crystalline structure, morphology, particle size and orientation. **[Vallet-Regı and Jose´MarıaGonza´lez-Calbet, 2004]**.The HApcrystals 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. Their small size is a very important factor related to the solubility of biological apatites when compared with mineral apatites (Figure 1).

1.3. Hydroxyapatite

The great similarity of X-ray diffraction patterns of enamel, dentin and bone to those of apatite mineral (HAp, fluorapatite, FAp), along with the chemical analyses, led to the belief that the inorganic components of bone or teeth are essentially calcium hydroxyapatite with the chemical formula: $Ca_{10}(PO_4)_6(OH)_2$. The exact structure of the biological apatites, however, is still not surly clear due to the myriad forms of their morphology and variations in non-stoichiometry. Furthermore, the stability of each of the phosphates is greatly affected by not only small compositional

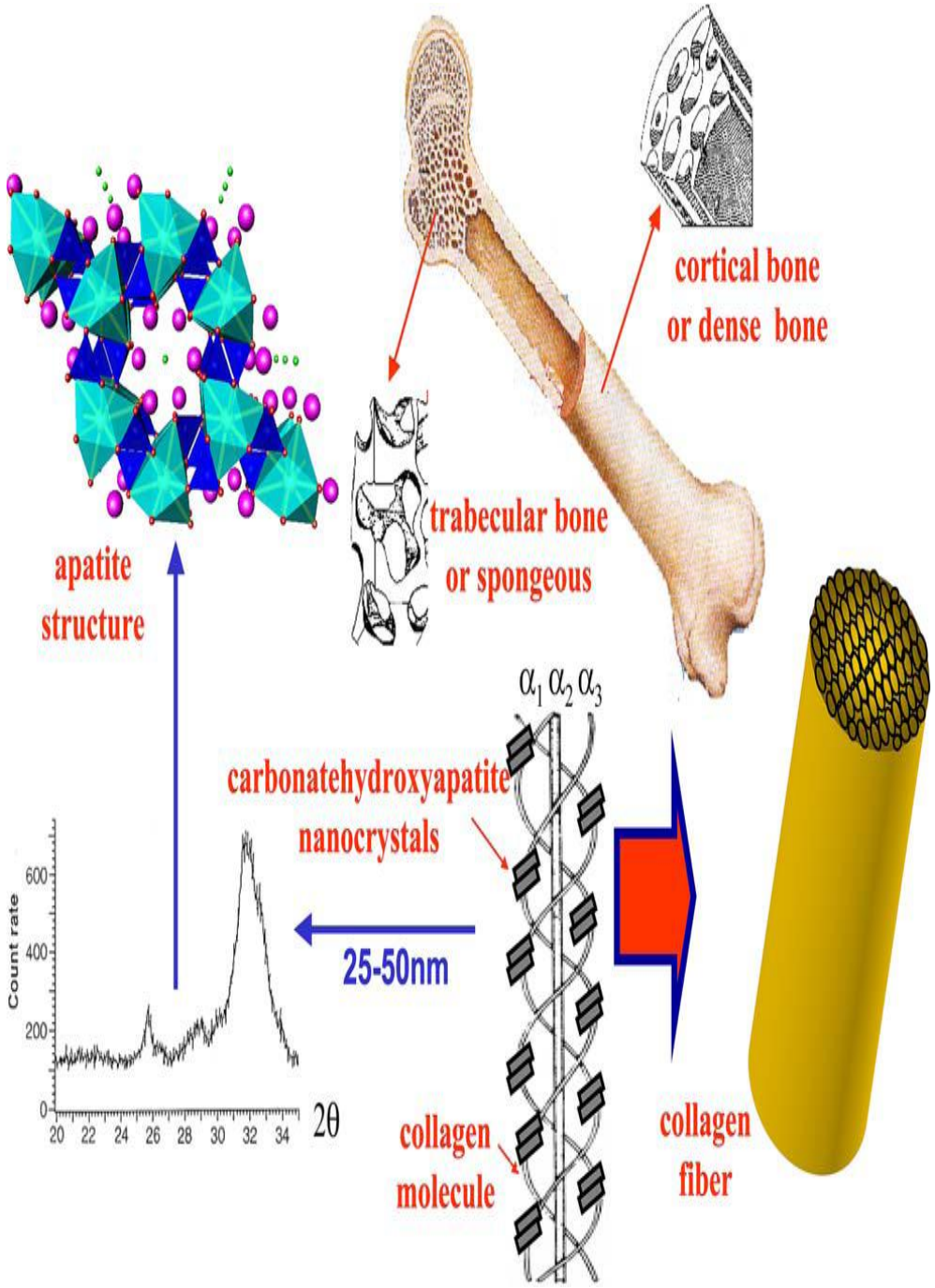

Figure 1: Cortical or compact bone, and trabecular or spongy bone: Arrangement of carbonate hydroxyapatite and collagen in the formation of hard tissues.

changes but also by the variations in pH and various other reaction conditions **[Hench, 1998]**.

Hydroxyapatite [HAp] is one of the most effective biocompatible materials. It is widely used as coating on femoral stems or ocetabular cups and as bone substitutes because of its bone bonding ability with the surrounding tissues **[Hench, 1998&Hardouin et al, 1992]**. Biological apatites differ chemically from hydroxyapatite mineral (HAp) in that they often include different ions such as Mg^{2+}, Na^{+}, K^{+}, Cl^{-} or F^{-} which can be introduced into its lattice by substitution of one or more of the Ca^{2+}. However, the major substituent in biological apatite is the carbonate which exists in bone mineral at levels typically of 5–8 wt. % **[Vallet-Regı and Jose´ Marıa Gonza´lez-Calbet, 2004]**. Moreover, biological apatites are always calcium deficient and their degree of crystallinity is almost poor. There are several forms of phosphate structure that form the apatites family which describe the compounds having similar structure **[Aoki, 1994]**.

The first generation of HAp bone substitutes was used to augment the alveolus of maxilla and mandible, to reconstruct periodontal defects, and as a craniofacial augmentation material **[Rabalais et al, 1981, Block and Kent, 1984 & Zide et al 1987].**

Hydroxyapatite [HAp] does not exhibit any cytotoxic effect while it shows excellent biocompatibility with hard tissues, skin and muscle tissues **[Hardouin, et al 1992 & Driessns and Verbeeck, 1990]**.

Hydroxyapatite is thermodynamically the most stable phase in physiological conditions and has the ability to direct chemical bonding to the bone. Moreover, it displays significant role in other areas; e.g. catalysis, sensors, optical, etc **[Best et al, 2008 & Jandt, 2007]**. The chemical species constituting HAp crystals (Ca, P, O and H) were concluded to have no toxicity. Among the

wide range of available calcium phosphates, or with potential formulation, it is important to know the close relation between the calcium / phosphorous (Ca/P) ratio, acidity and solubility. Thus, the lower the Ca/P ratio is, the larger are the acidity and solubility of the mixture. For Ca/P < 1, both acidity and solubility are extremely high, and both parameters decrease substantially for Ca/P ratios close to 1.67, which is the value of stoichiometric hydroxyapatite **[Aoki, 1994]**. Hydroxyapatite, HAp is more similar to natural bone tissue apatite than β- TCP and so it represents a better structural material for bone growth. However, the resorption rate of HAp is extremely slow as compared with β- TCP **[Driessns and Verbeeck, 1990 & De Groot, 1983]**.

1.4. Bioceramics

Bioceramics can have structural functions as joint or tissue replacements, be used as coatings to improve the biocompatibility of metal implants (**Vallet-Regı´, 2001)**, as well as function as resorbable lattices, providing temporary structures and frameworks those are dissolved and/or replaced as the body rebuilds the damaged tissues [**Kawahara, 1979 and Ducheyne, 1987)**.

Ceramic materials used in reconstructive surgery can be classified into two large groups: bioinert and bioactive; bioinert ceramics have almost no influence in the surrounding living tissue, and their examples are alumina and zirconia. Bioactive ceramics are, however, capable of bonding with living osseous tissues; several calcium phosphates and certain compositions of glasses and glass ceramics are examples.

They have the role in restitution and preservation of the physical, psychological and social well- being of the individual.

1.5. Calcium phosphate cements

Calcium phosphates are the most important family of biomaterials, due to their use in biological applications which include dental implant, percutaneous devices and use in periodontal treatment, fracture treatment, total joint replacement (bone augmentation), treatment of bone defects, orthopedics, cranio- maxillofacial reconstruction, otolaryngolgy and spinal surgery **[Doremus, 1992, Vallet-Regı´, 2001 & Best et al, 2008].**

A cement material consists of a solid powder phase which initially forms a plastic paste upon mixing with a liquid phase. This viscous paste will transform to a stiff paste during setting, increasing its mechanical strength progressively up to saturation (hardening). This setting is a result of dissolution and precipitation process. The interlocking between precipitated crystals is responsible for cement hardening. **[Fernaandez et al, 1999 a]**.

Most of the calcium phosphate cements (CPCs) form hydroxyapatite upon setting, with low crystallinity and high specific surface, which can incorporate different ions in its lattice depending on the composition of the starting materials. In general it can be stated that the formation of hydroxyapatite through a cement reaction is a biomimetic process, in the sense that it takes place at body temperature and physiological environment. Taking into account the hydroxyapatite lattice parameters (a = 0.95 nm and c = 0.68 nm), and its symmetry (hexagonal, space group P63/m) most likely its unit cell will be arranged along the c-axis **(Aoki, 1994.)**.

Hydroxyapatite does not exhibit any cytotoxic effect while it shows excellent biocompatibility with hard tissues, skin and muscle tissues among other good properties as a biomaterial, such as biocompatibility, bioactivity, osteoconductivity, direct bonding to bone, etc. **[Hench, 1998 and Hardouin et al, 1992]**.

Hydroxyapatite [HAp] is widely used as coating on femoral stems or ocetabular cups and as bone substitutes because of its bone bonding ability with the surrounding tissues. The solubility of other calcium phosphate ceramics is higher than the rate of bone tissue regeneration and they are, therefore, not useful for cavity filling and the gradual process of new bone tissue replacement. Other problems relating to these bone type substitutes include the inability to shape them in situ in the operating theatre, so that they must be used in the form of granules or blocks with the possible associated problems of lack of mechanical integrity due to their migration away from the implant site **[De Groot, 1983]**.

In the 1980s, the idea of a new bone substitute material was introduced and the materials were referred to as calcium phosphate bone cements (CPBC). They offer the surgeon moldability, injectability and complete filling of a cavity, in situ, within the operating theatre. Implanted bone tissue also takes benefits from initial setting characteristics of the material which gives, in an acceptable clinic time, suitable mechanical strength for a shorter tissue functional recovery. Further advantages relate to the ability of CPBCs to activate the osteoclastic and osteoblastic functions of bone regeneration with the additional advantage that now these functions work on the cement material changing it with time to an organized structure characteristic of a newly formed bone **[Fernaandez et al,1999 b]**.

All CPC are formed by a combination of one or more calcium orthophosphates, which upon mixing with a liquid phase, usually water or an aqueous solution, form a paste which is able to set and harden after being implanted within the body. Indeed, the hydroxyapatite formed in the setting of CPC is much more similar to biological apatites than ceramic hydroxyapatite.

Calcium phosphate cements (CPCs) show several advantages with respect to other materials which are used for bone repair; for example, they are injectable, non- toxic easy to shape and can be maintained locally. Therefore, they are very effective to fill bone defects with an irregular shape. Furthermore, CPCs are very bone compatible and osteoconductive (able to provide a scaffold or template for new bone formation) and support osteoblast adhesion and proliferation. On the other hand, they have poor mechanical properties. Currently, this prevents their use in loaded condition **[Fernaandez et al, 1999a & Del Reala et al, 2002]**.

The most used calcium phosphate in implant fabrication is hydroxyapatite since it is the most similar material to the mineral component of bones. It exhibits good properties such as biocompatibility, bioactivity, osteoconductivity, direct bonding to bone, etc. Furthermore, CPCs are very bone compatible and osteoconductive and support osteoblast adhesion and proliferation. This allows for an optimum tissue–biomaterial contact, necessary for stimulating the bone ingrowth **[Hulbert et al, 1987]**.

Among the existing calcium orthophosphates, only certain compounds are useful for biomedical applications, because those having a Ca/P ionic ratio less than 1such as monocalcium phosphate monohydrate (MCPM) and monocalcium phosphate anhydrous (MCPA) are not suitable for implantation into the body due to their high solubility and acidity. Tetracalcium phosphate (TTCP) alone is not suitable due to its basicity. However, for biomedical applications, the ‘‘unfit’’ calcium orthophosphates might be combined with either other calcium orthophosphates or other chemicals.

Natural sources of calcium phosphates (autographs) are almost inconvenient due to the limited amount of material that

can be taken from the own patient. Allograft or engrafts are also, inconvenient for their possible contamination with virus, bacteria or even being antigenic. In addition, bone composition and properties vary considerably within a population and are difficult to be controlled. Thus remodeling of the implant is very different from one person to another and from one implant to the other. Synthetic products, on the other hand, offer controlled composition and properties and can be optimized for any specific application **[Del Reala et al, 2002]**.

1.6. Synthesis of hydroxyapatite

Various routes for hydroxyapatite (HAp) preparation were mentioned in the literatures **[**as examples **Weng and Baptista, 1998 &Weng and Baptista, 1998]**. Hydrothermal synthesis used by **[Katsuki et. al, 1999 and Yoshmura et al, 1994]**, emulsion or microemulsion routes attempted by **[Lim et al, 1999]**, electrochemical deposition by **[Huang et al, 2000]** in addition to mechano-chemical synthesis by **[Kim et al, 2000]**, combustion preparation are some examples. Among the surveyed methods of preparation of HAp, chemical precipitation from aqueous solutions provides a versatile and economic route.

[Omori et al, 2006] studied the reaction of a mixture of 6 mol of $CaHPO_4.2H_2O$ and 4 mol of $Ca(OH)_2$ to produce hydroxyapatite (HAp) by spark plasma system (SPS).The reaction was carried out at 300–1200 ºC under pressure of 20–670 MPa for 10 min in vacuum. Moreover, the formation of HAp started at 300 ºC at 600 MPa and was completed at 500 ºC at 670 MPa, the same product being obtained at 1200 ºC in air using a furnace. The temperature of the HAp formation increased with decreasing pressure and was 1150 °C under 20 MPa.

[Fathi et al, 2008] prepared fine- grained poorly crystalline hydroxyapatite nano-particles, as well as carbonate apatite which showed the similar dissolution / resorption manner to biological apatite in simulated body fluid. The crystallinity and morphology of either of them were dependent on the sintering temperature. The crystallinity and crystallite size of the hydroxyapatite nano-powders increased with increasing of sintering temperature. The carbonated hydroxyapatite nanopowders with low-crystallinity were desired in vitro behavior. Moreover, the in vitro bioresorbability of the hydroxyapatite nano-powder was higher than bioresorbability of conventional hydroxyapatite and close to biological apatite, which they attributed to its high surface area owing to nanostructure processing.

[Padmanabhan et al, 2009] synthesized hydroxyapatite (HAp) nano-hexagonal rods with 70–90 nm diameter and 400- 500 nm length using a simple sol–gel route with calcium nitrate and potassium dihydrogen phosphate as calcium and phosphorus precursors respectively. Deionized water was used as a diluting media for HAp sol preparation and ammonia was used to adjust the pH= 9. After aging, the HAp gel was dried at 60°C and calcined at different temperatures ranging from 300 to 700°C. They added that the crystallite size of the HAp nano-articles increased with the temperature and showed an anisotropic crystal elongation resulting in nano-rods at 700°C. Besides particle size, the crystallinity of the powders also increased with temperature. HAp nano-rods with an aspect ratio value between 6 and 7 were obtained. XRD analysis showed that the final product of calcined material was pure HAp. FTIR showed the presence of minor CO_3^{2-} dissolution at high temperatures of 700 °C. This formation of HAp nano-rods was found wide applications in healing process because of large adsorption property associated with it.