International Journal of Scientific & Engineering Research, Volume Volume 13, Issue 6, June-2022
ISSN 2229-5518

Hydroxyapatite Formation Method : A Review

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Abstract— Hydroxyapatite is a bioceramic that is used in the health sector, notably in the process of bone fillers and bone implants. Hydroxyapatite has adaptability and is easily accepted in bone tissue (immunogenic) so it can accelerate the healing of damaged bone tissue, and its chemical composition is almost similar to bone. Research on hydroxyapatite has been done quite a lot with various methods and variations of the given treatment such as pH value, synthesis time, and material used. Several methods that have been studied to produce hydroxyapatite are sol-gel, mechanochemical, microwave, precipitation, hydrothermal, emulsion, and solid-state with advantages and disadvantages in both the process and the results obtained. Each method will produce different morphology, stoichiometry, grain size and crystal form of hydroxyapatite.

Index Terms— Bioceramic, implant, immunogenic, hydroxyapatite, bone, materials, synthesis.

1 Introduction

Hydroxyapatite (HAp) is one of the biomaterials used as biomedical materials, such as bone fillers, bioactive implant coatings, bone tissue repair, and drug delivery systems [1]. This can be applied because of the properties of HAp, namely biocompatibility, bioactivity, and osteoconductivity. Hydroxyapatite can accelerate the healing of damaged bone tissue, because it is easily absorbed by bone tissue (immunogenic) and is non-toxic, non-inflammatory, and has almost the same chemical content as bone. Bovine bones, fish scales, and fish bones have physicochemical properties similar to human apatite bone, so they can increase their potential just like HAp synthesis materials [2].

Extraction of biominerals from natural wastes is the best known method for producing HAp from biological sources. More than some excellent extract properties, it is also economical and environmentally friendly [3]. Figure 1 shows five different groups associated with the use of natural resources in the synthesis of hydroxyapatite. These include the extraction of minerals from natural wastes, synthesis from eggshells, synthesis from the bones of marine organisms, synthesis using natural biomolecules, and synthesis using biological membranes [4].

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Extraction of biominerals from natural wastes (especially bovine bones, fish scales, fish bones) is the most well-known method for producing HAp from biological sources. In addition to several excellent extract properties, it is also economical and environmentally friendly. The preparation of HAp using natural waste generally involves several hours of annealing during which organic material in bone is removed, leaving pure HAp as a residue [5]–[9].

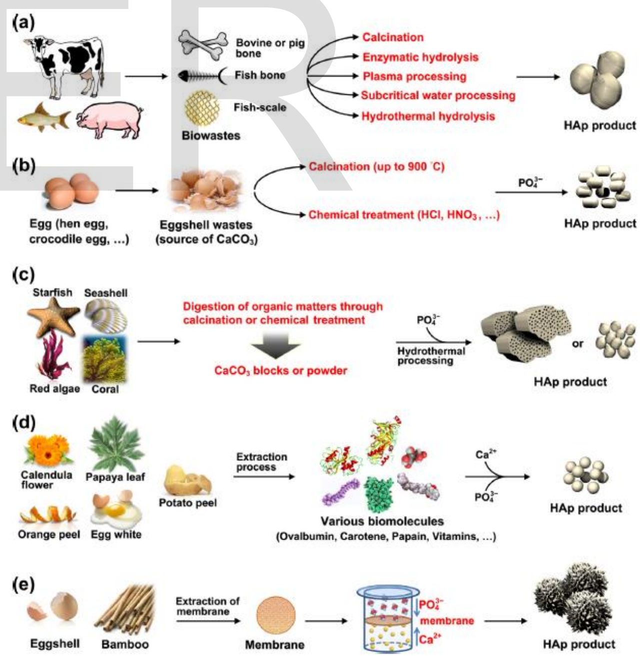

Figure 1 HAp preparation from biogenic resource: (a) mineral extraction from natural waste; (b) synthesis from egg shell; (c) synthesis from the exoskeleton of marine organism; (d) synthesis with biomolecule; (e) synthesis with biomembrane [4].

Calcium carbonate found in the bones of various marine species is a natural material used in the synthesis of HAp. Special procedures involving ion transfer under hydrothermal conditions, for example, based on several reactions [6], [8], [10].

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$$10CaCO_3 + 6(NH_4)_2HPO_4 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 6(NH_4)_2CO_3 + 4H_2O + 4CO_2 \quad (1)$$

Calcium carbonate from marine species generally has the same porosity and interconnectivity characteristics as human bone. To maintain this unique internal morphology, calcium carbonate is generally used in its original form [11]. Some clam shells contain 95-99% $CaCO_3$ by weight. Shellfish shells can be used as calcium precursors in the manufacture of HAp. Ni and Ratner explained that the surface of nacre shell pieces can be transformed into HAp in a phosphate buffer solution at atmospheric temperature by a surface reaction process. The mineral phase from the surface of the nacre shell was found to change from $CaCO_3$ aragonite phase to HAp phase. [12].

There are several synthesis methods that can be used to produce hydroxyapatite, such as sol-gel, mechanochemical, precipitation, hydrothermal, emulsion, and solid-state with advantages and disadvantages both in the process and the results obtained. Each method carried out will produce different morphology, stoichiometry, grain size, and crystal form of hydroxyapatite [13]. This journal will explain the advantages and disadvantages of the hydroxyapatite synthesis method from previous studies.

2 HYDROXYAPATITE SYNTHESIS METHODS

2.1 Sol-gel Method

The sol-gel method is one of the effective methods for the synthesis of nano-phase HA because the control of the synthesis process parameters can be carried out strictly. This method is carried out by mixing at the molecular level of calcium and phosphorus, which can improve the chemical properties of the resulting HA. A number of combinations of calcium and phosphorus precursors were used for the synthesis of HA using the sol-gel method. In addition, the chemical activity and temperature required to form the apatite structure are highly dependent on the chemical properties of each precursor. Balamurungan, et al. used $Ca(NO)_3.4H_2O$ and triethyl phosphate as precursors for calcium and phosphorus, when the stoichiometric Ca/P ratio was maintained at 1.67. The synthesized HA powder was dried and sintered at different temperatures up to 900°C [14]. Brendel, et al. has synthesized HA at low temperature (400°C) using $Ca(NO_3)_2.4H_2O$ and phenyl dichlorophosphite ($C_6H_5PCl_2$) as precursors. However, the resulting HA has low purity and poor crystallinity [15].

A further increase in temperature up to 900°C resulted in a pure HA phase with better crystallinity. Crystallinity is increased by increasing the temperature to 1100°C. In another approach, Vijayalakshmi, et al. synthesized monocrystalline HA powder from calcium acetate and triethyl phosphate in water and ethanol media [16]. Figure 2 illustrates the process of hydroxyapatite synthesis using the Sol-gel method which has been carried out by Lett Lett, et al. using $Ca(NO)_3.4H_2O$ and $(NH_4)_2HPO_4)$ as precursors for calcium and phosphorus, and added (NH_4OH) to adjust the pH values to 7, 9 and 11. The synthesized HA powder was dried and sintered at different temperatures up to 100° C for 24 hours [17].

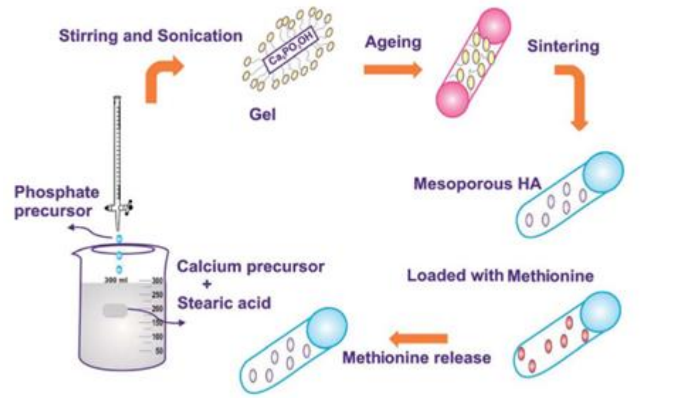

Figure 2 Hydroxyapatite synthesis scheme of sol-gel method [17]

2.2 Precipitation Method

The precipitation method is one of the well-known and widely used techniques for the synthesis of hydroxyapatite (HA). This is because, with this technique, large amounts of HA can be synthesized without the use of organic solvents and also at a low cost [18]. The size, shape, and surface of the HA particles obtained by this reaction are very sensitive to the rate of addition of phosphoric acid and the reaction temperature. The rate of addition of phosphoric acid is closely related to the pH obtained at the end of the synthesis and also to the stability of the suspension. The reaction temperature determines whether the synthetic HA crystal is monocrystalline or polycrystalline. The HA synthesized at low temperature (<60°C) was monocrystalline [19].

Many researchers have used this deposition technique to synthesize HA with different types of precursors. Calcium nitrate tetrahydrate [$Ca(NO_3)_2 \cdot 4H_2O$)] and diammonium hydrogen phosphate [$(NH_4)_2HPO_4$] were used as precursors for the reaction. The HA synthesis reaction with the precipitation method was carried out by Faiz et al. Figure 3 shows the scheme of making hydroxyapatite with the precipitation method that has been carried out. The pH value kept at 10 and the Ca/P stoichiometry was set at 1.67 [20].

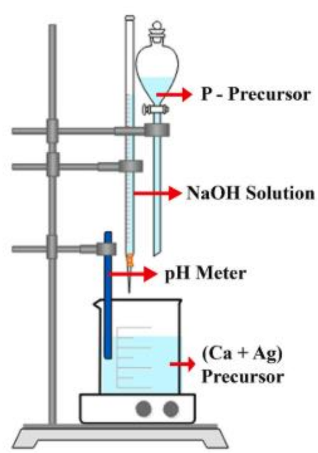

Figure 3 Hydroxyapatite synthetic scheme of precipitation method [20].

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2.3 Emulsion Method

An emulsion is a heterogeneous mixture of at least one immiscible liquid dispersed in the form of another droplet [21]. These systems are generally described as water-in-oil (W/O) or oil-in-water (O/W). The first stated step is the dispersed one and generally an O/W system is used to prepare the HA. Depending on the size of the water droplets, i.e. the size of the reaction domain, the technique may be referred to as emulsion or microemulsion. The reaction occurs when two different droplets containing the reactants collide with each other. Nano and micro HA particles can be formed through microemulsions and emulsions. Furthermore, the microemulsion technique is reported to be able to reduce the agglomeration of HA particles [22]. One particular application for this synthesis is the formation of spherical porous HA granules for drug delivery [23].

Based on several studies, the emulsion method requires a calcination temperature and a sintering step in the HAp synthesis process. The chemicals needed in the synthesis are very much compared to other methods since this synthesis method is also very dependent on the oil and surfactant used. Hence, the price required in this process is very much. In addition, the resulting HAp is not stoichiometric and has low crystallinity. Figure 4 shows a schematic of the preparation of hydroxyapatite by the emulsion method [4], [21]–[24].

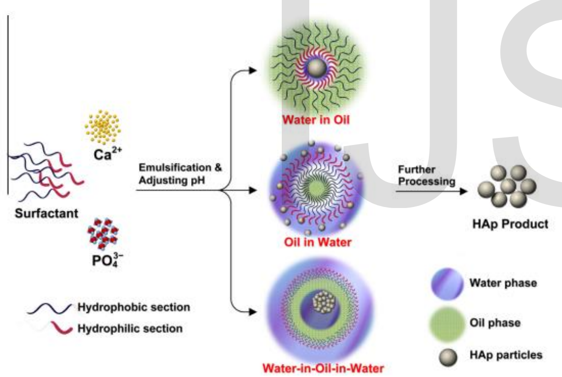

Figure 4 Hydroxyapatite synthetic scheme of emulsion method [4].

2.4 Mechanochemical Method

Mechanochemical synthesis is a solid process technique in which mechanical and chemical phenomena are combined at a molecular scale. It is possible to produce the desired product only by mechanical action (high pressure and mechanical stress between the reactants and the ball) at room temperature or lower temperatures than traditional solid-state synthesis [25]. Mechanochemical synthesis can be carried out under different conditions, such as using a reactive atmosphere (reactive ball milling [BM]), under cryogenic conditions (cryomilling), or in a solvent. In addition, other experimental parameters can be controlled that affect the characteristics of the final material: milling time, powder-to-ball ratio, milling temperature, milling frequency, milling atmosphere, selected gas pressure, etc. Depending on the synthesis parameters, different products can be obtained, such as metastable phase, high-pressure phase, and amorphous and irregular phase, leading to the development of ultrafine-grained and nanostructured compounds with homogeneous compositions. Therefore, chemical mechanics processing is a versatile technique that can be used to prepare various materials.

Research by Ferro and Guedes on the synthesis of hydroxyapatite with calcium precursors derived from cuttlefish bones and chicken eggshells. The method used is to mix CaCO3 from natural sources and H3PO4 solution as a phosphate precursor with a molar ratio of 1.67 in ball milling with variations in rotational speed and milling time. Both have a non-uniform shape and agglomerate [7]. Figure 5 shows the scheme of making hydroxyapatite by mechanochemical methods [25], [26].

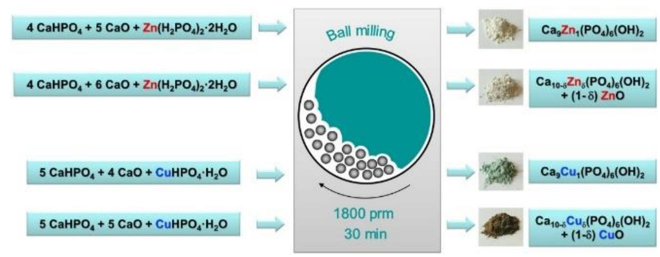

Figure 5 Hydroxyapatite synthetic scheme of mechanochemical method [26].

2.5 Solid-state Method

Research by Ferro and Guedes on the synthesis of hydroxyapatite with calcium precursors derived from cuttlefish bones and chicken eggshells. The method used is to mix $CaCO_3$ from natural sources and H_3PO_4 solution as a phosphate precursor with a molar ratio of 1.67 in ball milling with variations in rotational speed and milling time. Both have a non-uniform shape and agglomerate [7]. Figure 5 shows the scheme of making hydroxyapatite by mechanochemical methods [25], [26].

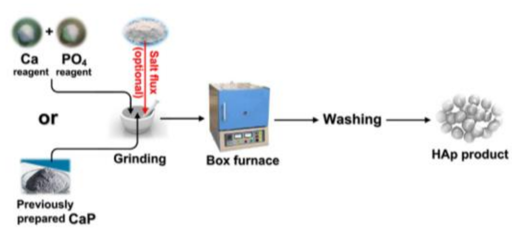

Figure 6 Hydroxyapatite synthetic scheme of solid-state method [4].

2.6 Hydrothermal Method

Hydrothermal processing involves the use of a solvent (with soluble ionic precursors), which is heated in a sealed vessel. In the case of hydrothermal synthesis, the solvent used is water. The temperature of the solvent is above the boiling point because the autogenous pressure in the vessel exceeds the ambient pressure. This technique is carried out by utilizing water vapor pressure and pressure in the synthesis of a ceramic material. This change in the properties of the solvent and reactants (e.g. solubility) at high temperatures means that ex-

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perimental variables can be controlled to a higher degree. This makes the reaction more predictable as crystal nucleation, growth, and aging can be regulated [27].

Hydroxyapatite produced by the hydrothermal method is influenced by hydrothermal temperature, hydrothermal reaction time, Ca/P ratio, and pH [28]. The main influence in the formation of hydroxyapatite crystals is the pH value. The growth of hydroxyapatite crystals resulting from a high pH value is isotropic and the resulting hydroxyapatite crystal form is spherical or short rod-like. In another study, increasing the pH and sintering temperature resulted in the growth and fusion of crystals having a porous capsule morphology. Figure 7 shows the scheme of making hydroxyapatite by the hydrothermal method [28], [29].

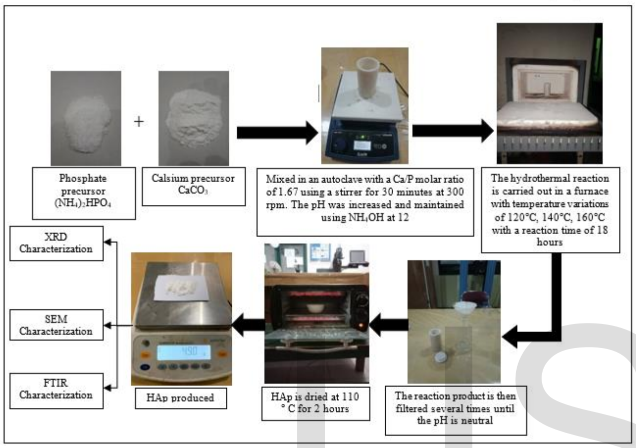

Figure 7 Hydroxyapatite synthetic scheme of hydrothermal method [28].

2.7 Microwave Method

Microwave irradiation provides an efficient, environmentally friendly, and economical heating method due to its improved reaction kinetics and fast preheating. Coupled with the reduction in reaction time when compared to conventional heating methods which ultimately culminates in the product being in the form of good, high purity, and homogeneous powder [30], [31]. Various methods of HAp synthesis using microwaves have been carried out to determine the effect on the resulting HA nanocrystals, including the Ca/P ratio, particle size and shape, crystal structure, and biological properties. Hassan concluded that the value of pH, temperature, pressure, microwave power, and synthesis time had a better effect on the phase structure and morphology of the HAp form. While the Ca/P molar ratio, the chelating effect of EDTA, and the synergistic effect of ultrasound have been shown to influence the morphology and size of the resulting HAp [32].

Microwave HAp synthesis is an effective method for synthesizing nano-crystalline HAp powder in a short time since the technique is simple, economical, easy to repeat and can be optimized for mass production. HAp powder with an average particle size of 12 nm was obtained after being synthesized using a microwave [33]. A study comparing the hydroxyapatite synthesis method was conducted by Logesh et al. The research was carried out using the microwave method and conventional hydrothermal method with a furnace to produce hydroxyapatite from chicken eggshells. The stoichiometry of the Ca/P solution was set at 1.67. The microwave method used 700 watts of power for 10 minutes. While the conventional hydrothermal method is carried out at a temperature of 600oC. The difference in hydroxyapatite produced can be seen in the morphology of hydroxyapatite with conventional microwave and hydrothermal methods.

Hydroxyapatite formed by microwave the surface of the interwoven fibers is clearly covered with hydroxyapatite crystals, while on the fiber surface of hydroxyapatite by conventional hydrothermal method the hydroxyapatite crystals formed are found to be scattered and larger. Figure 8 shows that the nucleation and growth processes depend on the synthesis method used. The size of the crystals formed generally depends on the balance of nucleation and the rate of crystal growth. Smaller crystals are formed when the nucleation rate is more dominant than the crystal growth rate. In this study, it can be concluded that the rate of nucleation can be influenced by the rate of heating that occurs [34].

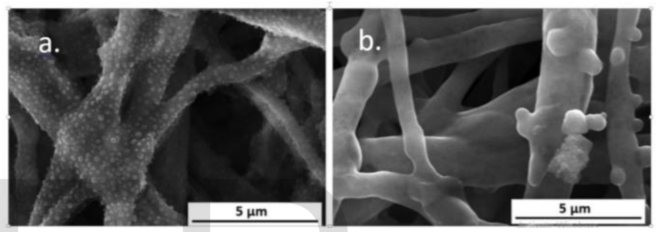

Figure 8 Morphology comparison of the HAp; (a) microwave method dan (b)conventional hydrothermal method [34].

3. Conclusion

This research article describes seven different methods for producing HAp and also reviews the latest research on synthetic methods that have been carried out so far. From the method ABOVE, by comparing various methodologies, the authors argue that the microwave method is the simplest and easiest way to produce homogeneous HAp with high purity and has the potential for further use in biomedical and orthopedic applications.

Acknowledgments

This research was funded by Ministry of Education, Culture, Research and Technology with research scheme PDUPT 2021 for Center for biomechanics, bimaterial, biomechatronics and biosignal processing (CBIOM3S) UNDIP.

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