OVERVIEW: PROCESS PARAMETERS FORHYDROTHERMAL SYNTHESIS OF HYDROXYAPATITE

Fatimah, M.[1], Shaaban, A.[2] and Seliman, S.[3]

[1,2]Faculty of Manufacturing Engineering,
Universiti Teknikal Malaysia Melaka (UTeM),
Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia.

[3]Faculty of Management and Human Resource Development,
Universiti Teknologi Malaysia (UTM),
Kampus Johor Bahru, 81310 Skudai, Johor, Malaysia.

Author's email: fatimahms@ymail.com

ABSTRACT: Hydroxyapatite is the most interesting subject to be studied especially for its suitability as an alternative to human bone and has become a biomaterial ceramic that resembles the composition of our bone minerals and are able to respond biologically. The preferred synthesis method is Hydrothermal which produces HA nano-sized particles with customized morphology and desired crystallinity by varying the process parameters. The morphology and the crystallinity of the synthetic powder particles influence the mechanical properties of manufactured products. This paper reviews the variable factors in hydrothermal method which includes type and concentration of starting material, temperature, time, pressure and pH conditions and presence of additives.

KEYWORDS: Hydroxyapatite, Hydrothermal Synthesis, Process Parameters, Morphology, Crystallinity, Nanoparticles.

1.0 INTRODUCTION

Calcium phosphate-based bioceramics, particularly apatites, have been of interest in orthopedic surgery and dentistry. Hydroxyapatite (HA) with Ca10(PO4)6(OH)2, is one of the most important bioceramic materials as bone substitutes due to its similarity with the mineral components of hard tissues of human body such as bone, dental enamel and dentin (Sadat-Shojai, 2009). The biocompatibility of HA supports bone tissue growth, and it is bioactive or surface-reactive (Billotte, 2007) thus making HA the most interesting subject to be studied especially for its suitability as an alternative to human bone (Sadat-Shojai, 2009). HA has become the biomaterial with escalating interest.

HA has the advantage of being the most stable phase of calcium phosphates ceramics (Thamaraiselvi and Rajeswari, 2004). The primary advantage of HA is biocompatibility that will implement the rapid integration into the human body and will bind to the bones with indistinguishable formations (Jayaswal, *et al*., 2010). The leading properties of biocompatibility and bioactivity of HA have helped in solving medical problems related to hard tissues of human body. The mechanical properties and microstructures of the resulting HA ceramics are mostly influenced by the microstructure of the produced HA powder, including crystallinity, agglomeration, stoichiometry, substitutions, and the processing conditions (Veljovic, et al., 2009). Thus, the synthesizing method must be wisely chosen to ensure desired nanosized powder.

2.0 HYDROTHERMAL METHOD

There are many methods to prepare synthetic HA. Some of the methods are, solid-state reactions (Earl, *et al*., 2006), chemical precipitation, sol-gel process, hydrothermal method, biomimetic deposition, and solvothermal (Sadat-Shojai, 2009). Hydrothermal synthesis method has been the preferred method to prepare nanoparticles of biomaterial (Felício-Fernandes and Laranjeira, 2000; Sadat-Shojai, 2009; Earl, *et al*., 2006). High degree of crystalline production is shown by the small-sized single crystals (Bayazit, *et al*., 2010; Dorozhkin and Epple, 2002) and whisker-like (Bayazit, *et al*., 2010) HA developed through hydrothermal synthesizing method.

Hydrothermal synthesis procedure involves single or heterogeneous phase reactions in aqueous at temperatures more than 25°C and pressures exceeding 100 kPa to initiate crystallization directly from solutions (Nayak, 2010). It is the reaction of aqueous solutions in closed recipients under controlled temperature and / or pressure. High pressure and temperature of hydrothermal conditions of the HA powder are suggested to produce more crystalline powders (Saheb and Joughehdoust, 2009). Conversely, hydrothermal method can also be prepared under mild conditions (Suchanek and Riman, 2006; Neira, *et al*., 2009), because low temperatures and high pH influence defect-free crystal growth.

Hydrothermal method produces HA nano-sized particles with similar microstructures as the natural bone tissue with good crystalline quality, physiological stability and similar maintenance of the morphological characteristics of the initial material (Felício-Fernandes and Laranjeira, 2000). The mechanical strength of the biomaterial mainly depends on properties such as grain size, grain size distribution, porosity, and other microstructural defects (Pramanik, *et al*., 2005). Thus, the resulting fine particles produced when hydrothermal method is used improve the microstructure of the compacted product that eventually influences the mechanical performances.

3.0 PROCESS PARAMETERS

Many parameters in hydrothermal process can be altered and compared to produce the desired morphology, size and condition of the powders (Suchanek and Riman, 2006; Neira, *et al*., 2009). The variable precursors include thermodynamic (temperature, reactant concentrations, additives and/or solvents etc.) and non-thermodynamic processing variables (stirring rate etc.) (Suchanek and Riman, 2006). Hydrothermal synthesis method allows a variation of factors that affect the morphology of the fine particles (Loo, *et al*., 2008). This paper reviews the variable factors in hydrothermal method which include the type of starting material, the concentration of stating material, the temperature profile, the synthesis temperature, the synthesis time, the synthesis pressure, the pH conditions and the presence of additives.

3.1 Starting Material

Synthesizing process of HA involves two types of ions which are the calcium ion, Ca^{2+} and the phosphate ions, $PO4^{3-}$ (Pramanik, *et al*., 2005) and there are various combinations of the ion sources. The most common ion sources are calcium nitrate tetrahydrate, Ca(NO3)2·4H2O (Earl, *et al*., 2006; Loo, *et al*., 2008; Neira, *et al*., 2009; Sadat-Shojai, *et al*., 2011; Chaudhry *et al*, 2011) and diammonium hydrogen phosphate, (NH4)2HPO4 (Zhang, *et al*, 2001; Earl, *et al*., 2006; Zhang and Vecchio, 2006; Loo, *et al*., 2008; Neira, *et al*., 2009; Montazeri, *et al*., 2010; Chaudhry, *et al*, 2011; Sadat-Shojai, *et al*., 2011).

Other Ca^{2+} sources used for HA synthesis are calcium nitrate (Ca(NO3)2) (Chaudhry, *et al*, 2011), calcim oxide (CaO) , calcium

hydroxide (Ca(OH)2 (Montazeri, *et al*., 2010), calcium carbonate (CaCO3) (Felício-Fernandes and Laranjeira, 2000; Zhang and Vecchio, 2006) and octacalcium phosphate (OCP, Ca8(HPO4)2(PO4)4·5H2O) (Kamitakahara, *et al*., 2009) whereas other $PO4^{3-}$ are from phosphoric acid (H3PO4) (Kamitakahara, *et al*., 2009) and ammonium di-hydrogen phosphate, (NH4H2PO4) (Loo, *et al*., 2008). α-TCP (α -Ca3(PO4)2) (Kawachi, *et al*., 2005) and other intermediate compounds (Felício-Fernandes and Laranjeira, 2000) can also become starting materials to prepare HA through hydrothermal method.

3.2 Amount of Reactant

HA powders are commonly prepared with Ca/P molar ratio in accordance to the stoichiometric amount in HA, 1.67 (Neira, *et al*., 2009; Nayak, 2010; Sadat-Shojai, *et al*., 2011). The resulting HA products are not usually stoichiometric due to partial substitutions of the anions ($PO4^{3-}$, and OH^{-}) by $CO3^{2-}$ groups (Neira, *et al.,* 2009; Sadat-Shojai, *et al.,* 2011) and thus the Ca/P ratio does not give significant influence (Sadat-Shojai *et al*., 2011). In contrast, when molar ratio is increased, the length of HA nanocrystals also increases and purer HA obtained (Du, *et al*, 2009). This is because, with the presences of the phosphate ion source, Na2HPO4, NaOH is hydrolyzed and this prevents anisotropic growth, resulting in the growth of short rods (Du, et al., 2009). Uniform and longer nanorods are produced with larger Ca/P molar ratio.

The concentration of the starting reactants can also give a certain degree of influence, such as on the number of phases of HA (Neira, *et al*., 2009) and the diameter of HA particles (Sadat-Shojai, *et al*., 2011). A single crystalline phase HA powder and finer plate-like morphology of particles are obtained when half of the initial concentration of the starting material is used even with different temperature profile (Neira *et al*., 2009). Concurrently, the diameter of the particles increases with the increment of reactant concentration because less concentrated chemical material limits the ion transportation. The increments of the mean length of these particles are also concluded to be greatly affected by the concentration of the initial material (Sadat-Shojai, *et al*., 2011).

3.3 Temperature Profile

Hydrothermal treatment to synthesis HA can be done in various temperature profiles designed as serious, stepwise, slow and intervallic

thermal heating. Four temperature profiles (I, II, III, and IV, refer Figure 1) are applied and the morphology of the powder products is evaluated. Scheme I is the normal and favorable profile used in most research with varying maximum temperatures (i.e. 90°C from Figure 1) and standing times (i.e. 72h). The morphologies of the resulting powder are plates, hexagonal prisms, needles, and fine-plates respect to the sequence of the scheme (Neira, *et al*., 2009). The heating changes have affected the growth of the particles and the decomposition of additives as urea that will further be discussed below (Additive part).

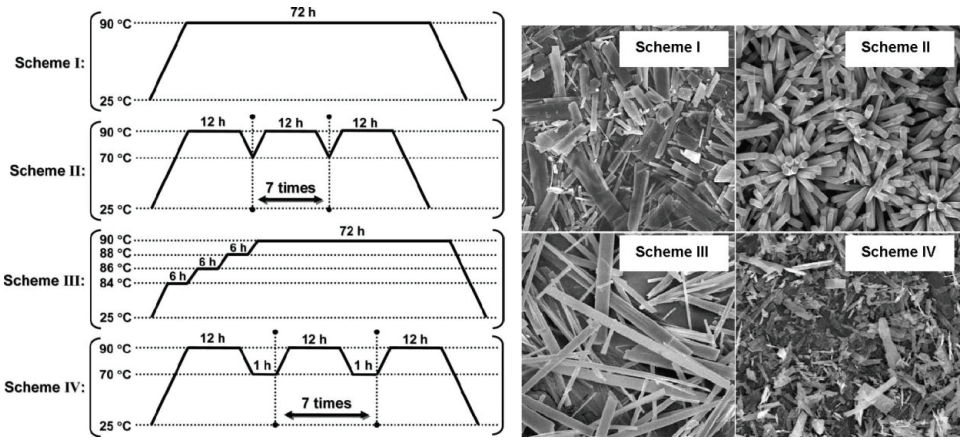

Figure 1: Schematic representations (I-IV) of controlled temperature profiles applied during the hydrothermal treatments and the resulting HA powder with heating or cooling rates of 0.5 °C/min (Neira et al., 2009).

3.4 Synthesis Temperature

A distinctive range of hydrothermal temperatures used are of either elevated or mild. Higher temperatures can be classified as temperatures above 100°C while mild conditions are under 100°C. The morphology of the particles is greatly affected by the synthesis temperature. This is because temperature regulates the driving force and reactant solubility of the reaction during hydrothermal process (Viswanath and Ravishankar, 2008). Many results show increasing length of particles with increasing synthesis temperature (Loo, *et al*., 2008). A more detailed interaction of synthesis temperature and diameter or length of particle is analyzed. The increased temperature gives decreased diameter but increased mean length showing synthesis temperature specifically expend only the particle growth along the c-axis (Sadat-Shojai, *et al*., 2011). Particle growth rate happens by amplifying temperature.

Two transition temperatures to particle growth can be at 160°C and a temperature between 200°C and 220°C. The first transition is for uniformity, where particles synthesized at temperatures above it are more uniform while the second limits the expansion of the particle length (Du, *et al*, 2009). Pure HA needle-like crystals are formed at a process temperature of 120°C without any monetite (CaHPO4) impurities (Liu, *et al*., 2003). Crystallinity features are also affected by the change of synthesis temperature. Temperature at 60°C becomes another transition where synthesis done at a temperature below it gives poor crystallinity. On the other hand, HA synthesis done at temperatures more than this give more crystalline particles (Loo, *et al*., 2008). Another research done with synthesis temperature of 90°C and 200°C also shows increased crystallinity with increased temperature because nuclei growth tends to occur at higher temperatures (Sadat-Shojai, *et al*., 2011). Figure 2 schematically shows the growth of the nuclei that occurs during hydrothermal. Similar results were obtained by Salarian, *et al*., (2008) with synthesis temperatures of 90, 120 and 150°C.

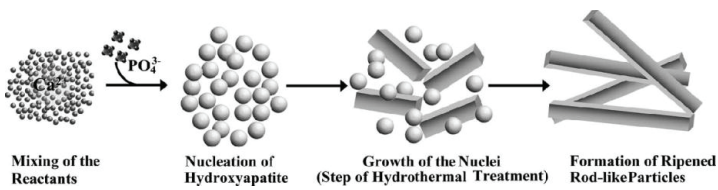

Figure 2: Hydrothermal crystallization process includes formation of crystalline nuclei and growth of nuclei steps (Sadat-Shojai, *et al.*, 2011).

3.5 Synthesis Time

Hydrothermal reaction time is another fundamental condition apart from synthesis temperature. The synthesized length of HA nanorods increases linearly with synthesis time whereas the diameter decreases as reaction prolonged and suggested that hydrothermal time is 24h (Earl, *et al*., 2006). Figure 3 shows the slightly thinner and longer HA nanorods synthesized as hydrothermal times increase. On the contrary, there is a continuous hydrothermal synthesis flow system designed that has enabled to accelerate the treatment time from hours (Earl, *et al*., 2006) to just a few seconds (Chaudhry, *et al*, 2011). Unfortunately, production of CaHPO4 is observed with lengthen of the treatment time. For the range of 24-72 hours of synthesis, crystallinity, morphology and

size are not significantly affected by the differences in synthesis duration. (Earl, *et al*., 2006).

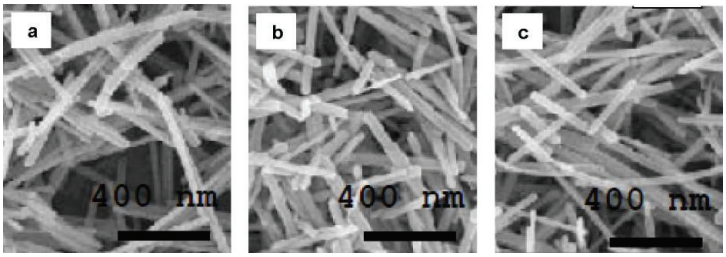

Figure 3: SEM micrographs of powders synthesized for different treatment times at 200°C
(a) 24 hrs, (b) 48 hrs, (c) 72 hrs (Earl, *et al.*, 2006.)

3.6 Synthesis Pressure

Most hydrothermal procedures were conducted without considering pressure conditions. The stability of certain ions can be affected by process pressure (Du, *et al*, 2009). The driving force of the reactions occurring during hydrothermal is also engaged on the pressure conditions (Viswanath and Ravishankar, 2008). Stainless autoclave reactor was used to synthesize HA with pressure set to 15.2atm (Montazeri, *et al*., 2010) or 1.54MPa. A similar experiment was done using pressure at 2MPa produced HA whiskers (Suchanek and Riman, 2006). In contrast, another experiment had used high pressure of 24MPa on a continuous hydrothermal flow system to produce HA nanoparticles (Chaudhry, *et al*., 2011). Commercial synthesis was reported to have used only mild conditions of hydrothermal crystallization with pressures less than 1.5MPa (Suchanek and Riman, 2006) while some refer hydrothermal process to be done at pressure of more than 100kPa (Nayak, 2010). We can conclude that the general process pressure should be between 0.1MPa and 1.5MPa.

3.7 pH Condition

HA nanoparticles with different morphologies can be synthesized at alkaline and acidic conditions. Higher pH or alkaline conditions produce smaller and less elongated particles at any certain orientation (Sadat-Shojai, 2009; Sadat-Shojai, *et al*., 2011) while other reports show the same results of a more rod-like or needle-like and c axis elongated HA particles were obtained with hydrothermal process done at acidic conditions (Liu, *et al*., 2003; Earl, *et al*., 2006; Salarian, *et al*., 2008, Sadat-

Shojai, *et al*., 2011). The level of pH has become one of the prime parameters that can be altered to obtain the desired morphology of HA powder. Particle elongations favor lower pH conditions due to the preferred absorption of Ca^{2+} and $PO4^{3-}$ ions on the c-axis at this specific circumstance (Sadat-Shojai *et al*., 2011).

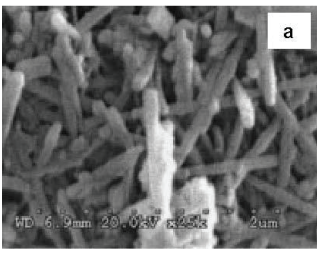

Figure 3: HA crystals at the same temperature 140°C of different pH, (a) pH 9 and (b) pH 14 (Liu, *et al.*, 2003).

In addition, Viswanath and Ravishankar (2008) evaluated ionic activity and driving force of the reaction differ at extreme pH levels excluding the range of pH 3 to 11, where preferential condition for forward reaction is at increased pH values. Crystallinity of HA nanoparticles depend on circumstances that can reduce the reaction rate of the ions during nucleation and increase the growth rate of the nuclei (Sadat-Shojai, *et al*., 2011). Apart from temperature, the degree of crystallinity is also affected by the difference in pH. More sharp peaks were observed through XRD analysis peaks in samples that were prepared at low pH conditions show higher crystallinity (Liu, *et al*., 2003; Sadat-Shojai, *et al*., 2011). Thus, the preeminent pH level to produce crystalline particles is above pH 3 and within the acidic conditions (less than pH 7).

3.8 Additives

Additional components of the hydrothermal synthesis method are usually included to obtain certain purposes such as precipitation and stabilization agents. Some of the common additives are urea ((NH2)2CO) (Neira, *et al*., 2009; Sadat-Shojai, *et al*., 2011), cetyltrimethyl ammonium bromide (CTAB) (Salarian, *et al*., 2008; Manafi, *et al*., 2008; Salarian, *et al*., 2009; Li and Tjong, 2010), polyethylene glycol (PEG) (Salarian, *et al*., 2008; Salarian, *et al*., 2009), polyvinyl pyrrolidone (PVP) (Du, *et al*, 2009), polyvinyl alcohol (PVA) (Kawachi, *et al*., 2005), polyacrylic acid (PAA) (Zhang, and Gonsalves, 1997), ethylenediamine tetraacetic acid (EDTA) (Xin, *et al*., 2010) and ammonium floride (NH4F) (Felício-Fernandes and Laranjeira, 2000).

Precipitation agents such as urea also alter the pH of the reaction and forming HA in a thermodynamically stable compound (Neira, *et al*., 2009). The decomposition of urea affects the morphology and crystallinity of the resulting synthesized particles which is controlled by the hydrothermal temperature (Sadat-Shojai,*et al*., 2011) and the heating profile (Neira, *et al*., 2009). The presences of urea has influenced the increase in diameter of HA nanoparticles because the hydrolysis of urea introduces $CO3^{2-}$ ions, incorporates with the crystal structure, controls the amount of Ca^{2+} ions and thus, controls HA crystal formation (Sadat-Shojai, *et al*., 2011). Intensive decomposition of urea (referring to the temperature profile, Figure 1, Scheme I) has increased supersaturation subsequently produces more nuclei and smaller crystals (Neira, *et al*., 2009) while stepwise urea decomposition (Figure 1, Scheme II) generates hexagonal prism-like shaped particles. Urea can decompose totally and there will be no difference observed at high hydrothermal temperatures (Sadat-Shojai,*et al*., 2011).

Surfactants as CTAB and PEG are usually used as morphology and size regulators. When both surfactants are used simultaneously, CTAB, the cationic surfactant, is added to the phosphate ion source and PEG which is non-ionic, is dissolved with the calcium ion source prior before the final solution is mixed together (Salarian, *et al*., 2008; Salarian, *et al*., 2009). From the resulting morphology of the particles, CTAB is responsible for the elongation of the crystals whereby PEG is able refine the particles and with increase amount of both surfactant has produced dandelion-like HA crystals (Salarian, *et al*., 2009). Another nucleation and crystal regulator is the PVP that acts as a capping agent and surface-regulating polymer by stopping growth at certain orientation and stabilizing them from forming aggregation of the nanoparticles (Du *et al*, 2009).

EDTA and PAA control the morphology and enhance the crystallinity of the synthesized nanoparticles (Zhang, and Gonsalves, 1997; Xin, *et al*., 2010). HA sheets of compiled rod-like crystals are synthesized from α-TCP with the presences of PVA (Kawachi, *et al*., 2005). NH4F is added during the synthesis steps when CaCO3 is the starting material, because the F^- ions facilitates the reaction but give non-stoichiometric HA product (Felício-Fernandes and Laranjeira, 2000). Even with each specific implication but experiments on the analysis of the presence of

additives are limited to small scale yield and less homogeneity of the material properties (Neira, *et al.*, 2009).

4.0 CONCLUSION

Hydrothermal method allows tailored HA nano-sized particles to be synthesized. The process parameters discussed demonstrated that the crystal products derived are composed of HA sheets, whiskers, plate-like, hexagonal prism-like, needle-like, rod-like, dandelion-like and fine spherical-shaped nanoparticle morphologies of varying sizes and length. Single-crystalline, uniform, structural defect-free and impurity-free powder samples can be achieved by altering the hydrothermal process conditions. This extensive range of variation can be useful for preparing improved synthetic biomaterials to be utilized in the biomedical fields and continuous research should be ventured especially on the mechanical properties of HA ceramics.

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