18 Recent Trends in Hydroxyapatite (HA) Synthesis and the Synthesis Report of Nanostructure HA by Hydrothermal Reaction

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Abstract

This research summary the trend in synthesis of Hydroxyapatite (HA) using different route such as dry method and wet method (co-precipitation method; emulsion method, hydrolysis method, sol-gel method, hydrothermal method). In addition, the research group also report the technique to synthesis nano-structure HA by hydrothermal reaction using $Ca(OH)_2$ and H_3PO_4 with the Ca/P molar ratio of 1.67. The mixture after homogenized for 2 h, follow by hydrothermal reaction at different hydrothermal temperature time (100 °C, 150 °C, and 180 °C) and different hydrothermal reaction time (0 h, 12 h and 24 h). The 180 °C-hydrothermal treated-HA has needle-like shape with the diameter of 10 ~ 20 nm and length of below 100 nm, which is similar with human bone. For the hydrothermal reaction, temperature is the key to form nanostructure HA.

Keywords

Nano structured hydroxyapatite · Hydrothermal reaction · Bone substitute · Calcium phosphate · Biomaterials

18.1 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 industry 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 18.1). The market for

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Table 18.1 Market share of orthopedic biomaterials over the world in 5 years from 2007 to 2011 [1]

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**

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.

The bone substitute 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. Among these bone graft substitute, Hydroxyapatite or HA [$Ca_{10}(PO_4)_6(OH)_2$] is the most attractive bone graft materials due to its excellent bone bonding to host surrounding implantation. Synthetic HA is a very important bone graft materials with the applicable in wide shape such as: bulk ceramic, a ceramic coating, or as one of the component of bone cement. HA is also used as a catalyst for the dehydration and dehydrogenation of primary alcohol due to its strong absorbent in water. Indeed, HA is a material of varying properties depend on its mode of preparation. The special structure of calcium and phosphate group in HA enables the possibility to use HA in divert application. For example, due to HA's similarity in chemical composition to the mineral phase of bone tissue, it is known for its applications in medicine as synthetic bone substitute [2]. In addition to its biological important, HA is researched for various applications such as fluorescent lamps [3], materials for fuel cell [4], or an absorption of waste and harmful materials [5]. For these applications, it has been noticed that a non-stoichiometric material is more efficient either in promoting the precipitation of biological apatite on its surface [6, 7] or increasing the reaction rate of water absorbent [8, 9]. The extend of the non-stoichiometry can be evaluated through various technique and expressed by value of x in the formula $Ca_{10-x}(HPO_4)_x(PO4)_{3-x}(OH)$.

Many methods have been used to synthesis HA such as dry methods [10, 11] by heat treatment of finely ground mixed precursor. For example, the mixture of Tricalcium phosphate [TCP: $Ca_3(PO_4)_2$ or $3CaO.P_2O_5$) and Tetracalcium phosphate [TTCP: $Ca_4(PO_4)_2O$ or $4CaO.P_2O_5$] follow by proper calcination can be used to form HA as shown in Eqs. (18.1) and (18.2)

$$2Ca_3(PO_4)_2 + Ca_4P_2O_9 + H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 \tag{18.1}$$

$$3Ca_3(PO_4)_2 + CaO \rightarrow Ca_{10}(PO_4)_6(OH)_2 \tag{18.2}$$

In general, the solid state reaction result in yield well-crystallized product. However, the disadvantage of this method is the employee of high temperature to produce HA.

Another method use to synthesis HA is wet method. This method comprising co-precipitation method [12–14], emulsion method [15–17], hydrolysis method [18–23], sol-gel method [24–30], hydrothermal method [31–39] due to its advantage in simplicity of the procedure. These methods allow to control the structure, crystallinity, morphology of HA. The wet method can be done in water or in organic solvent. These methods can be performed at room temperature or elevated temperature, under the normal pressure or high pressure using hydrothermal technique. The major disadvantage of wet method is that they sometimes give impurity to the structure of HA or other phase of phosphate present together with HA. In addition, various ions can be incorporated into the structure of HA, leading to the trace impurity. The classification and over view of wet method to synthesis HA are listed as below:

18.1.1 Co-precipitation Method

This method is the common method for the preparation of HA. The chemical process consists of a chemical reaction source of Ca, and P in the present of other additives with the acidic or base environment. The conditions of the co-precipitation method are variable, but in general, this process is usually carried out at pH value vary from 3 to 12 and at temperature vary from ambient to the elevated temperature of water. In somehow way, this method is sometimes performed in the present of templates.

18.1.2 Emulsion Method

The emulsion method is used to synthesis HA which more efficient, simple and suitable for producing nanostructure HA powder. The advantage of emulsion method is the precise control of the morphology and distribution of HA's grain size. This technique was originally used to create porous materials as well as to overcome the issue of particle agglomeration. Several sources of Ca and P have been used, but the most popular used are calcium nitrate and phosphoric acid due to its economic and easy to found on the market. Among the surfactant used to prepare the emulsion, some chemical include: dioctyl sodium sulfosuccinate salt, dodecyl phosphate, polyoxyethylene, nonpolyphenol ether, polyoxyethylene ether, cetyltrimethyl ammonium bromide and sodium dodecyl sulfate. The key factor to study is type of surfactant, ratio of aqueous and organic phase, pH, temperature condition, concentration of Ca and P source etc.

18.1.3 Sol-Gel Method

The sol-gel process is a method of mineralization from precursor in a solution, preferably organometallic compounds or other suitable precursors. This useful method can be used for the synthesis of porous, dense, bulk, xerogel film coating ceramic as well as aerogel HA. The procedure sol-gel method is given in Fig. 18.1.

During the gelation, sol are harden and form the gel network as shown in Fig. 18.2. The sol-gel process has limitation that hinder its scale up to industry scale production. The main disadvantage are: (a) the high cost and scarcity of often used alkoxide-based precursors and (b) the delicate process control culminating in usually time consume process. This process involves hydrolysis of the precursors and the formation of micelles around templates in either an aqueous or an organic phase followed by the gelation of these sol. The key factor to control the gelation depends on: (a) the nature and what kind of solvent used; (b) the temperature and pH used and (c) the chemical nature of the reagent used. In addition, lack of control of certain parameters during the growth of HA may cause the appearance of secondary phases such as CaO, $Ca_2P_2O_7$, $Ca_3(PO_4)_2$ and/or $CaCO_3$.

18.1.4 Hydrolysis Method

The aqueous hydrolysis of calcium phosphate to form HA usually follows 2 stages: (a) dissolution and precipitation depending on the source of Ca and P. In the aqueous solution, the Ca and P source are dissolved with respect to the surrounding environment then its concentration become supersaturated with respect to HA, leading to the precipitate of HA. The hydrolysis process applicable to these precursors depends strongly on pH and temperature of environment. The addition of other calcium and phosphate sources are sometimes required to control the stoichiometry HA.

18.1.5 Hydrothermal Method

The hydrothermal process is a technique for the growth of crystalline HA with nanoscale. This process is the generic term used to describe a reaction between the calcium source and phosphate precursors in the present of the following conditions: (a) water or organic solvent; (b) a mixture of water/organic solvent. In case of the water used, it is called the term hydrothermal

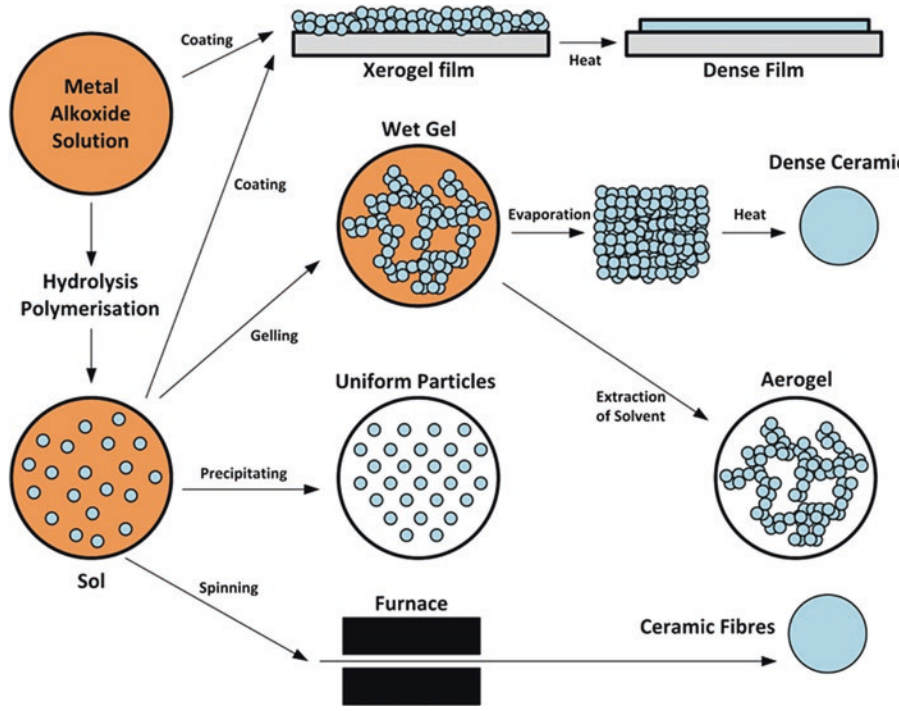

Fig. 18.1 Principle procedure of sol-gel method. (Courtesy: https://commons.wikimedia.org/wiki/File:Sol-Gel_Technology_Scheme.png)

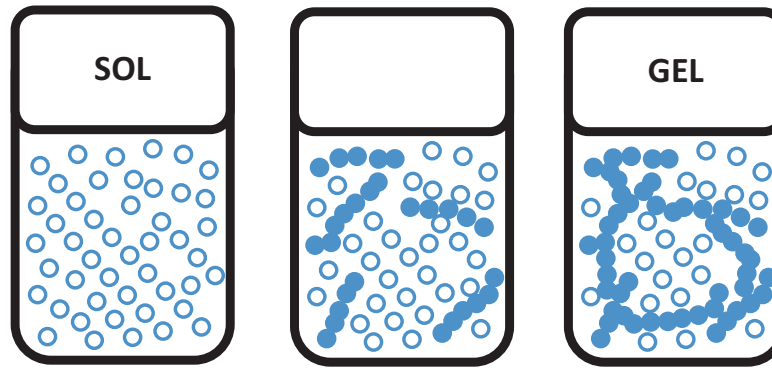

Fig. 18.2 The transformation of sol to gel. (Source: http://www.uk-finishing.org.uk/N-COAT70/sol_gel.htm)

while organic solvent used is called the term solvothermal; and in case of water/organic solvent system, it is called solvo-hydrothermal. The process happen in the close environment with a high temperature and pressure greater than autogenously ambient pressure, for example inside an autoclave or a pressure vessel. The illustration of autoclave is shown in Fig. 18.3. During the hydrothermal reaction, the medium could be subcritical or supercritical, depending on the pressure and temperature. Through the effect of medium evaporation and condensation, the pressure increase of reactivity and support for the chemical reaction between chemical reactant. It should be noted that the high pressure permits the formatting of HA in the form of micro or nano crystal size HA, with controlled morphology and porosity through the control of temperature and pressure.

The hydrothermal method can be used to control the interaction between solid/solvent,

Fig. 18.3 The autoclave system used to synthesis HA. (Courtesy at Department of Ceramic Materials, Faculty of Materials Technology, Ho Chi Minh City University of Technology)

Fig. 18.4 The ball milling system use for grinding starting materials. (Courtesy at Department of Ceramic Materials, Faculty of Materials Technology, HCMUT)

especially in terms of solubility and also function as a mean to control the nucleation and growth processes. In addition, this technique is often combined with conventional method such as co-precipitation or sol-gel routes.

18.1.6 Grinding-Assisted Method

In order to increase the chemical reactivity of Ca and P starting materials, the grinding method is used is the first step. This method is also termed as mechano-chemical process, which often used the ball milling equipment as shown in Fig. 18.4. The advantage of this method is simplicity, reproducibility and large-scale production of HA. The control of growth HA by this technique focus on the types of chemical agent used, the grinding medium, the diameter and milling medium, the ratio of milling medium, the duration of milling steps and interval pauses, the powder-to-ball mass ratio and the rotation speed.

18.1.7 The Microwave (MW)-Assisted Method

In order to active the chemical reaction of Ca and P starting materials, the output energy supplied equipment used common is microwave oven. The MW-assisted preparation of HA produces an increase yield of perfectly crystalline powder. In addition, the obtained HA by MW-assisted method gains particularly homogenous in term of size, porosity and morphology. The activation results from two key factors: (a) purely thermal origin, resulting in molecular agitation that is caused by the inversion of dipole with the extremely rapid heating by the alternation of electric moment field and (b) an electrostatic origin, involving interactions like dipole-dipole between polar molecules and the electric field. The MW-assisted method cause direct effect on the kinetics of activation energy.

18.1.8 Ultrasonic-Energy-Assisted Method

The ultrasonic-energy-assisted method or sonochemical approach can be used to synthesis nanostructure of HA. This method results in nanosized products and perfect to control the morphology, porosity and size of HA. In addition, this ultrasonic-assisted method enhance stimulation of the reaction between the calcium and phosphate precursors to accelerate the rate of reaction in a remarkable manner.

Based on consideration of these references to synthesis HA above, my research group at Department of Ceramic Materials aim to synthesize nanoprecipitated HA by hydrothermal reaction method. The research group succeeded to fabricate HA and Tricalcium phosphate (TCP) [40–47], with the aim to be used as bone substitute. In order to focus on the side effect of nanostructured HA, we aim to use hydrothermal reaction between $Ca(OH)_2$ and H_3PO_4 used as precursor. This research report the technique to prepare nanostructure HA by coprecipitation method follow by hydrothermal reaction.

18.2 Materials and Method

18.2.1 Experimental Preparation

All the chemical was purchased from company without purification. The $Ca(OH)_2$ and H_3PO_4 were supplied by Guangdong Chemical Co (China). In brief, 0.3 mol H_3PO_4 was dropped into 0.5 mol $Ca(OH)_2$ suspension, so that the Ca/P molar ratio of the mixture was 1.67, according to the stoichiometric of HA. The CaP mixture was homogeneous by stirring at 400 rpm (IKA stirring) for 2 h at room temperature, follow by hydrothermal reaction at different hydrothermal reaction (100 °C, 150 °C and 180 °C) for different duration time (0 h, 12 h and 24 h). The samples after hydrothermal reaction were filtered and washed with double distilled water (DDW) for at least 3 times then follow by the characterization. In comparison with synthesis HA, the human teeth were used for characterization. In brief, the human teeth was supplied by Ho Chi Minh University of Pharmacy by collecting from dental clinic, follow by immersion in phosphate buffer solution (PBS).

18.2.2 Material Characterizations

18.2.2.1 X-Ray Diffraction Analysis

The composition of sample before and after hydrothermal reaction were determined using X-Ray diffraction (XRD; D2 Bruker), operated at 40 kV and 40 mA.

18.2.2.2 Scanning Electron Microscopic Observation

The morphology changes of sample before and after hydrothermal reaction were observed using a scanning electron microscope (SEM, S-3400N, JEOL) with an acceleration voltage of 15 kV, after the deposition of gold-palladium coating (Magnetron Sputtering Machine, MSP-1S).

18.2.2.3 Transmission Electron Microscopic Observation

The morphology of sample before and after hydrothermal reaction was observed at nano-scale

using transmission electron microscope (TEM, Hitachi-7000) with an acceleration voltage of 10 kV. The samples were dispersed into ethanol with ultrasonic cleaning, then drop into copper grid for TEM observation.

18.2.2.4 Fourier Transform Infrared Spectroscopy

The chemical bonding of samples was identified by Fourier transform infrared spectroscopy (FTIR, Bruker 400D) in the range of 400–4000 cm^{-1} using KBr pellet technique.

18.2.3 Statistical Analysis

For statistical analysis, a one-way factorial ANOVA and Fisher's LSD method, as a post-hoc test, were performed using KaleidaGraph 4.0. Values are expressed as mean ± SD. A *p*-Value of <0.05 was considered to be statistically significant.

18.3 Results and Discussion

Figure 18.5 shows the typical XRD pattern of samples before and after hydrothermal treatment at different hydrothermal temperature (100 °C, 150 °C and 180 °C) and different hydrothermal time (0 h, 12 h and 24 h). The XRD of $Ca(OH)_2$ starting materials and HA standard are shown as reference. Basically, at 100 and 150 °C, the $Ca(OH)_2$ is still remained up to 24 h reaction (Fig. 18.5a–f). However, when elevate the hydrothermal temperature up to 180 °C, HA single crystal phase can be obtain after 12 and 24 h, respectively (Fig. 18.5h–i). The synthesis condition of hydrothermal reaction at 180 °C for 24 h is selected to synthesis HA for the next experiment.

Figure 18.6 shows the typical XRD image of human tooth; synthesize HA by hydrothermal condition at 180 °C for 24 h and sintering HA at 900 °C. Basically, the synthesize HA by hydrothermal condition has the crystal structure

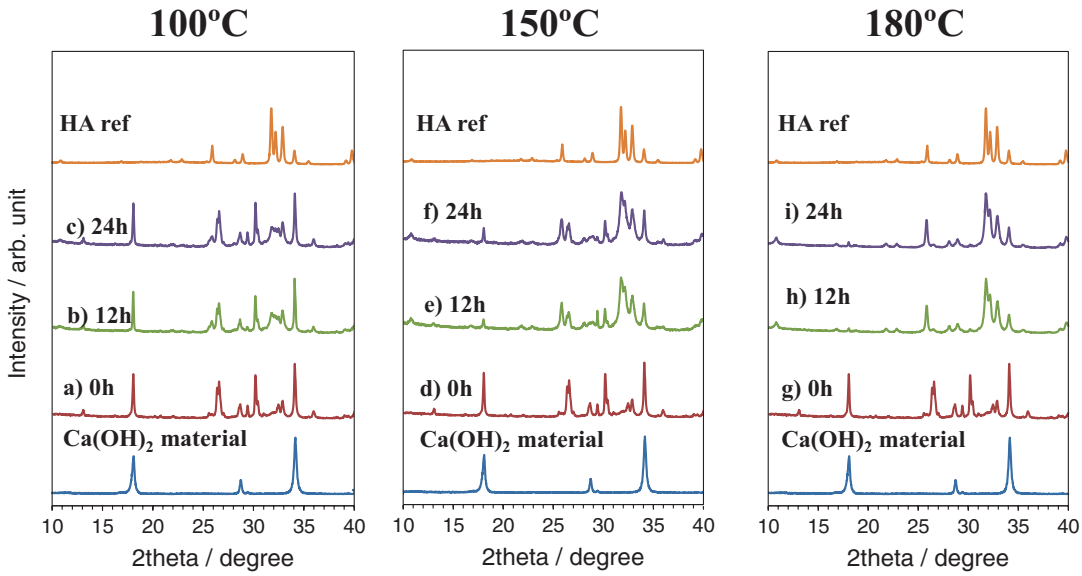

Fig. 18.5 XRD pattern of samples before and after hydrothermal treatment at different hydrothermal temperature (100 °C, 150 °C and 180 °C) and different hydrothermal time (0 h, 12 h and 24 h)

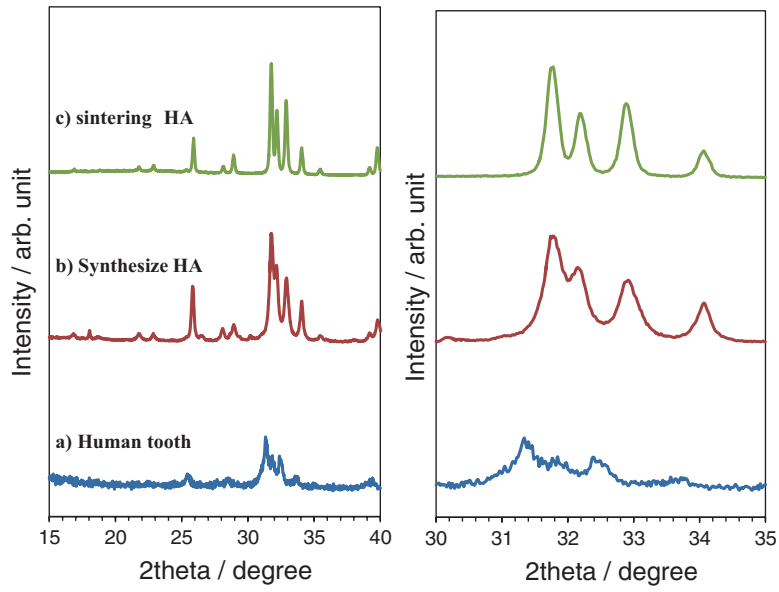

Fig. 18.6 XRD pattern of (**a**) human tooth, (**b**) synthesize HA by hydrothermal condition at 180 °C for 24 h and (c) sintering HA at 900 °C

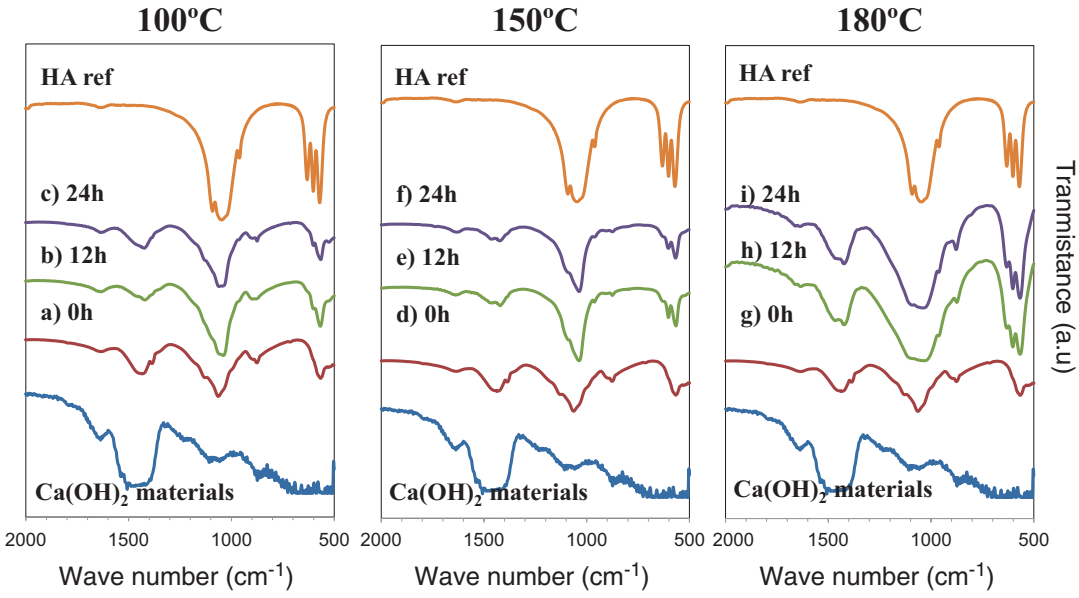

Fig. 18.7 FTIR patterns of samples before and after hydrothermal treatment at different hydrothermal temperature (100 °C, 150 °C and 180 °C) and different hydrothermal time (0 h, 12 h and 24 h)

similar with that of human teeth. However, the peak shifting at 31.8° can be observed at synthesis HA and sintering HA. It can be explain that in human tooth, there is the minor trace of another element like Zn, Mg, Si co-exist, and substitute to the network of human tooth.

Figure 18.7 shows the FTIR patterns of samples before and after hydrothermal treatment at different hydrothermal temperature (100 °C, 150 °C and 180 °C) and different hydrothermal time (0 h, 12 h and 24 h). The FTIR of $Ca(OH)_2$ starting materials and HA

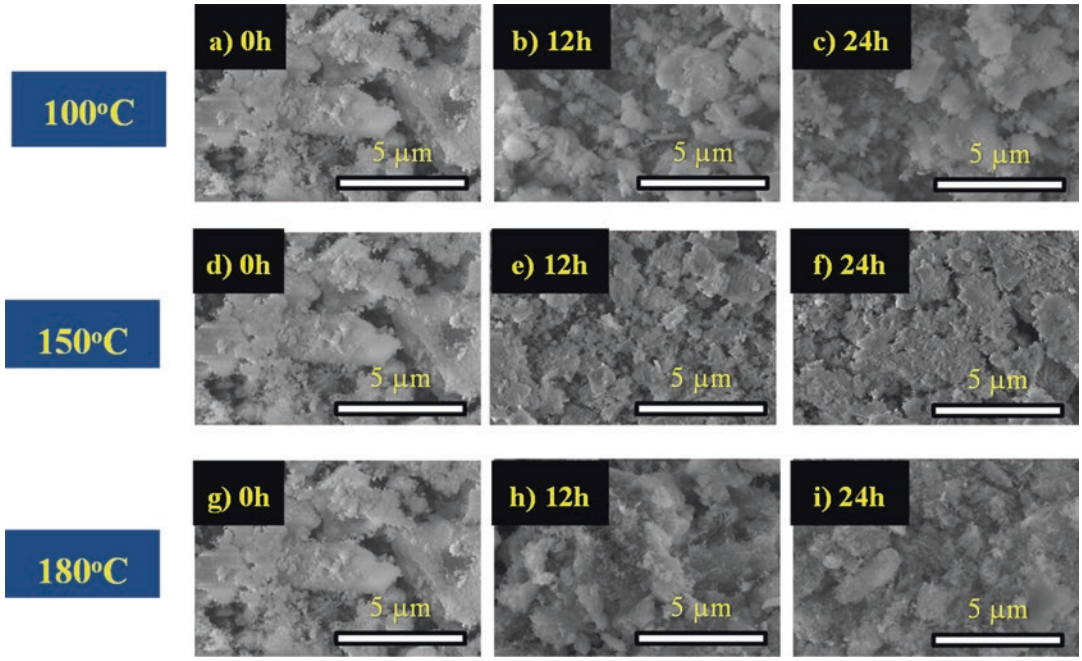

Fig. 18.8 Typical morphology of samples at magnification of 10,000X before and after hydrothermal treatment at different hydrothermal temperature (100 °C, 150 °C and 180 °C) and different hydrothermal time (0 h, 12 h and 24 h)

standard are shown as reference. Basically, the chemical bonding of PO_4^{3-} can be observed at 1100 cm^{-1} while the present of HPO_4^{2-} can be found at 560 and 605 cm^{-1}. In addition, we can observe the CO bonding at 1458 cm^{-1}. These CO bonding might be derived from CO_2 in atmosphere, due to the highly absorption of CO_2 from $Ca(OH)_2$ starting materials. There is no different in chemical bonding at 150 °C and 180 °C. these data are support for XRD data shown in Figs. 18.5 and 18.6.

Figure 18.8 shows typical morphology of samples at magnification of 10,000X before and after hydrothermal treatment at different hydrothermal temperature (100 °C, 150 °C and 180 °C) and different hydrothermal time (0 h, 12 h and 24 h). After hydrothermal reaction, the sample contain many needle-like shape crystal and interlock together. The size of needle-like shape crystal increase with the increasing of hydrothermal temperature.

Figure 18.9 shows typical morphology of sample before and after hydrothermal reaction at 180 °C for 12 and 24 h. In addition, the morphology of human tooth also show as reference. The morphology of 180 °C-hydrothermal treated-HA is similar with that of human tooth, indicate that 180 °C-hydrothermal treated-HA can be used as excellent candidate for bone substitute.

Figure 18.10 shows the typical TEM images of human tooth, synthesize HA by hydrothermal condition at 180 °C for 24 h and sintering HA at 900 °C at 100,000X. The upper-left photo show the same condition with the magnification of 30,000X. The 180 °C-hydrothermal treated-HA has needle-like shape structure with the average diameter of 10 ~ 20 nm and length of below 100 nm. These nano structure of 180 °C-hydrothermal treated-HA is very similar with that of human tooth, indicate that 180 °C-hydrothermal treated-HA can be used as bone substitute materials.

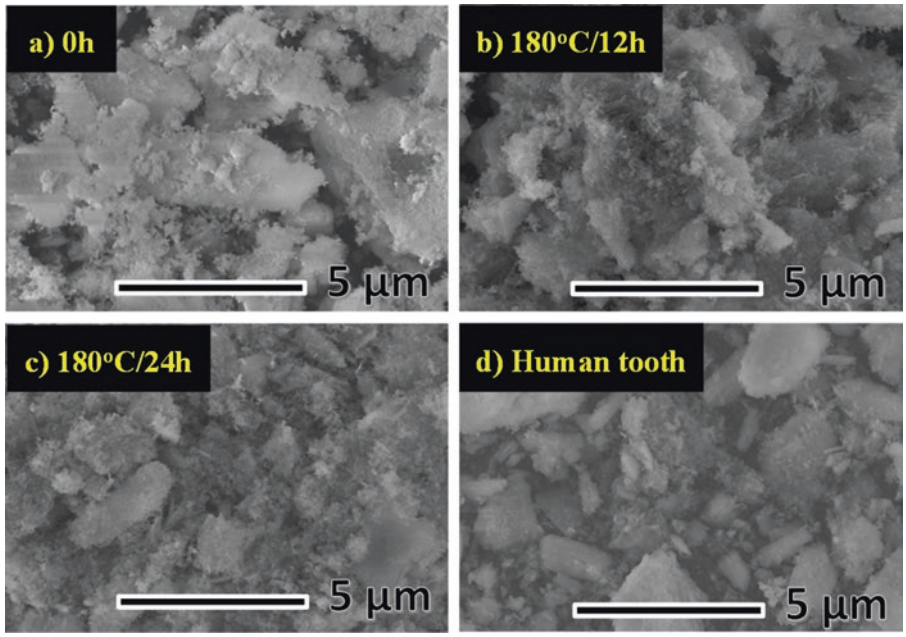

Fig. 18.9 Typical morphology of (**a**) sample before hydrothermal reaction; (**b**) hydrothermal reaction at 180 °C for 12 h; (**c**) hydrothermal reaction at 180 °C for 24 h and (**d**) human tooth

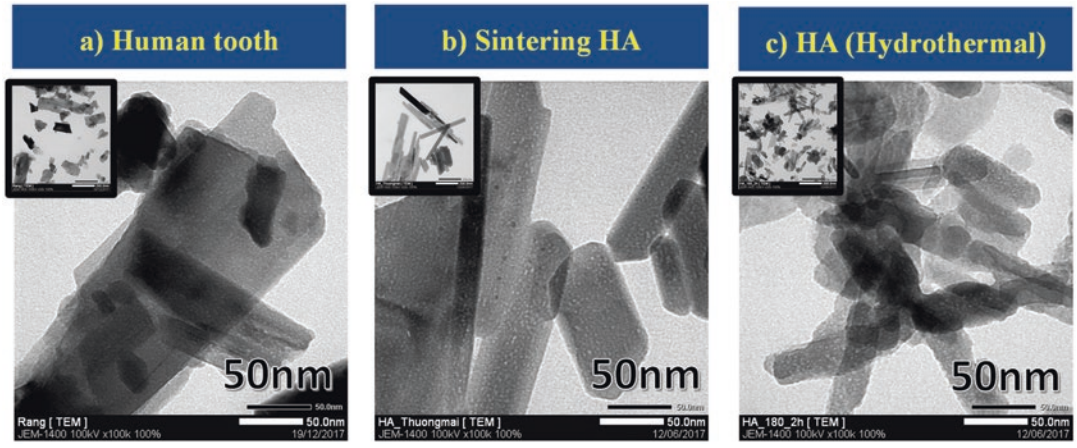

Fig. 18.10 Typical TEM images of (**a**) human tooth; (**b**) sintering HA at 900 °C and (**c**) synthesize HA by hydrothermal condition at 180 °C for 24 h at 100,000X. The upper-left images show the TEM at 30,000X

18.4 Conclusions

In this report, the author reviewed the trend of HA synthesis as well as report the process to fabricate nanostructure HA by co-precipitation method of $Ca(OH)_2$ and H_3PO_4 follow by hydrothermal reaction method. The hydrothermal treated-HA has needle-like shape with the diameter of 10 ~ 20 nm and length of below 100 nm, which is similar with human bone. For the hydro-

thermal reaction, temperature is the key to form nanostructure HA. These data will be useful for researcher who are looking for different forms of nanostructure HA to suit their intended application.

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