

Preparation of Biphasic Calcium Phosphate Ceramics Powders and Conversion to Porous Bodies

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ABSTRACT

The aim of the study was to develop porous bioresorbable bone implants via polymeric sponge method for biomedical applications. HA-TCP were obtained as submicrometer-sized, chemically homogeneous and high-purity ceramics powders prepared by chemical precipitation method using diammonia hydrogen phosphate $[(NH_4)_2HPO_4]$ and calcium nitrate tetrahydrate $[Ca(NO_3)_2 \cdot 4H_2O]$ as the starting material. By using obtained fine HA-TCP powders, porous β -TCP has been prepared via polymeric sponge method. After impregnation of cellulose sponges into the stable slurries, the green bodies of β -TCP porous were subjected into sintering process of varied temperature $1100^\circ C$, $1150^\circ C$, $1200^\circ C$ and $1250^\circ C$. The surface morphology of the powder and sintered sample was observed under FESEM and SEM. XRD and FTIR result indicated that evolution of β -TCP phases occur at sintering temperature above $1150^\circ C$. Mechanical testing results show that maximum compression strength of TCP porous bodies was 0.025 MPa.

Keywords: *Bioresorbable, Hydroxyapatite, Tricalcium Phosphate and Polymeric Sponge Method.*

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1. INTRODUCTION

Synthetically produced calcium phosphate (CaP) ceramics and implants have an important position among other biomaterials because they are considered to be almost fully biocompatible with living body when replacing the hard bone tissues. Calcium hydroxyapatite ($\text{Ca}_3(\text{PO}_4)_6(\text{OH})_2$ (HA)) and tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$ (TCP)) are currently recognized as ceramics materials that significantly simulate the mineralogical structure of bone [1]. HA and TCP are the two important members of the CaP bioceramics compound. HA behaves as an inert implant while TCP has been shown to be bioresorbable with new bone growth replacing the implanted TCP. This property imparts significant advantages on the use of TCP compares to other biomedical materials that are not resorbed and replaced by natural bone. As a result, β -TCP has been developed as a biodegradable bone replacement [2].

Tricalcium phosphates (TCPs) are bonesubstitute materials that are marked out by their high biocompatibility, favourable resorption properties and osteoconductivity, Pure-phase beta-tricalcium phosphate (β -TCP), available since 1997, is one such TCP. In comparison with other bone substitutes, TCP is characterized by its precisely defined physical and chemocrystalline properties, high level of uniformity of chemical composition and purity, so that its biological reactions can be predicted reliably. TCP is available in 2 forms: a high-temperature modification, α -TCP (α - $\text{Ca}_3(\text{PO}_4)_2$), which is produced at temperatures in excess of 1125 °C and a low temperature modification, β -TCP (β - $\text{Ca}_3(\text{PO}_4)_2$), produced at temperatures below 1125 °C². In contrast to α -TCP, β -TCP is thermodynamically stable in a biological environment and within a normal temperature range. Despite a similar degree of solubility, biodegradation of β -TCP is faster than that of α -TCP because the latter form hydrolyses either partially or completely to hydroxyapatite $\text{Ca}_5[\text{OH}(\text{PO}_4)_3]$. The resulting crystals have a non-physiological morphology, are not resorbed due to their very low level of solubility and may enter the lymphatic system by phagocytosis. Previous clinical studies with a multiphase, only partially resorbable TCP ceramic granulate (α - and β -TCP, hydroxyapatite) have demonstrated a correlation between bone-substitute resorption and bone regeneration that was dependent on the density and purity of the ceramic material, defect size, implant bed type, and individual osteogenetic potency of the bone [3].

Bioceramics implant can be applied both in the compact and porous forms as well as granules. In the case of porosint, a number of *in vivo* studies have demonstrated the occurrence of bone formation in the pores of the calcium phosphate ceramics such as β -TCP and HA [4]. However, most of the investigations on the implantation of the porous calcium phosphate ceramics showed that the degree of infiltration of living tissue into the pores and formation of new bone depended greatly on the pore characteristics such as porosity, pore size, pore size distribution and pore shape.

2. BIOMATERIALS

During the last 90 years, man-made materials and devices have been developed to the point at which they can be used successfully to replace parts of living systems in the human body. These special materials able to function in intimate contact with living tissue, with minimal adverse reaction or rejection by the body are called biomaterials. Devices engineered from biomaterials and designed to perform specific functions in the body are generally referred to

as biomedical devices or implants. The earliest successful implants were bone plates, introduced in the early 1900s to stabilize bone fractures and accelerate their healing. Advances in materials engineering and surgical techniques led to blood vessel replacement experiments in the 1950s, and artificial heart valves and hip joints were under development in the 1960s. As early as the first bone plate implants, surgeons identified material and design problems that resulted in premature loss of implant function, as evidenced by mechanical failure, corrosion, and poor biocompatibility. Design, material selection, and biocompatibility remain the three critical issues in today's biomedical implants and devices. When a man-made material is placed in the human body, tissue reacts to the implant in a variety of ways depending on the material type. Therefore, the mechanism of tissue attachment depends on the tissue response to the implant surface. In general, materials can be placed into three classes that represent the tissue response they elicit: inert, bioresorbable, and bioactive as shown in Table 1. Inert materials such as titanium, UHMWPE, and alumina (Al_2O_3) are nearly chemically inert in the body and exhibit minimal chemical interaction with adjacent tissue. A fibrous tissue capsule will normally form around inert implants.

Table 1. Classes of Biomaterials according to tissue responses

Classes of Biomaterial	Tissue Responses	Examples
Inert	Mechanical interlock, separation by a fibrous tissue of various thickness	Tantalum, Titanium Alumina, Zirconia (PSZ), UHMW Polyethylene, Stainless Steel
Bioactive	Direct biochemical bond	High Density Hydroxyapatite, Glass Ceramics A-W, Certain Bioglasses
Bioresorbable	Gradual dissolution, Replacement of implants by the tissue	Porous Hydroxyapatite, Tricalcium Phosphate Polyurethane, Polylactic- polyglycolic Acid Copolymer

Tissue attachment with inert materials can be through tissue growth into surface irregularities, by bone cement, or by press fitting into a defect. This morphological fixation is not ideal for the long-term stability of permanent implants and often becomes a problem with orthopedic and dental implant applications. Bioresorbable materials, such as tricalcium phosphate and polylactic-polyglycolic acid copolymers, are designed to be slowly replaced by tissue (such as bone) or for use in drug-delivery applications. Certain glasses, ceramics, and glass-ceramics that contain oxides of silicon, sodium, calcium, and phosphorus (SiO_2 , Na_2O , CaO , and P_2O_5) have been shown to be the only materials known to form a chemical bond with bone, resulting in a strong mechanical implant/bone bond. These materials are referred to as bioactive because they bond to bone (and in some cases to soft tissue) through a time-dependent, kinetic modification of the surface triggered by their implantation within living bone. In particular, an ion-exchange reaction between the bioactive implant and surrounding body fluids results in the formation of a biologically active hydrocarbonate apatite (calcium phosphate) layer on the implant that is chemically and crystallographically equivalent to the mineral phase in bone.

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This equivalence is responsible for the relatively strong interfacial bonding. Although bioactive materials would appear to be the answer to biomedical implant fixation problems, available bioactive glasses are not suitable for load-bearing applications, and so are not used in orthopedic implants. In fact, their use for other implants, even some dental applications, is limited because they have a low resistance to crack growth [5].

3. BONE IMPLANT

Most artificial bones nowadays are made from hydroxyapatite, which has the same chemical formula as bone itself. Synthetic hydroxyapatite, however, is neither as porous as real bone nor as strong. Pores are important, they are conduits for blood flow (blood is generated in bone marrow) and they allow bones to be strong without being too heavy. Pores also provide a way for living bone to attach itself permanently to an implant. Researchers have also tried sea coral as a bone substitute because it's porous enough but it lacks strength. Sea coral is mostly used for cranial restructuring. The solution is ceramics because it's possible to synthesize ceramic materials with the right combination of strength and inter-connected pores to mimic real bone [6].

4. DEVELOPMENT OF TCP

TCP powders can be synthesised via numerous production routes, using a range of different reactants. Some processing techniques includes wet chemical methods [1,2,4,13,14,19], hydrothermal techniques, hydrolysis of other calcium phosphate [17] and sol-gel methods [11,15,16]. For hydrothermal reaction, it involves reacting a mixture of calcium carbonate (CaCO_3) and di-ammonium hydrogen phosphate at high temperatures and pressures such as 275°C and 1200 psi. The resulting TCP is carbonate substitute but commonly well crystallised and chemically homogeneous. For hydrolysis of other calcium phosphate, at pH of greater than 9, orthophosphoric acid solution added is dropwise manner to a dilute solution of calcium hydroxide. The acid is added at controlled rate with stirring being maintained throughout the process. The precipitation reaction is slow. Reaction temperatures of between 25 and 90°C are common the higher temperature producing a higher crystallinity product. Sol-gel technique is a method for preparation of highly pure powder due to the possibility of a strict control of the process parameters. The sol-gel method offers a molecular-level mixing of the calcium and phosphorus precursors, which is capable of improving chemical homogeneity of the resulting HA to a significant extent in comparison with conventional methods such as solid state reactions, wet preparation, and hydrothermal synthesis. The sol-gel product is characterized by nano-size dimension of the primary particles and this small domain is very important parameter to improve the contact reaction and the stability at the artificial/natural bone interface [11]. Moreover, the reactivity of the sol-gel powder allows a reduction of the processing temperature and of any degradation phenomena occurring during sintering. The major limitation to sol-gel technique application is linked to the possible hydrolysis of phosphates and high cost of the raw materials. A sol-gel method enables the powder less processing of glasses, ceramics and thin films or fibers directly from solution. Precursors are mixed at the molecular level and variously shaped materials may be formed at much lower temperatures than it is possible by traditional methods of preparation. One of the major advantages of sol-gel processing is the possibility to synthesize hybrid organic networks

facilities the design of new engineering materials with exciting properties fro wide range of application [11]. Of these methods, the first method that is wet chemical method is used for this project. TCP bioceramics have been synthesized by using a this method in aqueous solution by several researchers. Aqueous solutions of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$ were selected as the starting materials in all the HA and TCP precipitation studies [1]. This technique involves calcium nitrate, diammonium hydrogen phosphate and ammonium hydroxide. This method results in a faster production rate, with ammonium hydroxide being added to maintain a constant pH. Compared to the hydrolysis of other calcium phosphate method, this method approach requires washing of the precipitate to remove nitrates and ammonium hydroxide. In taking these factors into account, the production rate of this method is similar to hydrolysis of other calcium phosphate method. Continued stirring and ageing are usually carried out after the reactants have been combined as the calcium is slowly incorporate into the apatitic structure. This process also helps the material to approach stoichiometric Ca/P ratios. A morphological change from needle-like crystals to more blocky crystals is associated with the maturation process.

5. PREPARATION OF TCP POROUS

A lot of methods have been developed to fabricate the porous β -TCP ceramics with diversified pore characteristics such as the use of polymeric sponge, foaming processes and techniques using organic additives. These materials must allow bone in growth, when used as bone filler. For tissue engineering, the scaffolds must be a three-dimensional substrate to support cells undergoing events of spreading, proliferation are differentiation. It is well known that the pores must be interconnected. Pore sizes depend on the type of cells used and on the material. If the bioceramic is a bioresorbable one, like tricalcium phosphate (TCP), it is assumed that pores interconnections will undergo dissolution, allowing larger pores [4]. This study involves the infiltration of a polymer sponge (polymeric sponge method) with ceramic slurry until the inner polymer walls are completely coated by the ceramic powders. Subsequently, the sample is fired to remove the polymer and form a ceramic skeleton that is strengthened by sintering at high temperature. The polymer sponge method produces open cell porous ceramic scaffolds through replication of a porous polymer template. The scaffolds prepared by the polymer sponge method have a controllable pore size, interconnected pores, and desired geometry but poor mechanical strength for load-bearing applications [18].

Some researchers prepared porous (35% porosity) calcium hydroxyapatite ceramics by impregnating a polyurethane-based sponge or foam with a basic ($\text{pH} > 9$) slurry that consisted of a suspension of fine $\text{Ca}(\text{OH})_2$ precipitates in the presence of dissolved H_3PO_4 [19]. Fabbri *et al.* [20] on the other hand, used commercial calcium hydroxyapatite (HA, $(\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2)$) powders to prepare pH-regulated ceramic slurries to impregnate cellulose-based foam bodies that had different porosities (in the range of 70%–83%).

6. EXPERIMENTAL PROCEDURE

6.1 Materials

For preparation of TCP powders, di-Ammonia hydrogen phosphate $[(\text{NH}_4)_2\text{HPO}_4]$, calcium nitrate tetrahydrate $[\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}]$ supplied by Merck KgaA, Germany and ammonium hydroxide from R&M Marketing Essex, UK were used as starting materials. For preparation of porous sample, cellulose sponges purchased from Spontex SpA, Italy were used as the porosifier. Cellulose sponge was prepared in the form of cylinder with 1 mm height and 1 mm diameter. This sponge is the selection material to assure a proper pore size distribution characterized by the existence of micro and macropores with a sufficient connection degree. Dispersing agent (Duramax D3005) was purchased from Rohm and Haas, USA and distilled water used as received.

6.2 Powder preparation

All the starting material must be prepared in the solution form before the precipitation process. Di-ammonia hydrogen phosphate (20.614 g) was dissolve in 1000 ml distilled water at room temperature and the solution was then stirred for a few minutes until the nitrate salt completely dissolved. Calcium nitrate tetrahydrate (188.92 g) was placed into a beaker at room temperature. The powder was then readily dissolved by stirring in 2000 ml of distilled water for a few minutes. Then, Ammonia hydroxide (100 ml) is mix with 100 ml distilled water and stirred for a few minutes. Since ammonia hydroxide is evaporating chemical, mixing process is handled under the fume hood.

Di-Ammonium hydrogen phosphate solution of the proper concentration was added to the solution of calcium nitrate at the rate of 2 ml/min under continuous stirring. The resulting precipitate was filtered and washed repeatedly to remove ammonia content in the precipitate. The collected precipitates was dried at 50-65°C before it being ground to a fine powder. This process is similar to project by C H Cik Rohaida et al. [2] which focus on the preparation of HA and TCP by precipitation method.

6.3 TCP porous preparation

The fine TCP powder (7 g) was then mixed in a distilled water (15 ml) with Duramax D3005 (10 ml) as a dispersion agent. The cellulose sponge then was dip into the slurry until the sponge was fully recovered by slurry. The infiltrated sponges were dried in an oven at 60°C for 72 hours before sintering.

6.4 Sintering

Sintering process has been done in a furnace, where at first stage the heating has done at 1°C/min to remove the organic material (cellulose sponge) and the second stage at 3°C/min to sinter porous TCP. The temperatures for sintering were varied at 1100°C, 1150°C, 1200°C and 1250°C with sample name A1, A2, A3 and A4 respectively.

6.5 Sample characterization

To determine the phase's purity present and the degree of crystallinity of TCP powder and sintered porous TCP samples, XRD analysis were used. The scanning was done from 20° to 70° at rate of 2°/min rate. The thermogravimetric (TG) and differential thermal analysis (DTA) were conducted on TCP powder. The analysis was performed with heating rate of 10°/min from 26°C to 1400°C under nitrogen flow. The Field Emission Scanning Electron Microscopy (FESEM), was used to evaluate the morphology of the TCP powder and Scanning Electron Microscopy (SEM), for analyzing porous bodies' structure. The samples first were sputter-coated with a layer of platinum alloy (150 Å thick). The functional groups of the compounds were performed by Fourier Transformed InfraRed Spectrometer (FTIR) analysis, with a resolution of 2.0 cm⁻¹ in the spectra range of 4000.00 – 380.00 cm⁻¹. The compressive strength of the TCP porous bodies were measured on cylindrical specimen 10 mm x 10 mm (height x diameter) using Biomedical Testing Machine. The load speed of 0.4 mm/min was applied to the samples until the sample failure. The shrinkage properties were analyzed to determine the shrink range of the sample after the sintering. The dimension of the porous sample was measured before and after sintering process. This study done on the cylinder shape samples where the height and diameter was measured using Electronic Vernier Caliper. The percentage of shrinkage was measured by this formula:

$$\% \text{ shrinkage} = \frac{L_1 - L_2}{L_1} \times 100 \quad (1)$$

Where: L_1 = length before the sintering and L_2 = length after the sintering.

The density and porosity of the samples were measured using the Archimedes principle with the following formula:

$$\text{Apparent density, } \rho_{\text{app}} = \frac{\text{Mass (g)}}{\text{Volume (cm}^3\text{)}} \quad (2)$$

$$\text{Relative density, } \rho_r = \frac{\text{Apparent density}}{\text{Theoretical density}} \times 100\% \quad (3)$$

Where the theoretical ρ_{TCP} (Whitlockite) = 3.14x 10³ kg/m³.

$$\text{Porosity} = 100\% - \text{Relative density} \quad (4)$$

7. RESULTS AND DISCUSSION

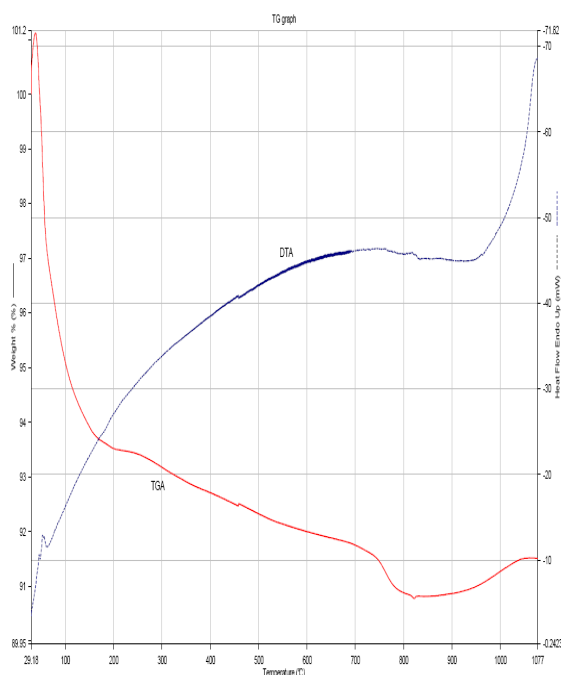


Figure 1. TG and DTA curve for TCP powder

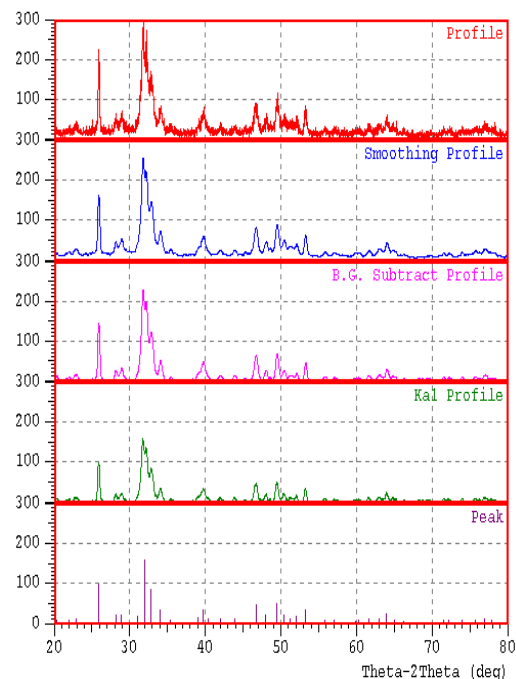


Figure 2. XRD result for TCP powder

The TG/DTA plot in Fig.1 report drops in weight and the thermal effects along the investigated temperature range for TCP powder sample. Graph shows the weight % of TCP powder decreased as temperature increase. The first drop at $\sim 100^{\circ}\text{C}$ was due to evaporation of water. It has experienced about 1% weight loss between $\sim 750\text{--}850^{\circ}\text{C}$ that may indicate the decomposition of HPO_4^{2-} . The phase purity and constitution of all TCP porous samples were analyzed using XRD result as shown in Fig.2 and 3. Fig. 2 shows the XRD pattern for an obtained TCP powder synthesized by chemical precipitation method. It can be seen that the highest peak was belong to HA. The porous samples were sintered over a temperature range of $1100\text{--}1250^{\circ}\text{C}$ for 7 hours so that the phase evolution schemes in these precursors could be followed. The two phases HA and TCP present in all sintered temperature of porous bodies as shown in Fig.3. The decomposition of HA to TCP occurred in accordance with the polymorphic transformation observed in TCP phase. It demonstrated that sintering temperature plays an important role in the formation of TCP. As sintering temperature is increased from 1100 to 1250°C , several of TCP peaks becomes more distinct at higher temperatures and also the widths of the lines become narrower, which suggests an increase in the crystalline degree. In other words, when the temperature was above 1100°C , HA present in the mixture decomposed to β -TCP.

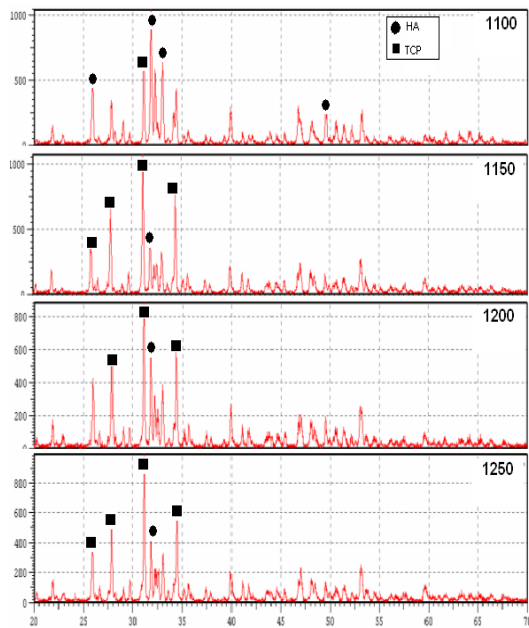


Figure 3. XRD result for varied temperature porous sample

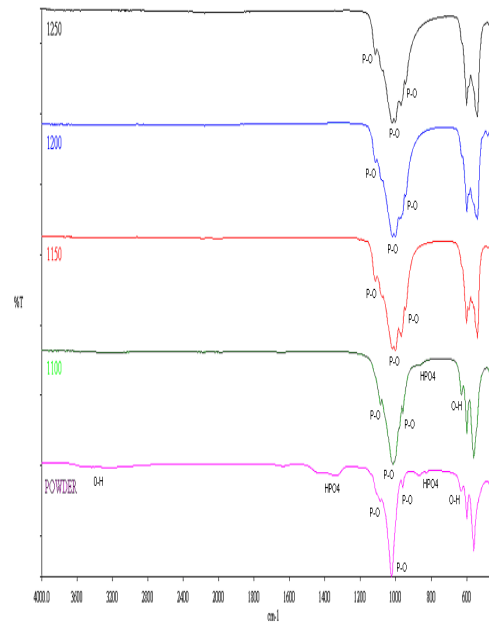


Figure 4. FTIR spectra of powder and sintered porous TCP

Fig. 4 shows FTIR spectra of powder and sintered porous TCP. As the sample sintered, the O-H band at $3200\text{ cm}^{-1} - 3600\text{ cm}^{-1}$ disappeared gradually. When the samples were sintered from 1100-1250C, the result exhibits small differences of the peak. The peak around 1000 cm^{-1} to 1200 cm^{-1} are derived from the P-O mode belongs to TCP.

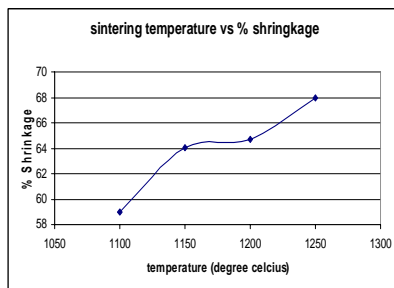


Figure 5. Graph percentage of average shrinkage versus temperature

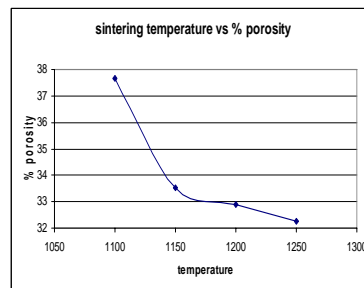


Figure 6. Graph percentages of porosity versus sintering temperature

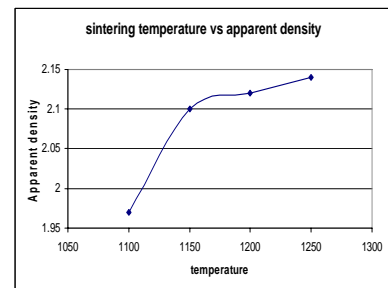


Figure 7. Graph of apparent density versus temperature

Table 2. Density and porosity of the samples

Sample	Apparent density ρ_{app}	Relative density ρ_r	% porosity
A1	1.97	62.34	37.65
A2	2.10	66.45	33.54
A3	2.12	67.08	32.91
A4	2.14	67.72	32.27

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The average of the shrinkage after the sintering was about 64%. Fig. 5 shows that the average shrinkage increased with increasing of sintering temperature. High shrinkage resulting in increasing of density as pore size decreased. Table 1 show the apparent density, relative density and % porosity of four samples after sintering process. The apparent density was found to be between 1.97 - 2.14 gcm^{-3} whereas the relative density was in the range of 62 – 68 gcm^{-3} . The percentage porosity was 30-37% respectively. Fig. 6 and 7 indicated that porosity decreased as increasing of apparent density.

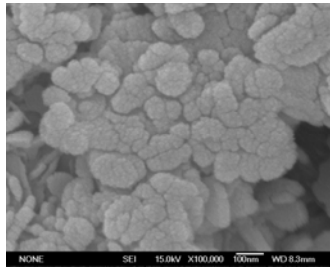


Figure 8. FESEM photograph showing surface appearance of TCP powder before sintering

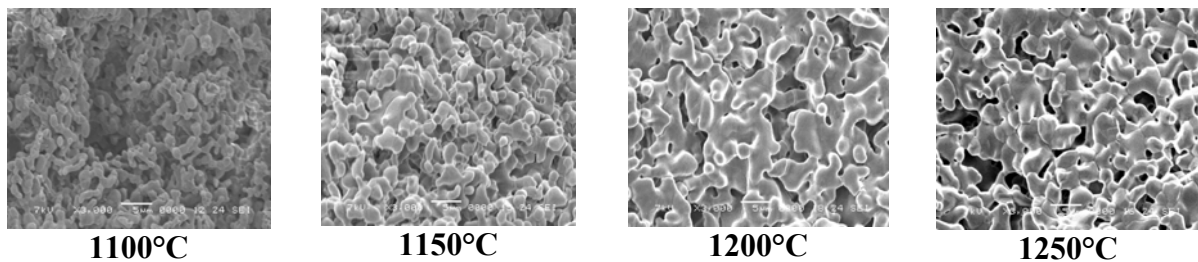


Figure 9. SEM micrograph of porous sample at X3000 for four different temperatures

Fig. 8 shows the FESEM image of the prepared TCP powder which revealed that most of the TCP particles agglomerated together with the particle size ranged from 70 -120 nm. On the other hand, Fig. 9 shows the images 1100°C, 1150°C, 1200°C and 1250°C sintering temperature of TCP porous bodies at magnification 3,000. It is clear from the images that progressive of densification and fusion with increasing of sintering temperature. In other words, the density of the sample increased with increasing of temperature. As shown in Fig.10, the compressive stress of the sintered TCP within the range of 0.01-0.03 MPa and increased with increasing of temperature. When sintering temperature increase, the strength will be increase. It is because, when sintering temperature increase, the sample become denser, more crystallinity and less voids or holes. This is also approved in SEM result as we can see the progressive of densification with increasing of temperature.

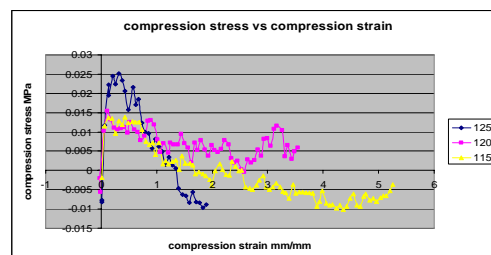


Figure 10. Compression stress *versus* compression strain

8. CONCLUSIONS

Chemical precipitation method has been successfully used to synthesize ceramics powder TCP. This method is simpler and result in faster production rate with ammonium hydroxide being added to maintain constant pH. From the TG/DTA evaluation, the weight % of TCP powder decreased as temperature increase because it has experienced about 1% weight loss between $\sim 750\text{-}850^\circ\text{C}$ that indicated the decomposition of HPO_4^{2-} . XRD result shows that when the temperature was above 1100°C , HA present in the mixture decomposed to β -TCP. It demonstrated that sintering temperature plays an important role in the formation of TCP because as sintering temperature is increased from 1100 to 1250°C , several of TCP peaks becomes more distinct. FTIR shows when the samples were sintered from $1100\text{-}1250^\circ\text{C}$, the peak around 1000 cm^{-1} to 1200 cm^{-1} are derived from the P-O mode that belongs to TCP. In term of density and porosity, the increasing of temperature lead to increase in density which also increasing of compression strength. SEM result clearly shows the decreasing in crystallinity of the sample with increasing of sintering temperature

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