JOURNALOF

Ceramic Processing Research

# Synthesis and thermodynamic analysis of Mg-doped calcium phosphate-based porous scaffolds

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A strategy using the sucrose evaporation technique for producing highly macroporous ceramic scaffolds with magnesium (Mg)-doped multiphasic or biphasic calcium phosphates was proposed. X-ray diffraction was performed to identify the ceramic phases, and thermogravimetric analysis and simultaneous differential scanning calorimetry (TGA/DSC) were used to analyze thermal behavior under different sintering temperatures. Product compositions with Ca/P molar ratios between 1.5 and 1.67 were synthesized and thermally treated up to 1050-1400 °C. Results showed that controlling the sintering temperature enabled various adjustable biphasic and multiphasic calcium phosphates to be prepared. Hydroxyapatite (HA) was obtained by increasing the sintering temperature of the reactants with sucrose and multiphasic á-tricalcium phosphates (TCP) and  $\beta$ -TCP were stabilized by the addition of MgO. The spaces occupied by the sucrose (~ 200 µm) produced non-uniform pores after sucrose vaporized. These pores had dimensions ranging from several micrometers to hundreds of micrometers in the final fabricated scaffolds with an interconnected network. Considering phase decomposition and transfer into TCP, the phase amount and grain size of HA decreased with increased sintering temperature. Calculation of the Arrhenius equation revealed that the grain size with Mg doping was relatively larger and had reduced activation energy and smaller exothermic enthalpy, indicating that the formation of  $\beta$ -TCP was stabilized by the MgO additive.

Key words: Tricalcium phosphate, Hydroxyapatite, Porous scaffolds, Activation energy.

# Introduction

Analyses of bone minerals have shown that hydroxyapatite [HA;  $Ca_5(PO_4)_3OH$ ], tricalcium phosphate [TCP;  $Ca_3(PO_4)_2$ ], and calcium carbonate (CaCO<sub>3</sub>) are the major components of bones [1]. Better osteoconductive properties are obtained when calcium phosphates are used in bone restoration compared with other metal oxide ceramics such as zirconia and alumina [2-5]. During bone reconstruction stages following filler implementation, particular materials dissolve and subsequently provide essential or enhancing elements to activate the mineralization process, thereby speeding up the regeneration mechanisms that involve biological interfaces with bone fillers, cell adhesion and remineralization primarily depend on the dissolution of materials.

The three-dimensional scaffolds with permeable pores represented key components for tissue engineering. The pore size and material controlled the rate of cell biological interactions with the scaffolds. Various synthetic calcium phosphate restoration particles have been proposed and applied in bone damage repair using synthetic methods that utilize high-temperature thermal decompositions and composite additives. The restored particles generally include a biphasic compound that comprised HA and  $\alpha$ - or  $\beta$ -TCP phases [7, 8]. Preparation strategies of interconnected pores in scaffolds include the application of lyophilization to generate pores in an organic matrix, solvent casting and particulate leaching process in organic and inorganic matrices, and vaporization of pore-forming agents at high temperatures in a ceramic matrix. High-temperature sintering with a poreforming agent is generally performed to fabricate porous calcium phosphate-based materials for bone implantation. The sintering procedures used to synthesize the multiphasic porous scaffolds were simpler, safer, less expensive, and more environment friendly than procedures that involving organic solvents and salt leaching.

Composites of porous scaffold matrices have gained increasing interest because of their compositional advantages (e.g., preservation of structural and biological functions of damaged bone tissues, provision of ions for tissue reconstruction, which are generally performed by osteoblasts, and the formation of new tissues similar to a natural system). In tissue engineering, a porous

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scaffold is required to function as a template and guide for blood vascular growth. This scaffold also carries osteoprogenitor cells and provides sites for cell adhesion, extension, proliferation, and differentiation during tissue development. Therefore, a target tissue should be in a growth period when the scaffold undergoes biomimesis of the physiological need of the regenerating tissue. Controlling the pore size, pore distribution, network structure, and scaffold composition are significantly crucial to initiate tissue formation [9-12]. General cera mic scaffold processing sintering techniques are used in the development of temperatureinduced filler vapor-ization, gas foaming, network pore formation, and high temperature-induced phase separation.

Due to the slurry forms can be shaped into a specific form during operation, which can be fitted into a restorative cavity perfectly, calcium phosphate bone cement (CPC) is widely used as a filling material in orthopedic, craniofacial and dental prosthesis, and periodontal operations. The initial paste reactants of CPC which majorly comprised an mixture of tetracalcium phosphate [Ca<sub>4</sub>(PO<sub>4</sub>)<sub>2</sub>O, TTCP] are combined with anhydrous dicalcium phosphate [CaHPO<sub>4</sub>, DCPA], dicalcium phosphate dihydrate [CaHPO<sub>4</sub>,  $2H_2O$ , (DCPD)], or with monetite [Ca(H<sub>2</sub>PO<sub>4</sub>)<sub>2</sub> · H<sub>2</sub>O, MCPM] [13, 14].

The slurry form of CPC has a significant function as a specific matrix template during the fabrication processes for scaffold preparation. Synthetic scaffolds with characteristics of the final CPC product and the interconnective pores have similar composition and structure of the cancellous/trabecular. Moreover, the poor crystallinity HA after CPC reaction would decompose this substance into  $\alpha$ -TCP,  $\beta$ -TCP, TTCP, or CaO at a high sintering temperature of over 1000 °C. Decomposition of HA into different phases depends on the initial reactant ratios of calcium to the phosphorus (Ca/P) atomic rate. Studies have reported that the high-temperature limit of the stability domain of β-TCP increases upon addition of magnesium oxide (up to 5 wt% of equivalent MgO). Our preliminary study has shown that the diameter of  $\beta$ -TCP crystal with MgO additive increased and became more dominant at higher sintering temperatures [15]. Hence, this study aims to obtain a more detailed survey of CPC, which comprised DCPA and TTCP powders, as a green compact with sucrose as a pore size controller, and MgO as a sintering stabilizer to set at a low temperature. Systemic survey of thermodynamic properties, pore distribution, phase and grain size identification with and without MgO-stabilized ceramics were characterized through the green compact, which has raised the temperature to form a porous scaffold.

# Materials and Experimental Method

## **Preparation of CPC templates**

TTCP powder was prepared from the reaction of

dicalcium pyrophosphate (Ca<sub>2</sub>P<sub>2</sub>O<sub>7</sub>; Alfa Aesar, Johnson Matthey Company, MA, USA) and calcium carbonate (CaCO<sub>3</sub>; Shimakyu's Pure Chemicals, Osaka, Japan), and was used as an ionic supplement in the surface modification of DCPA particles. This method is expressed in the following reaction, according to Brown and Epstein [16]:

$$2CaCO_3 + Ca_2P_2O_7 \rightarrow Ca_4P_2O_9 + 2CO_2$$
(1)

The mixed component of CPC with constant amounts of DCPA (1 im) and TTCP (10  $\mu$ m, one-fold molar ratios) were used. The pore fabricating agent of sucrose passed through a #70 (212  $\mu$ m) mesh sieve, and the green compact of CPC/sucrose with and without MgO (Katayama Chemical, Japan) was operated under 3.5 MPa pressure.

### **Specimen preparation**

A neutral sodium hydrogen phosphate solution (1 M) was used as the hardening solution, and the powder-toliquid ratio was controlled at 9.8 g/mL. The sample preparation ratio was controlled by setting the molar ratio between TTCP, DCPA, MgO, and sucrose at 1:1.3:0.9:3.8 after mixing. Sintering was done in a furnace. First stage of heating to 600 °C was performed at 1 °C/min to remove the organic material (sucrose), whereas the second stage of heating to target temperatures was performed at 3 °C/min to sinter porous ceramic scaffolds. The sintering temperatures were set at 1050, 1250, and 1400 °C. When the respective temperatures were reached, the sample was processed with prolonged sintering for 8 h. The samples were then furnace cooled to room temperature (25 °C). Five replicate specimens were prepared and analyzed for each process.

#### **Specimen characterizations**

## Phasic and pore distribution characterizations

The scaffolds, which were sintered at different temperatures, were crushed and ground into finely powdered samples, and prepared for X-ray diffraction (XRD) characterization. XRD was carried out at 40 kV, 30 mA, and 2° per scanning min (Rigaku D-max IIIV, Tokyo, Japan). Cu-K $\alpha$  radiation ( $\lambda = 0.15405$  nm Bragg–Brentano geometry) was used to analyze the structure and phase composition transitions. The scanning width angle (2 $\theta$ ) was operated at a range of 20° to 60°. The various phases of the scaffold composites were identified based on the files of Joint Committee on Powder Diffraction Standards. The pores in the scaffolds were observed through optimal images to verify the pore distribution under different temperatures after sintering.

The Scherrer Equation is used to calculate the crystallite size  $(D_{hkl})$  by using XRD radiation at a wavelength  $\lambda$  (in nm) [17]. The full width at half

maximum of the peaks ( $B_{hkl}$ , in radians) can be located at any  $2\theta$  in the pattern. The average crystallite size  $D_{hkl}$  from the Scherrer formula is given by:

$$D_{hkl} = K\lambda / (\mathbf{B}_{hkl} \cos \theta) \tag{2}$$

where  $\lambda$  is the X-ray wavelength at 0.15405 nm, and *K* is a constant related to crystallite shape, normally taken as 0.89 for the B<sub>*hkl*</sub> of spherical crystals with cubic unit cells. *B<sub>hkl</sub>* is the width of the diffraction peak profile at half the maximum height, and can be obtained from the crystalline size in radians [18].

#### Phase vaporization tests

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) devices were subjected to the differences of the green compacts with and without MgO, where the temperature has to be raised to set temperatures, as well as through in situ measurement of TGA and DSC curves (MDSC 2920 and TG 2950 analyzers, TA Instrument, Inc.). The temperatures in TGA and DSC tests were operated with a heating rate of 10 °C/min, and a nitrogen air flow rate of 100 mL/min. The general weight of the specimen for the thermal analysis was about 2.0 mg, and the reference powder was  $Al_2O_3$ .

#### Activation energies based on $\beta$ -TCP transformation

The crystalline activation energy of different sintering compositions in relation to heating temperature and grain size was calculated using the following equation [19]:

$$\log D_{hkl} = [-Q/(2.303R)]/T + A$$
(3)

where  $D_{hkl}$  is the grain size and A is the intercept. In the abovementioned equation, log  $D_{hkl}$  versus the reciprocal of absolute temperature (1/T) exhibit a linear trend, with the slope given by -Q/(2.303R). The calculated activation energy of grain growth can also be obtained from this equation.

## Morphological observation

The pore distribution and morphology of the foam scaffolds were characterized by observing the dried scaffolds through an optical camera. The topographies at different magnitudes of as-hardened calcium phosphate cement bulks with MgO after sintering at 1050 °C were analyzed using a scanning electron microscopy (SEM) system (Hitachi S-3000N, Hitachi, Tokyo, Japan).

### **Results and Discussions**

#### XRD

The XRD patterns show that all CPCs with sucrose as pore forming agent and MgO as stabilizer could still be converted into the HA phase after CPC reaction



Fig. 1. XRD pattern of the as-hardened calcium phosphate cement bulks with MgO sintered at 1050, 1250, and 1400 °C for 8 h.

(Fig. 1). HA is still the dominant phase at sintering temperatures below 1000 °C. At sintering temperatures beyond 1000 °C to 1050 °C, the partial HA phase transformed into  $\beta$ -TCP. Figure 1 also shows the dominance of the HA main phase in diffraction peaks at  $2\theta$  of 28.1 °, 32.1 °, 31.2 °, and 34.6 ° for the samples sintered at 1050 °C. The main diffraction TTCP peaks at  $2\theta$  of 29.2 ° and 29.8 ° were still not apparent at high temperatures, and even at a sintering temperature of 1400 °C as previously mentioned [20].

Lin et al. (2000) showed that when the sintering temperature was between 1300 and 1400 °C [20], the product with Ca/P atomic ratios of 1.50 and 1.67 means HA partially decomposes and transform into  $\alpha$ -TCP and TTCP based on the following reaction [20, 21]:

$$Ca_{9}(HPO_{4}) (PO_{4})_{5}(OH)_{2} \rightarrow 2\alpha - Ca_{3}(PO_{4})_{2} + H_{2}O \uparrow$$
(4)

$$\begin{array}{l} Ca_{10}(PO_4)_6(OH)_2 \rightarrow \\ 2\alpha - Ca_3(PO_4)_2 + Ca_4(PO_4)_2O + H_2O \uparrow \end{array}$$
(5)

Following the reaction, the CPC products with a Ca/P ratio of 1.67 should be converted into HA, which is the dominant product. These sintered reactions should occur after  $\alpha$ -TCP and TTCP transfer processes. This result differed from those previously reported [20, 21]. TCP stabilization was caused by the addition of MgO, which functioned as stabilizer of the  $\beta$ -TCP phase. Evidence of the incorporation of Mg into the  $\beta$ -TCP lattice has been identified by Kannan et al. (2006) [22]. The added Mg interacted with TTCP, which resulted in a Ca/P ratio lower than 1.67. The stabilized  $\beta$ -Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub> was prepared from Mg-substituted Ca-deficient apatite. The function of Mg in stabilizing the  $\beta$ -TCP phase can be represented by the following equation:

$$Ca_{9-x}Mg_x(HPO_4)(PO_4)_5(OH) \rightarrow 3\beta - Ca_{3-x/3}Mg_{x/3}$$

$$(PO_4)_2 + H_2O\uparrow$$
(6)



**Fig. 2.** (a): TGA heating curves (green lines) of the as-hardened calcium phosphate cement bulks with MgO as a function of time after sintering at 1050, 1250 and 1400 °C (from bottom to top, respectively); (b): DSC heating curves (blue lines) of the as-hardened calcium phosphate cement bulks with MgO at different sintering temperatures (arrows indicate the respect quantities of heat flows and weight loss).

For each experimental group, particularly in groups with increasing sintering temperature, the residual HA peak at  $2\theta$  of  $31.2^{\circ}$  also decreased with increasing sintering temperature. Moreover, the phase mainly decomposed into TCP even if the double diffraction peaks of HA and  $\beta$ -TCP were observed at  $2\theta$  of 25.9 ° and 28.1 °. The confidential diffraction  $\beta$ -TCP peak at  $2\theta$  of 32.2 ° was clearly shown at temperatures beyond 1050 °C, because HA decomposed at temperatures between 600 and 800 °C. A previous work has reported [23] that additives or untreated reactants of CPC did not rapidly decompose into  $\beta$ -TCP, and the MgO additive was a result of the slow-phase transfer reaction of apatite into  $\alpha$ -TCP and TTCP. Based on the following reaction, HA would be phase transferred into β-TCP at sintering temperatures below 1000 °C [24]:

$$Ca_{10}(PO_4)_6(OH)_2 \rightarrow 3\beta - Ca_3(PO_4)_2 + CaO + H_2O \uparrow$$
(7)

# **TGA/DSC** tests

Figure 2a shows the TGA curves at respective sintering temperatures of 1050, 1250, and 1400 °C. At sintering temperatures near 800 °C, the phase transformation into HA occurred via water vaporization [25]. The weight loss rates of the green body with MgO were more significant compared with the sintering without MgO. From Equation (3) and upon comparison with the DSC curves, phasic decomposition of HA into TCP occurs at about 1000 °C [24, 26, 27]. Figure 2b shows the different thermal properties of the sintered calcium phosphate based on DSC analysis. DSC results of the three different scaffold analyses show the narrow bands for heat flow groups presented in the given groups with

MgO. Exothermic peaks are observed at temperatures above 1000 °C, which implies the phase transition of HA into  $\beta$ -TCP, and then into  $\alpha$ -TCP.

#### Grain size calculations

Figure 1 shows the XRD analysis results of the peak from the three different sintering temperatures of scaffolds, and Table 1 shows the calculated grain diameters upon application of Equation (2) and referencing the diffraction angle to  $\cos\theta$ . A higher sintering temperature enhances the  $\beta$ -TCP grain sizes because of enhanced atomic diffusion ability and larger grain size [28]. The TCP variation in the diffraction peak at  $2\theta$  of 34.5 ° was compared with the presence of biphasic HA and  $\beta$ -TCP at a sintering temperature of 1050 °C. Although the sintering temperature was raised to 1250 °C, the other phase of  $\alpha$ -TCP was inserted into biphasic HA and  $\beta$ -TCP, thereby producing a multiphase product. At a sintering temperature of 1400 °C and diffraction pattern shifted to the left, a noticeable right shoulder peak was observed at  $2\theta$  of  $34.5^{\circ}$ , which indicates that the stabilization of MgO leads to the decomposition of HA into other phases (e.g., α-TCP and  $\beta$ -TCP). HA decomposition in samples without MgO was reflected from the reduction in HA/â-TCP grain size from 5.27 µm (sintered at 1050 °C) to 5.14 µm (sintered at 1400 °C). Upon comparison with the results, samples with MgO stabilization increased the grain size from 5.56 µm to 6.51 µm, with respective sintering temperatures of 1050 and 1400 °C.

#### Comparison of activation energies

At higher temperatures, the atomic diffusion ability could be enhanced, and a higher diffusion rate could

Temperature (°C)	2 <i>θ</i> (°)	Substance (phases)	Half-peak width ratio (with/ without MgO)	Grain size (with/without MgO)
1050	27.9	ΗΑ/ β-ΤСΡ	0.254/ 0.267	5.56/ 5.27 μm
1050	31.2	β-ΤСΡ	0.169/ 0.183	8.42/ 7.77 μm
1050	34.5	β-ΤСΡ	0.212/ 0.260	6.67/ 5.51 μm
1250	27.9	ΗΑ/ β-ΤСΡ	0.237/ 0.236	5.96/ 5.98 μm
1250	31.2	β-ΤСΡ	0.151/ 0.166	9.42/ 8.57 μm
1250	34.5	$\beta$ -TCP/ $\alpha$ -TCP	0.228/ 0.248	6.28/ 5.78 μm
1400	27.9	НА/ β-ТСР	0.217/ 0.257	6.51/ 5.14 μm
1400	31.2	β-ΤСΡ	0.145/ 0.149	9.82/ 9.54 μm
1400	34.5	$\beta$ -TCP/ $\alpha$ -TCP	0.220/ 0.329	6.53/ 4.35 μm

Table 1. Grain sizes (in diameter) of phases at various sintering temperatures based on the Scherrer equation with and without MgO additive stabilization.



**Fig. 3.** Variation in grain size and the reciprocal of absolute temperature (1/T) with sintering for 8 h.

result in higher kinetic energy, which affects the activation energy of the reaction. Equation (3) shows that a linear plot of grain size (Fig. 3) can be obtained by plotting log D against the reciprocal of absolute temperature (1/T). The relationship between the rate of grain growth and its temperature can be quantitatively determined by the Arrhenius equation [Equation (3)] [19, 29]. The slope of the resultant equation is -Q/(2.303R), and the value of activation energy Q is shown in Table 2, in which Q ranged from 32 kJ/mol to 42 kJ/mol. Results indicate that an increase in the sintering temperature corresponds to an increase in the activation energy.

A TCP ceramic belongs to the calcium phosphate

family, which is available in two construction forms. One is  $\alpha$ -TCP, which can be achieved via hightemperature modification, and is generally produced at sintering temperatures higher than 1125 °C. The other is  $\beta$ -TCP, which can be produced via low-temperature modification, and is produced at sintering temperatures below 1125 °C. The phase of  $\beta$ -TCP is more thermodynamically stable in a biological environment compared with  $\alpha$ -TCP. The biodegradation of  $\beta$ -TCP is noticeably faster compared with that of  $\dot{a}$ -TCP in vivo, although their solubilities are almost the same [2, 5]. However, the undesired exceedingly high biodegradation rate of single-phase  $\beta$ -TCP generally leads to damage and failure of tissue construction, because the regeneration speed could not match the degradation speed [24, 30].

#### Pore sizes distribution

Choosing the correct pore-making agent using a flexible manufacturing process is important to obtain an even and permeable pore distribution in scaffolds. The recognized scaffolds for tissue engineering possess essential properties [30-32], such as the macro-pores of about 100  $\mu$ m to 300  $\mu$ m that are essential for cell proliferation and mineralization following the cell cultures. Another property is the micropores about several microns, which enhance initial cell adhesion. In addition, distribution of pore sizes and interconnected pore networks are important factors for the growth of osteo-progenitor cells, which is important in bone regeneration. General strategies including foaming and hole-making agents are added into the ceramic matrix to obtain a porous bone-filling scaffold via high-

Table 2. Activation energies at various sintering temperatures based on the Arrhenius equation with and without MgO additive stabilization.

Temperature (°C)	2 <i>θ</i> (°)	Substance (identified phase)	Grain sizes (with/without MgO; μm)	Activation energy (with/ without MgO; kJ/mol)
1050	31.2	β-ΤСΡ	8.42/7.77	31.71/32.99
1250	31.2	β-ΤСΡ	9.42/8.57	36.50/37.98
1400	31.2	β-ΤСΡ	9.82/9.54	40.09/41.72



**Fig. 4.** Optical and SEM morphologies of the as-hardened calcium phosphate cement bulks with MgO sintered at 1050 °C for 8 h.

temperature sintering and salt leaching, respectively. The distribution in Fig. 4 corresponds to the interconnected porosity, and should have a pore volume greater than 50 vol%.

Based on the adjustment of the sintering temperatures of HA decomposition, XRD patterns (Fig. 1) show an interconnected scaffold network with a biphasic or multiphasic product, which indicates that the phasetransferred a-TCP may improve the mismatched biosorption rate of  $\beta$ -TCP in the human body. In clinical applications, a basic calcium phosphate family with Ca/ P atomic ratios larger or equal to 1.5 can only exist in a basic body fluid. The final product exhibited a suitable pore distribution in scaffolds when biphasic or multiphasic products were obtained aside from single-phase β-TCP at different sintering temperatures. Biphasic or multiphasic ceramic scaffolds, which are derived from sintering temperatures between 1050 and 1400 °C, with reactant particles of TTCP and DCPA with MgO stabilization, have exhibited excellent pore size distribution and improved biodegradation ability. These advantages indicate the relevance of this study in proposing a potential method to increase the surgical success of alveolar bone augmentation in clinical practice.

#### Conclusions

Within the limitations of the study and from the results, the following conclusions were drawn.

1. The HA phase that decomposed to  $\beta$ -TCP could improve the biosorption rate, and the transformation of  $\beta$ -TCP into  $\alpha$ -TCP may adjust the mismatched biosorption rate of  $\hat{a}$ -TCP in the human body.

2. With its advantages, the relatively developed porous scaffold through CPC green samples with MgO stabilization can stabilize TCP phases and increase the success rates of bone augmentation in clinical practice.

3. Adjusting the sintering temperatures of HA

decomposition produces an interconnected scaffold network with a biphasic or multiphasic product.

## Acknowledgments

This work would like to thank National Science Council of the Taiwan, for partially financial supporting this research under Contract NSC 100-2622-E-035-011-CC3 and 102-2622-E-035-018-CC2.

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