Ceramics International **23** (1997) 19–25
© 1996 Elsevier Science Limited and Techna S.r.l.
Printed in Great Britain. All rights reserved
0272-8842(95)00135-2
0272-8842/97 $17.00+.00

Hydroxyapatite Synthesized by a Simplified Hydrothermal Method

H. S. Liu,[a] T. S. Chin,[a] L. S. Lai,[a] S. Y. Chiu,[a] K. H. Chung,[b] C. S. Chang[b] & M. T. Lui[b]

[a]Department of Materials Science and Engineering, National Tsing Hua University, Hsinchu, 300, Taiwan, Republic of China
[b]National Yang-Ming Medical University and Veterans General Hospital-Taipei, Taipei, Taiwan, Republic of China

(Received 28 August 1995; accepted 26 September 1995)

Abstract: A simplified hydrothermal method of synthesizing hydroxyapatite powder is described. Heating powders of $Ca(OH)_2$, $Ca(H_2PO_4)_2 \cdot H_2O$ and distilled water in a pressurized pot at 109°C for 1–3 h results in powders consisting of crystallized hydroxyapatite in a needle shape, 130–170 nm in length and 15–25 nm in width. The specific surface area is 31–43 m^2/g and the Ca/P ratio is 1·640–1·643. The obtained HA powder can be sintered to a high density at 1200–1300°C. No decomposition was identified by X-ray diffraction. The optimally sintered ceramic has a pore-free surface structure with a flexural strength of 120 MPa, a micro-Vickers hardness of 5·1 GPa and fracture toughness of 1·2 $MPa \cdot m^{1/2}$. The biocompatibility of the pulverized sintered-ceramic is excellent and comparable to that of a commercial grade hydroxyapatite by evaluating the implantation in a dog. The synthesis method is simple, economic, and results in a high quality powder which is useful in hard tissue reconstruction applications.
© 1996 Elsevier Science Limited and Techna S.r.l.

1 INTRODUCTION

Hydroxyapatite (HA, $(Ca_5(PO_4)_3OH)$) is a good material to use for hard tissue replacement because its chemical and crystallographic characteristics match closely with some of the properties of human bones and teeth.[1] In fact, HA is the main mineral constituent of bones and teeth, and its compatibility with these biological tissues has been proven to be superior to any other artificial material. Synthetic HA is finding considerable success in clinical applications,[2] particularly in the orthopaedic field, owing to its bioactivity, which promotes bone growth directly on to its surface. So far two modifications of HA have been developed; a highly porous one[3,4] and a densely sintered one. The applicability of this material, however, is restricted to non-stressed regions of the skeleton. This is because of the inferior strength and the low toughness of the materials.[5–11]

Recent progress in the chemistry of calcium phosphates, especially apatites, has been reviewed by Kanazawa.[12] The HA powders can be synthesized by various techniques, and their characteristics depend on the synthesis method.[12–18] Roughly speaking, there are three chemical methods, namely: a dry process; a wet (precipitation or hydrolysis) process; and a hydrothermal process. The dry method has the great advantage of attaining a stoichiometric composition (Ca/P = 1·67) in comparison with the wet method. The wet method utilizes either precipitation from mixed aqueous solutions or the hydrolysis of calcium phosphates. HA powders produced by the wet process generally possess a high surface area and fine particle size, however they are non-stoichiometric (Ca-deficient) and are of low crystallinity, the degree of which depends on factors such as pH, ageing time and temperature, as well as the type and concentration of the starting materials. HA powders with various Ca/P ratios (1·50–1·67) can be obtained easily from hydrothermal synthesis.[12]

Blocks of HA with various densities and strengths can be prepared by conventional sintering,[19,20]

microwave sintering,[21] and hot isostatic pressing.[22] Many efforts have been made to improve the strength of dense HA. A method reported by Jarcho *et al.*,[23] which involves the wet synthesis of powder and the direct pressureless sintering of filter cake of the as-precipitate powder without drying, is also attractive for achieving a high strength, high density and fine microstructure. Further, an almost fully transparent HA ceramic can be formed by using the method of hot isostatic pressing filter cake of HA.[24]

In the present article, a simplified hydrothermal process of synthesizing high quality HA powders by utilizing a pressurized cooking utensil will be introduced. The characteristics of the synthesized powder, and the mechanical strength, thermal stability and biocompatibility of the sintered-ceramic, are studied.

2 EXPERIMENTAL PROCEDURES

2.1 Material preparation

Reagent grade $Ca(H_2PO_4)_2{\cdot}H_2O$ and $Ca(OH)_2$ powders were mixed using a conventional ball-milling technique with alumina balls immersed in ethanol for 1 h. The molar ratio of $Ca(H_2PO_4)_2{\cdot}H_2O$ to $Ca(OH)_2$ was 3:7, which is based on the HA stoichiometric composition. After mixing, the slurry was dried under an infrared lamp. The HA powder was synthesized by heating powders of 100–200 g batch mixtures and 2000 ml distilled water in a commercially available pressurized pot (e.g. Quanta, made in Italy) for 1–3 h. The pressurized pot was heated by an electric oven which maintained a power of 800 W. After reaching thermal equilibrium, the temperature of the pressurized pot was measured to be 109°C and the pressure was 1·37 atm according to a saturated steam chart.[25] The reaction product was filtered and washed three times with distilled water for the complete removal of PO_4^{3-} and Ca^{2+} ions, then dried at 90°C. The dried powder was hydrostatically pressed into disk-shaped compacts at 160 MPa. Without calcination, the compacts of the 3 h synthesized powder were heated up at a rate of 5°C/min and sintered in air at 1100–1300°C for 2 h to produce dense bulk specimens.

2.2 Powder characterization

The synthesized powder was dissolved in nitric acid and analysed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) to determine the calcium/phosphorus ratio. The specific surface area was measured by a BET method. The synthesized powder was examined by a Rigaku X-ray diffractometer with Cu-K_α radiation at a scan rate of 4°/min. The morphology of the synthesized powder was examined using a transmission electron microscope (TEM).

2.3 Characterization of the sintered bulk specimens

The sintered bulk density and porosity were measured by the fluid displacement method with distilled water. The crystalline phase of the sintered specimen was identified using a standard X-ray powder diffraction method. The microstructure of the sintered body was investigated by scanning electron microscopy (SEM) on polished samples etched with 1 wt% phosphoric acid for about 30 s and coated with a gold film.

2.4 Mechanical properties of the sintered bulk specimens

Flexural strength (σ_f) was measured by a three-point bending method with a span length of 20 mm and a cross-head speed of 0·5 mm/min, using bevelled edge 3 mm×4 mm×40 mm specimens abraded down to 1000 grit SiC paper.

A micro-Vickers indentation method was carried out to determine the Vickers hardness and fracture toughness (K_{Ic}) of the samples. Loads of 2·94 N for 30 s and of 0·147 N for 10 s were applied to measure toughness and hardness, respectively. Toughness was calculated by using Niihara's equation:[26]

$$K_{Ic}/(H{\cdot}a^{1/2}) = 0{\cdot}203(c/a)^{-3/2}$$

where H is the micro-Vickers hardness, a is a characteristic dimension of the impression and c is a characteristic crack dimension.

2.5 Biological evaluation

The sintered HA (3 h of reaction time, fired at 1200°C for 2 h) was ground to less than 1 mm before evaluation. The particulate form of commercial HA, Calcitite 2024 (Calcitek, Inc., San Diego, CA, USA), was also employed as control. Dogs were used for this implant study. After anaesthesia and preparation, the right side premolar and molar teeth in the mandible were extracted in order to create an edentulous ridge for implantation of the tested materials. After healing for 5 months, the edentulous ridges were exposed. Holes were prepared by drilling, 4 mm in diameter and 10 mm in depth. The tested materials were implanted into the respective holes and the wound was closed routinely. Cross examination and X-ray radiographs of the biological reaction of implant

materials to the soft tissue and bone tissue were performed at 1, 5 and 10 weeks post-operation.

3 RESULTS AND DISCUSSION

3.1 Characterization of the synthesized powders

Typical X-ray diffraction patterns of the synthesized powder heated in a pressurized pot after 1, 2 and 3 h are shown in Fig. 1. After heating for various times, the diffraction patterns of the obtained powders did not contain any peaks other than those shown in the JCPDS card for HA. Thus, the powders are determined to be well-crystallized X-ray pure HA. All the $Ca(H_2PO_4)\cdot H_2O$ has fully reacted with $Ca(OH)_2$. Substantial peak broadening denotes a submicron crystallite size. The diffraction peak intensity becomes stronger with increasing heating time indicating that the crystallinity of the HA powders increases with heating time.

Table 1 lists the Ca/P ratio, specific surface and powder size versus heating time in the pressurized pot. The Ca/P molar ratio analysed by ICP-AES was determined to be 1·640–1·643. Since the HA has a nominal Ca/P ratio of 1·667, it is manifest that the synthesized powders are slightly calcium-deficient. The major impurity of the prepared powder was manganese, whose concentration was determined to be 50 ppm by ICP-AES. It is worth mentioning that the Ca/P ratio in natural bone is lower than 1·667, so the calcium-deficient HA is of greater biological interest than stoichiometric or calcium-rich HA. It has been suggested by Posner that calcium-deficient HA plays important roles in several processes such as bone remodelling and bone formation.[27] When the two types of HA, the calcium-deficient and the stoichiometric, are used as synthetic biomaterials their behaviours are different. It has been reported that the calcium-deficient HA elicits an immediate precipitation of biologically equivalent apatite on its surface when immersed in a simulated physiological fluid, whereas precipitation on stoichiometric HA requires some induction time.[28] However, the calcium-deficient HA may serve as a thermochemical precursor to transform to tricalcium phosphate (TCP) phase during sintering as reported by Jarcho *et al.*[23] The presence of TCP in sintered HA may deteriorate fracture strength as also depicted by Jarcho *et al.*[23] The thermal stability of synthesized hydroxyapatite by pressurized heating will be discussed later.

The specific surface area, measured by a BET method, varied with heating time as listed in Table 1. All the prepared powders had a high BET specific area of 31–43 m^2/g, which increased with increasing heating time. Finally, an ultrafine, easy-sintering HA powder with a high specific surface area was prepared successfully.

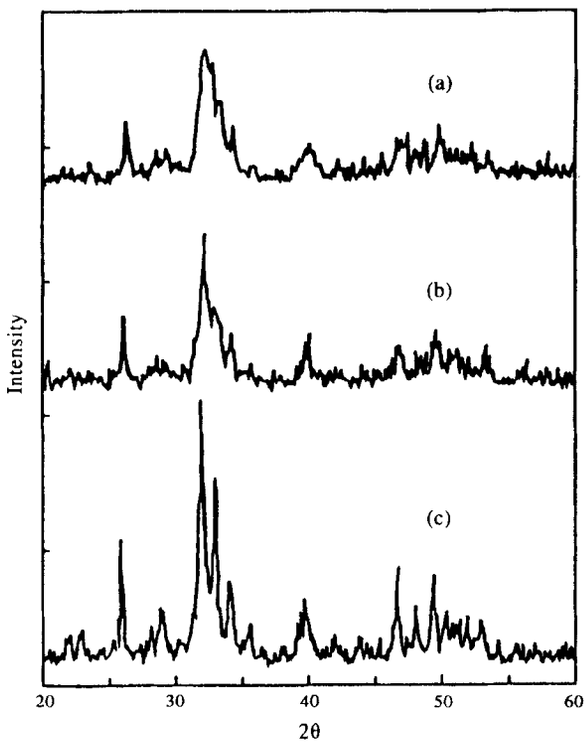

Fig. 1. X-ray diffraction patterns of the pressurized-heating-pot synthesized products at 109°C for different reaction times: (a) 1 h; (b) 2 h; and (c) 3 h.

Table 1. Ca/P ratio, specific surface area and particle size of the synthesized powder for various reaction time

Reaction time	1 h	2 h	3 h
Ca/P ratio	1.643	1.643	1.640
Specific surface area (m^2/g)	31	40	43
Particle size (nm)			
Length	130	150	170
Width	15	20	25

Transmission electron microscopy (TEM) was used to investigate the morphology of the synthesized powder and also for calculating the particle size. A typical TEM image of a synthesized powder heated for 3 h at 109°C is shown in Fig. 2. Slight particle agglomeration is visible and the powder is needle-like with a length of about 170 nm and a diameter of about 25 nm. Particle sizes resulting from various heating times as calculated from TEM images are also listed in Table 1. Prolonging the reaction (heating) time will cause the HA needle crystal to grow. Apparently, it is of particular interest that increasing the heating time not only increases the particle size, but also increases the specific surface area. In general, increasing the particle size lowers the specific surface area, so the BET values were so unexpected that the experiment was

Fig. 2. Transmission electron micrograph of the synthesized hydroxyapatite powder reacted in a pressurized-heating-pot at 109°C for 3 h.

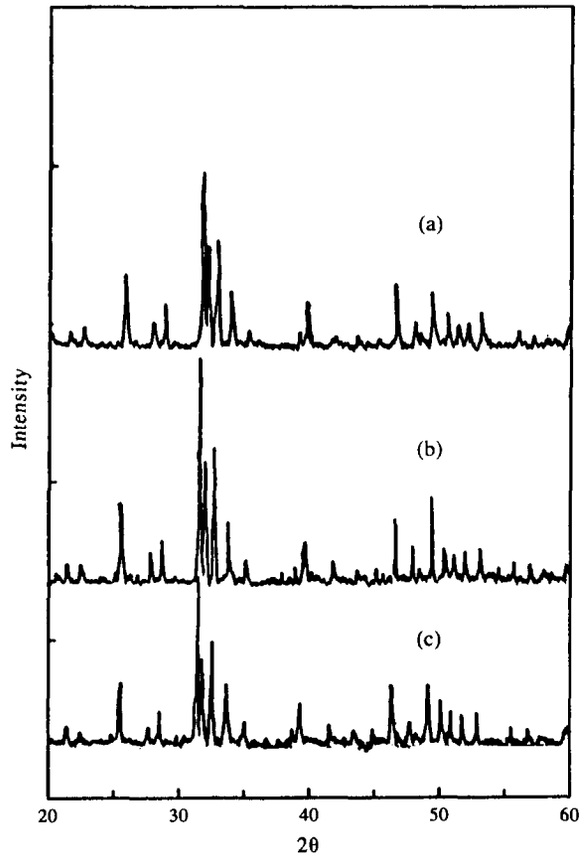

Fig. 3. X-ray diffraction patterns for the bulk ceramics sintered at various sintering temperatures: (a) 1100°C; (b) 1200°C; and (c) 1300°C.

repeated, with similar results and good reproducibility. It is proposed that increasing the reaction time results in surface roughening of the HA powder probably because of the nucleation of new HA on the particle surface. That is to say, particle growth may be a result of continuing nucleation instead of an Ostwald ripening type of growth. This is possible because the reaction temperature of 109°C may be too low for crystal growth. However, there is no direct evidence and further study is needed to prove this.

There are many methods of preparing HA powder from an aqueous medium. In the past, pure HA could only be obtained in small quantities using time-consuming and tedious methods. It is a great challenge to prepare a large quantity of HA by a simple method. The method introduced here provides a simple and efficient synthesis route for a large quantity of high quality HA powder.

3.2 Characterization of the sintered bulk specimens

The calcining process can be omitted because the as-prepared powder is well-crystallized HA crystal. Without undergoing calcination, sintering was carried out directly at various temperatures in air to produce polycrystalline bulk HA. Figure 3 shows X-ray diffraction patterns for sintered powder compacts of synthesized powder sintered at different temperatures. From X-ray diffraction, the crystalline phase of the sintered specimen is identified to be HA and no other phases such as α- or β-TCP can be observed after firing at temperatures as high as 1300°C. In other words, it is an X-ray pure HA and there is no phase transformation, as identifiable from X-ray diffraction patterns, of HA during firing in the temperature range 30–1300°C.

Sintering of HA is complicated by two processes, namely dehydroxylation and decomposition at elevated temperatures, according to previous reports.[6,29–31] During dehydroxylation, HA loses OH radicals upon heating according to the following equation:[30]

$$Ca_{10}(PO_4)_6(OH)_2 \rightarrow Ca_{10}(PO_4)_6(OH)_{2-2x}O_x\square_x + xH_2O \quad (1)$$

The hydroxyl-ion-deficient product, $Ca_{10}(PO_4)_6(OH)_{2-2x}O_x\square_x$ (□: non-charged vacancy, $x < 1$) is known as oxyhydroxyapatite whose existence has been identified by X-ray diffraction[6,30] and infrared spectroscopy studies. In air, oxyhydroxyapatite is formed at around 900°C and in a water-free environment it is formed at around 850°C. Upon heating, HA can be decomposed into tricalcium phosphate and tetracalcium phosphate according to:[23]

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

These two decomposition effects of HA are more serious for the non-stoichiometric HA,[12] and can be suppressed by a moisturized sintering atmosphere.[32] Wang and Chaki.[7] also reported that dehydroxylation of HA in air and in vacuum occurs in the temperature range 850–900°C, and decomposition of HA takes place at higher temperatures. Firing in moisturized air, HA does not show any indication of dehydroxylation or decomposition even at a temperature as high as 1350°C.

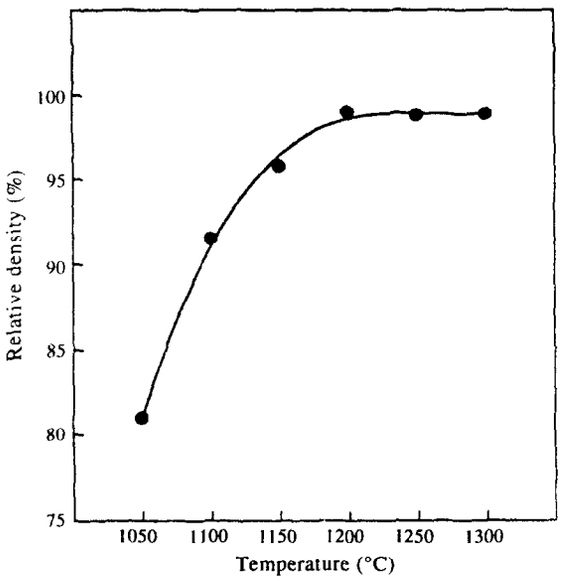

Fig. 4. Relative density of the 2h-sintered bulk ceramics plotted against the sintering temperature.

However, the decomposition did not occur in this study, though the as-prepared powder is non-stoichiometric and the sintering atmosphere was just plain air not moisturized. This is probably because of the local humid atmosphere (the relative humidity is higher than 70% all year around), the sintering atmosphere not being moisturized may in fact contain enough water vapour to stabilize the HA phase of the synthesized powder.

Figure 4 shows the relative density (r) presented as a percentage of the theoretical density against sintering temperature (sintering for 2 h) by assuming the theoretical density of 3·156 g/cm^3 for HA. Raising the sintering temperature results in the increment of density at first, but there is an end density at 1200°C. The density does not increase significantly over this end value despite sintering at higher temperatures. So densification appears to be completed near 1200°C with a measured relative density higher than 98%. Scanning electron micrographs of the synthesized HA ceramic sintered at 1250 and 1300°C for 2 h are shown in Fig. 5. No porosity is found on the surface of any of these specimens. The grain size of the 1250°C-fired sample is small, approximately 2–11 μm. Considerable grain growth is observed for samples sintered at 1300°C.

3.3 Mechanical properties of the sintered bulk specimens

Figure 6 shows a plot of flexural strength vs sintering temperature. There is a maximum flexural strength of 120 MPa at the sintering temperature of 1200°C. For specimens sintered above 1200°C, the flexural strength drops slightly because of considerable grain growth.

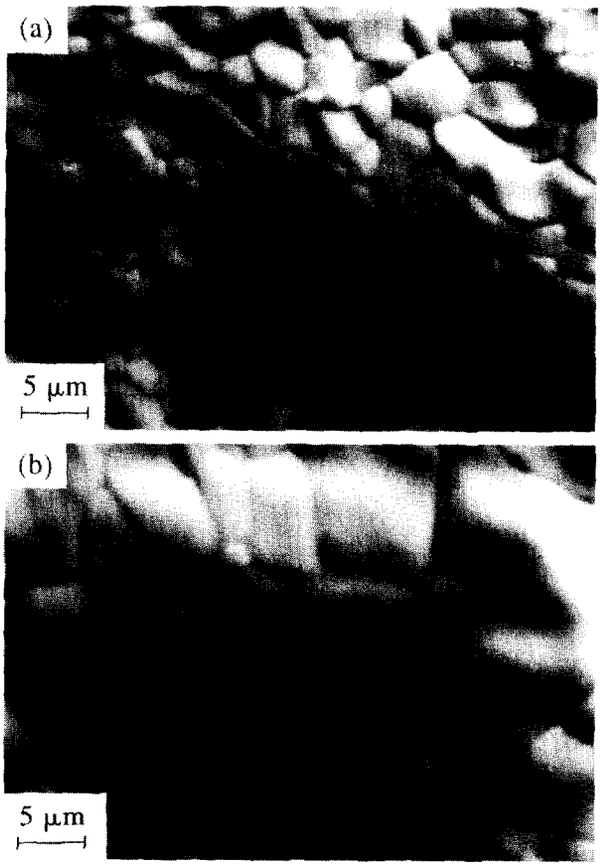

Fig. 5. Scanning electron micrographs of the bulk ceramics sintered for 2 h at (a) 1250°C, and (b) 1300°C.

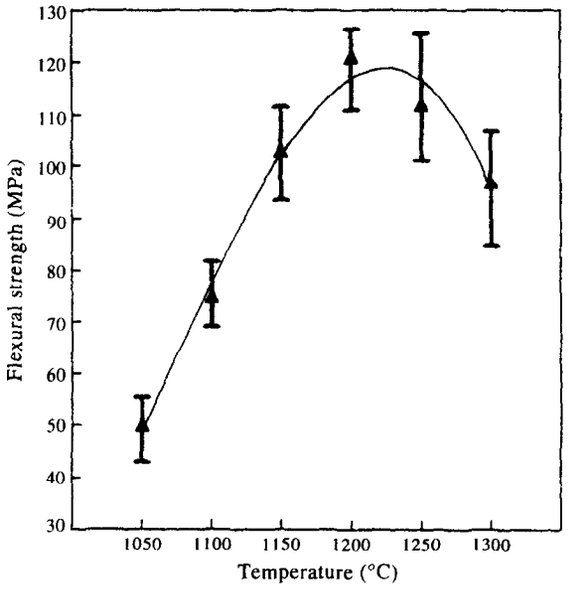

Fig. 6. Flexural strength of the sintered bulk ceramics plotted against the sintering temperature.

The fracture toughness and the micro-Vickers hardness of the sintered specimens are shown as a function of sintering temperature in Fig. 7. Both toughness and hardness increased with increasing temperature up to 1250°C, and tended to decrease at higher temperature. Here too an increase of microhardness and toughness with relative density is observed. The hydroxyapatite ceramics sintered

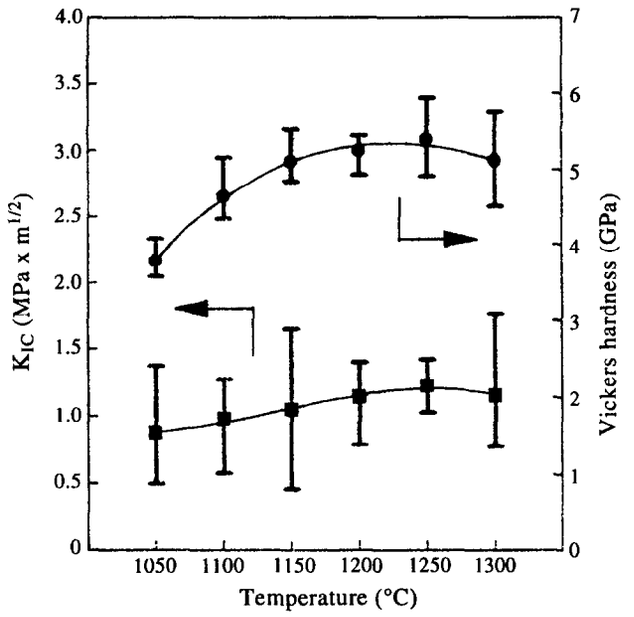

Fig. 7. Fracture toughness (■) and micro-Vickers hardness (●) of the sintered bulk ceramics plotted against the sintering temperature.

at 1250°C had the highest Vickers hardness (5·3 GPa) and the highest fracture toughness (1·4 MPa·$m^{1/2}$).

3.4 Biological evaluation of the sintered bulk specimens

After implantation for 1, 5 and 10 weeks, both the synthesized and commercial HA showed good healing of the surgical wound. Figure 8 shows X-ray radiographs of the implanted materials *in situ*. After 1 week, the soft tissue healing was excellent, neither any symptoms of infection nor abnormal phenomena were discovered. Starting from the 5th week, the death space under implanted HA showed calcification and ossification. Neither absorption nor loss of both the synthesized and control materials were identifiable from the radiographs. The results showed that biocompatibility of the synthesized HA is excellent and comparable with those of commercial control. So the synthesized HA possesses a high potential for hard tissue implantation in a clinical situation.

4 CONCLUSIONS

A very simple and efficient method for the preparation of hydroxyapatite (HA) powder has been described. Heating powders of $Ca(OH)_2$, $Ca(H_2PO_4)_2{\cdot}H_2O$ and distilled water in a pressurized pot is quite a new and economic way to synthesize a large quantity and high quality HA powder. The synthesized powders consisted of needle-crystallites

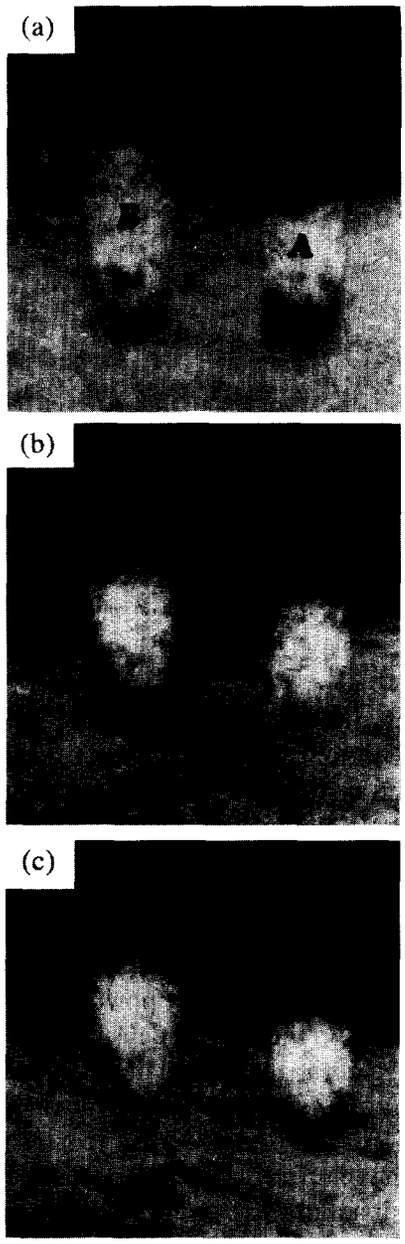

Fig. 8. X-ray radiographs of the implants in a dog [(A) the experimental material, (B) control]: (a) 1 week, (b) 5 weeks, and (c) 10 weeks after surgery.

identified to be HA phase and with the size ranges 130–170 nm in length and 15–25 nm in width. The specific surface area (BET) and the Ca/P ratio were 31–43 m^2/g and 1·640–1·643, respectively. This powder can be sintered to pore-free at temperatures of 1200–1300°C without X-ray identifiable decomposition during sintering. The optimum sintering condition was determined to be 1200°C for 2 h, resulting in a sintered bulk with a flexural strength of 120 MPa, micro-Vickers harness of 5·1 GPa and fracture toughness of 1·2 MPa·$m^{1/2}$. The implantation study in a dog of the experimental HA material and a control demonstrated excellent biocompatibility, without infection nor rejection. The HA powder synthesized by the proposed simplified method is of good crystallinity, does not require

high temperature calcination and possesses high surface area and good sinterability. Since the sintered ceramic shows high strength with excellent biocompatibility compared with the commercial product, it is noteworthy in applications such as hard tissue implantation.

ACKNOWLEDGEMENTS

The authors are indebted to the financial support of Veterans General Hospital and Tsing Hua University under the grants VGHTH80-14-2, VGHTH81-18-2 and VGHTH82-14-2.

REFERENCES

1. JARCHO, M., KAY, J. F., GUMAER, K. I., DOREMUS, R. H. & DROBECK, H. P., Tissue, cellular and subcellular events at a bone–ceramic hydroxylapatite interface. *J. Bioeng.*, **1**(2) (1977) 79–92.
2. AOKI, H., *Science and Medical Applications of Hydroxyapatite*. Japanese Association of Apatite Science, Takayama Press, Tokyo, 1991, pp. 1–15.
3. YAMASAKI, N., KAI, T., NISHIOKA, M., YANAGISAWA, K. & IOKU, K., Porous hydroxyapatite ceramics prepared by hydrothermal hot-pressing. *J. Mater. Sci. Lett.*, **9** (1990) 1150–1.
4. LEHUEC, J. C., SCHAEVERBEKE, T., CLEMENT, D., FABER, J. & LEREBELLER, A., Influence of porosity on the mechanical resistance of hydroxyapatite ceramics under compressive stress. *Biomaterials*, **16**(2) (1995) 113–18.
5. AKAO, M., AOKI, H., KATO, K. & SATO, A., Dense polycrystalline β-tricalcium phosphate for prosthetic applications. *J. Mater. Sci.*, **17**(2) (1982) 343–6.
6. KIJIMA, T. & TSUTSUMI, M., Preparation and thermal properties of dense polycrystalline oxyhydroxyapatite. *J. Am. Ceram. Soc.*, **62**(9–10) (1979) 455–60.
7. WANG, P. E. & CHAKI, T. K., Sintering behaviour and mechanical properties of hydroxyapatite and dicalcium phosphate. *J. Mater. Sci.: Mater. in Med.*, **4** (1993) 150–8.
8. THOMAS, M. B., DOREMUS, R. H., JARCHO, M. & SALSBURY, R. L., Dense hydroxyapatite: Fatigue and fracture strength after various treatments from diametrical tests. *J. Mater. Sci.*, **15** (1980) 891–4.
9. DOREMUS, M. B. & DOREMUS, R. H., Fracture strength of dense hydroxyapatite. *Am. Ceram. Sci. Bull.*, **60**(2) (1981) 258–9.
10. AKAO, A., AOKI, H. & KATO, K., Mechanical properties of sintered hydroxyapatite for prosthetic applications. *J. Mater. Sci.*, **16** (1981) 809–12.
11. DE WITH, G., VAN DIJK, H. J. A., HATTU, N. & PRIJS, K., Preparation, microstructure and mechanical properties of dense polycrystalline hydroxyapatite. *J. Mater. Sci.*, **16** (1981) 1592–8.
12. KANAZAWA, T. (ed.), *Inorganic Phosphate Materials*, Materials Science Monographs 52. Elsevier, Tokyo, 1989, pp. 1–55.
13. KANDORI, K., YASUKAWA, A. & ISHIKAWA, T., Preparation and characterization of spherical calcium hydroxyapatite. *Chemistry of Materials*, **7**(1) (1995) 26–32.
14. LAZIC, S., Microcrystalline hydroxyapatite formation from alkaline-solutions. *J. Cryst. Growth*, **147**(1–2) (1995) 147–54.
15. SHAREEF, M. Y., MESSER, P. F. & VANNOORT, R., Fabrication, characterization and fracture study of a machinable hydroxyapatite ceramic. *Biomaterials*, **14**(1) (1993) 69–75.
16. SHIRKHANZADEH, M. & AZADEGAN, M., Hydroxyapatite particles prepared by electrocrystallization from aqueous-electrolytes. *Mater. Lett.*, **15**(5–6) (1993) 392–5.
17. HATTORI, T. & IWADATE, Y., Hydrothermal preparation of calcium hydroxyapatite powders. *J. Am. Ceram. Soc.*, **73**(6) (1990) 1803–5.
18. HATTORI, T., IWADATE, Y. & KATO, Y., Hydrothermal synthesis of hydroxyapatite from calcium pyrophosphate. *J. Mater. Sci. Lett.*, **8**(3) (1989) 305–6.
19. DENISSEN, M., MANGANO, C. & VENINI, G., *Hydroxyapatite Implants*. Piccin Nuova Libraria, SPA, Padua, 1985, p. 19.
20. PUAJINDANETR, S., BEST, S. M. & BONFIELD, W., Characterization and sintering of precipitated hydroxyapatite. *Brit. Ceram. Trans.*, **93**(3) (1994) 96–9.
21. FANG, Y., AGRAWAL, D. K., ROY, D. M. & ROY, R., Microwave sintering of hydroxyapatite ceramics. *J. Mater. Res.*, **9**(1) (1994) 180–7.
22. WAKAI, F., KODAMA, Y. & SAKAGUCHI, S., Superplasticity of hot isostatically pressed hydroxyapatite. *J. Am. Ceram. Soc.*, **73**(2) (1990) 457–60.
23. JARCHO, M., BOLEN, C. H., THOMAS, M. B., BOBICK, J., KAY, J. F. & DOREMUS, R. H., Hydroxyapatite synthesis and characterization in dense polycrystalline form. *J. Mater. Sci.*, **11**(11) (1976) 2027–35.
24. UEMATSU, K., TAKAGI, M., HONDA, T., UCHIDA, N. & SAITO, K., Transparent hydroxyapatite prepared by hot isostatic pressing of filter cake. *J. Am. Ceram. Soc.*, **72**(8) (1989) 1476–8.
25. VAN WYLEN, G. J. & SONNTAG, R. E., *Fundamentals of Classical Thermodynamics*, 2nd edn. John Wiley and Sons Inc., New York, 1978, p. 646.
26. NIIHARA, K., Indentation microfracture of ceramics — its application and problems. *Ceram. Jap.*, **20** (1985) 12–18.
27. POSNER, A. S., Crystal chemistry of bone minerals. *Physiol. Rev.*, **49**(4) (1969) 760–92.
28. RADIN, S. R. & DUCHEYNE, P., The effect of calcium-phosphate ceramic composition and structure on *in vitro* behaviour — 2. Precipitation. *J. Biomed. Mater. Res.*, **27**(1) (1993) 35–45.
29. YAMASHITA, K., OWADA, H., NAKAGAWA, H., UMEGAKI, T. & KANAZAWA, T., Trivalent-cation-substituted calcium oxyhydroxyapatite. *J. Am. Ceram. Soc.*, **69**(8) (1986) 590–4.
30. TROMBE, J. C. & MONTEL, G., Some features of the incorporation of oxygen in different oxidation states in apatite lattice — I. On the existence of calcium and strontium oxyapatites. *J. Inorg. Nucl. Chem.*, **40** (1978) 15–31.
31. VAN RAEMDONCK, W., DUCHEYNE, P. & DE MEESTER, P., *Metal and Ceramic Biomaterials, Vol. 2*, ed. P. Ducheyne & W. Hasting. CRC Press, Boca Raton, Florida, 1984, p. 149.
32. YAMASHITA, K., KITAGAKI, K., UMEGAKI, T. & KANAZAWA, T., Effects of sintering ambient H_2O vapour on the protonic conduction properties of ceramic hydroxyapatite. *J. Mater. Sci. Lett.*, **9** (1990) 4–6.