Synthesis and evaluation of various layered octacalcium phosphates by wet-chemical processing

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Octacalcium phosphate was synthesized by hydrolysis of α-tricalcium phosphate through a wet-chemical processing. Using the same wet-chemical processing in presence of various succinate ions, the preparation of some complexed octacalcium phosphates was attempted. The products were examined by X-ray diffraction method. These complexed octacalcium phosphates intercalated with succinic acid, L-asparatic acid, and methyl succinic acid showed an expanded basal spacing in the octacalcium phosphate unit cell dimensions. The microstructure was observed by scanning and transmission electron microscopy.

1. Introduction

Octacalcium phosphate ($Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$, OCP: Ca/P molar ratio = 1.33) is one of the most important calcium compounds in the human body [1]. Although this compound is thermodynamically metastable, it is useful as a precursor for the hydroxyapatite in bone and teeth. Furthermore, octacalcium phosphate can be used as a catalyst for dehydrating alcohols, in chromatography and as a separator of protein, because of its chemical interaction with organic substances, such as nucleic acids.

Octacalcium phosphate has a layered structure, as schematically shown in Fig. 1, which is composed of apatitic layers (A-layer) and hydrated layers (B-layer) [1–3]. Octacalcium phosphate has two kinds of HPO_4^{2-} groups in the B-layer. One group connect the A-layer and the other is located between A-layers like Ca-HPO_4Ca, as a pillar with interlayer H_2O molecule, which supports the A-layer in the structure of octacalcium phosphate. Since the presence of this unique layer structures enable HPO_4^{2-} in a octacalcium phosphate to exchange various ions, this calcium phosphate possesses a potential to apply as an intercalated compound. Therefore, many applications such as that as a vehicle to bring slow release of substituted molecules from hydrated layer in octacalcium phosphate for drag delivery system can be considered.

Monma reported about the preparation of octacalcium phosphate by hydrolysis of α-tricalcium phosphate (α-TCP: Ca/P molar ratio = 1.5) [4]. Moreover, Monma *et al*. [5] found that octacalcium phosphate complexed with a series of dicarboxylates through the hydrolysis of α-tricalcium phosphate in dicarboxylic acids. A succinate-complexed octacalcium phosphate has been synthesized by conducting hydrolysis of α-tricalcium phosphate in presence of succinate ions. Mathew *et al*. [6] proposed a structural model for octacalcium phosphate succinate pentahydrate, which was similar to octacalcium phosphate and calcium succinate trihydrate with respect to the unit cell dimensions and structure. This model suggests the possibility of incorporating dicar-boxylate ions (–OOCRCOO–: R = organic groups) in octacalcium phosphate structures and their effect on biological mineralization processes.

In this paper, the effect of synthetic conditionsm, such as pH, synthetic time and temperature, on syntheses of pure octacalcium phosphate through the wet-chemical processing were examined in detail. The second purpose was that of synthesizing dicarboxylic acid-intercalated complexed octacalcium phosphate prepared by conducting the hydrolysis of α-tricalcium phosphate in the presence of dicarboxylic acids, such as succinate acid, L-aspartic acid and methyl-succinic acid through the wet-chemical processing. In particular, the effect of side groups of dicarboxylic acids on the synthesis of dicarboxylic acid-intercalated complexed octacalcium phosphate during wet-chemical processing was investigated.

2. Experimental procedure

2.1. Synthesis of octacalcium phosphate without dicarboxylic acid

Commercially available α-tricalcium phosphate as a starting material was supplied by Taihei Chemical Co. (Nara, Japan). This powder was produced by grinding

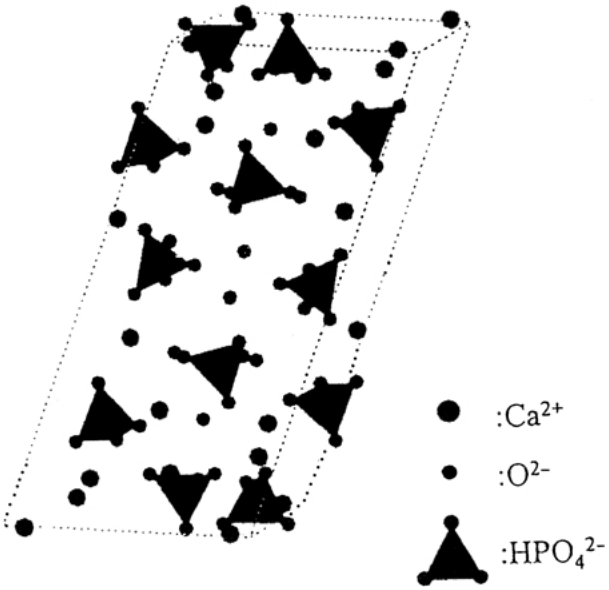

Figure 1 Structural model of octacalcium phosphate.

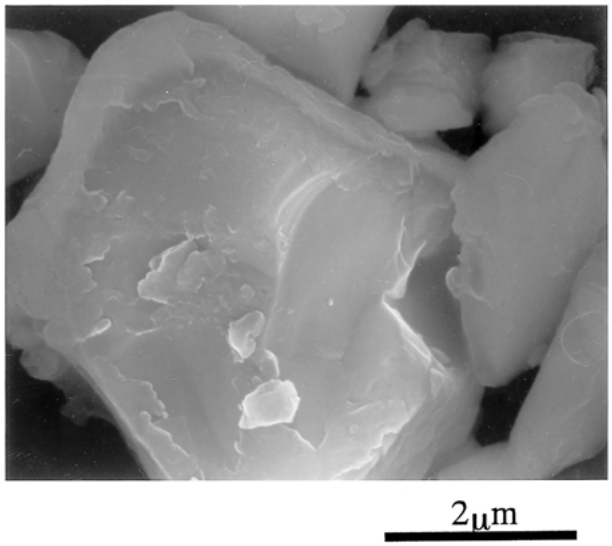

Figure 2 SEM photograph of α-tricalcium phosphate powder.

sintered bodies of α-tricalcium phosphate [7]. The characteristics of α-tricalcium phosphate powder are summarized in Table I. Fig. 2 shows a scanning electron microscopy (SEM) photograph of the α-tricalcium phosphate powder. This powder was highly pure with a particle size less than 10 μm. 2.0 mmol of α-tricalcium phosphate was suspended in 18 ml of CH_3COOH/CH_3COONa buffer solution, which was added in order to maintain the pH during the hydrolysis of α-tricalcium phosphate. The initial pH of this suspension was maintained between 3.9 to 4.7 during hydrolysis reaction. The hydrolysis reaction of α-tricalcium phosphate was performed in an oil bath at 50–70 °C for 3–24 h with using a magnetic stirrer. The solid products after hydrolysis were separated with a filter. The products were washed with de-ionized water and ethanol and dried at 50 °C in a dry oven for 24 h.

2.2. Synthesis of intercalated complexed octacalcium phosphates

Intercalated complexed octacalcium phosphates were synthesized at 50–70 °C by hydrolysis of α-tricalcium phosphate in presence of dicarboxylic acid, three kinds of dicarboxylic acid, succinic acid, L-aspartic acid and methyl-succinic acid. Reagent grade disodium succinate hexahydrate, sodium L-aspartate monohydrate and methylsuccinate acid were selected. 4.5 mmol of either disodium succinate hexahydrate or sodium L-aspartate monohydrate as a dicarboxylic acid was added into 18 ml of CH_3COOH/CH_3COONa buffer solution. On the contrary, 4.5 mmol of methylsuccinate acid was mixed into CH_3COOH/CH_3COONa buffer and then 6.75 ml of 1N NaOH solution was added into them and adjusted around 4.5–5.5 of a pH. 2.0 mmol of α-tricalcium phosphate was added to their solutions. The hydrolysis was done in an oil bath at 50 °C for 3–12 h with a magnetic stirrer. These products were filtered, washed with de-ionized water and ethanol and then dried.

2.3. Evaluation of products

The powder of dried-well products was identified by X-ray powder diffractometry (XRD) (Rigaku: Rint-2500) at 40 kV and 100 mA with Cu-Kα. The microstructure of octacalcium phosphate and intercalated complexed octacalcium phosphate was observed by scanning electron microscopy (SEM, Hitachi S-800). The high resolution tranmission electron microscopy (TEM, JEOL 2010) was used to examine the detail microstructure of the products.

3. Results and discussion

3.1. Synthesis of octacalcium phosphate without dicarboxylic acid

Table II shows the synthesis condition of octacalcium phosphate. A-series showed the dependence of initial pH in the preparation of octacalcium phosphate. In B-series, the effect of hydrolysis time on the synthesis of octacalcium phosphate was examined at a constant initial pH.

In Fig. 3, the result of XRD about the effect of initial pH on the hydrolysis are shown for the products in A-series. The patterns of the products prepared at the initial pH of 3.9–4.7 for 3 h was in good agreement with the standard peaks of octacalcium phosphate [8]. Therefore, octacalcium phosphate was successfully synthesized in this initial pH range of 3.9–4.7 by this processing in A-series. However, the peaks of the reaction products hydrolyzed at 4.7 of initial pH were slightly broader. These results suggest that the products synthesized at initial pH = 3.9 showed the best crystallinity, as clarified

TABLE I Characteristics of α-tricalcium phosphate powder as a starting material

Ca/P(mol)	Cl	SO_4	Pb	As	Fe	Mg	Mn
1.50	20 ppm	50	5 ppm	1 ppm	10 ppm	50 ppm	20 ppm

TABLE II Synthesis conditions of octacalcium phosphate with CH_3COOH/CH_3COONa buffer

Series	Time (h)	Initial pH	Final pH
A-series	3	3.9	4.9
A-series	3	4.3	5.1
A-series	3	4.7	5.4
B-series	3	4.7	5.4
B-series	4	4.7	5.4
B-series	24	4.7	5.4

in Fig. 3. Octacalcium phosphate was thermodynamically metastable in comparion with hydroxyapatite or brushite ($CaHPO_4 \cdot 2H_2O$), and their formation was significantly dependent on pH and temperature, as pointed out by Monma *et al*. [4] and Newesely [9]. According to the results by Newesely [9], the formation of octacalcium phosphate was limited within a considerably narrow region, strongly dependent on pH and temperature during hydrolysis. Therefore, the formation of octacalcium phosphate was at too high or too low pH to exist stablly, which leads to the existence of an optimum region of pH on hydrolysis. Spencer succeeded in the synthesis of octacalcium phosphate at a slow rate by conducting hydrolysis at 80 °C and pH6 [10]. Also, as pointed out by Monma [4], it was thought that the formation of octacalcium phosphate proceed through the step such that amorphous calcium phosphate ($Ca_3(PO_4)_2 \cdot xH_2O$) precipitated, solute in water, and then transformed to octacalcium phosphate.

Fig. 4 shows the XRD results of products in B-series. XRD patterns of the products prepared in B-series well fitted with the standard peaks of octacalcium phosphate [8]. The components of the products synthesized for 3 and 4 h were pure octacalcium phosphate without other calcium phosphate phases. The product synthesized for 2 h contained not only octacalcium phosphate, but also a small amount of α-tricalcium phosphate powder, suggesting that hydrolysis was not sufficiently finished. In the case of samples prepared by hydrolysis for 24 h, the main peak of $2\theta = 4.70°$, (1 0 0), was confirmed to be broad, compared to that from synthesis for 4 h, which result from the decrease of cystallinity of octacalcium phosphate, and contained a slight amount of hydroxyapatite ($Ca_{10}(PO_4)_6 \cdot (OH)_2$). It was found that too long period of hydolysis of α-tricalcium phosphate inhibits the formation of octacalcium phosphate. In general, octacalcium phosphate is not more stable than hydroxyapatite from a thermodynamic point of view. Furthermore, the supersaturation of octacalcium phosphate is lower than that of hydroxyapatite, as pointed out by Iijima [11]. Iijima *et al*. reported that H^+ and PO_4^{3-} increased with the hydrolysis time and resulted in the decrease of supersaturation of octacalcium phosphate. Therefore, the presence of optimum reaction time on hydrolysis of

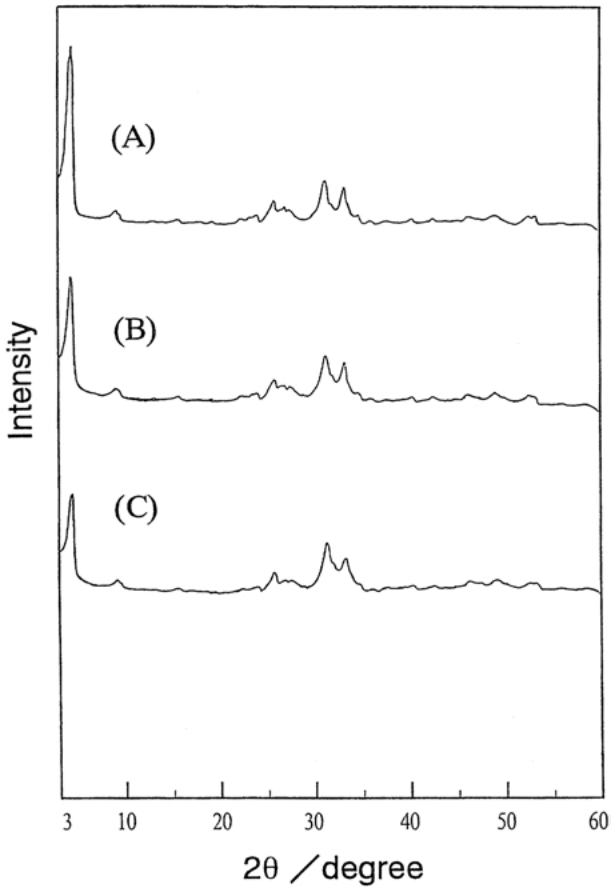

Figure 3 XRD results of products in A-series: (A) pH 3.9, (B) pH 4.3, and (C) pH 4.7.

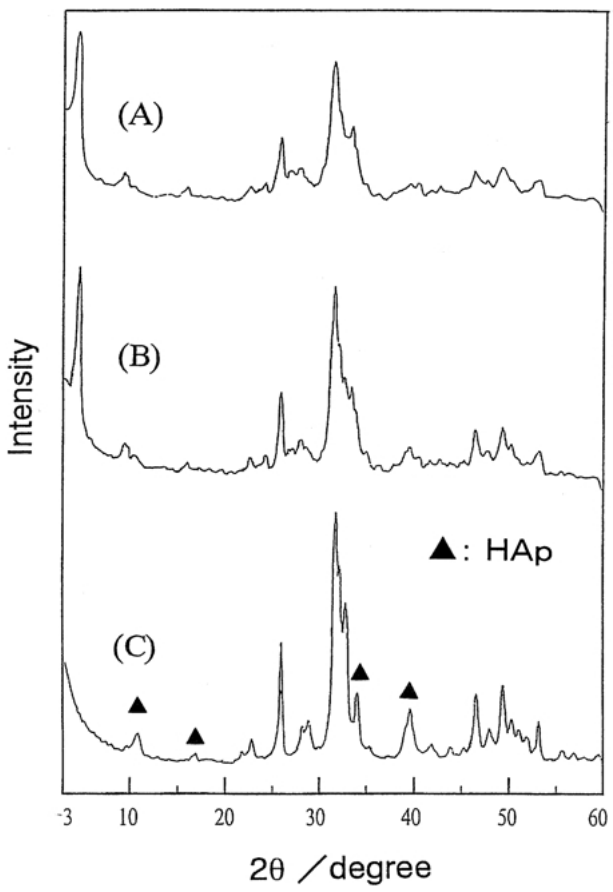

Figure 4 XRD results of products in B-series: (A) 3 h, (B) 4 h and (C) 24 h.

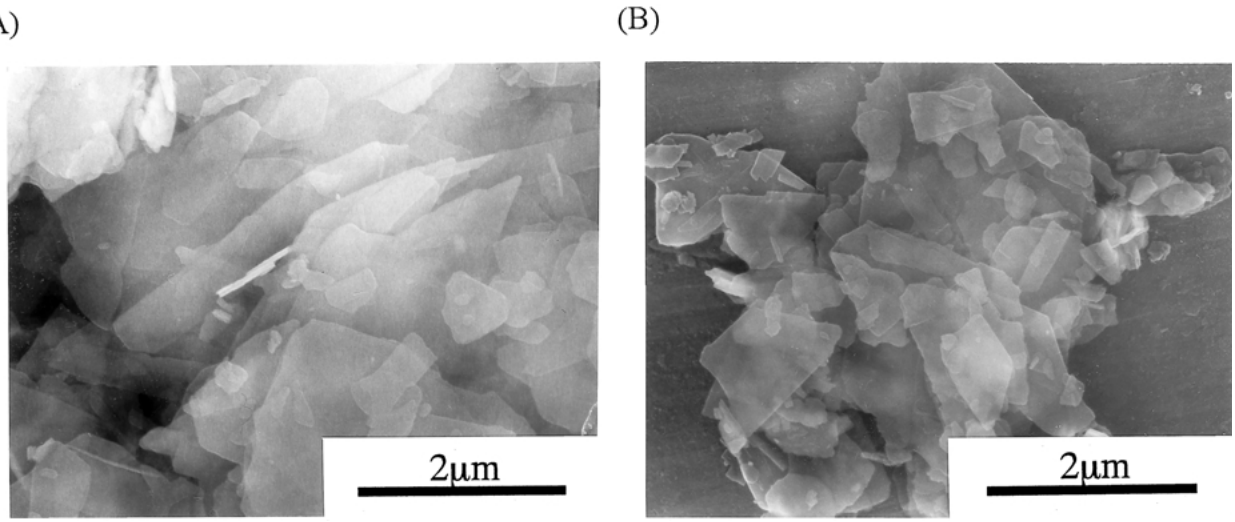

Figure 5 SEM photograph of octacalcium phosphate products obtained at 70 in initial pH of 3.9. (A) 3 h, pH = 3.9; (B) 24 h, pH = 4.7.

α-tricalcium phosphate to octacalcium phosphate is explained by the supersaturation of octacalcium phosphate.

Fig. 5(A) shows the particle morphology of octacalcium phosphate products obtained at 70 °C in initial pH of 3.9, which pattern of XRD was sharpest among all products prepared under the synthesis conditions shown in Table II. From SEM observation, two types of morphology in octacalcium phosphate were observed, very thin plate-like and whisker-like particles. Whisker-like particles with length and diameter of 2 and 0.05 μm, respectively, are thought to grow along the [0 0 1] crystallographic direction of the octacalcium phosphate structure. The size of plate-like particles was 2–3 μm. In plate-like particles, the flat structure was presumed to reflect the basal plane of octacalcium phosphate. However, as shown in Fig. 5(B), the products synthesized for 24 h indicate finer particles. These were mainly thin small plate-like particles, in part mixed with very fine whisker particles.

3.2. Synthesis of intercalated complexed octacalcium phosphates

In this experiment, intercalated complexed octacalcium phosphates were synthesized at 50 °C by hydrolysis of α-tricalcium phosphate in presence of L-aspartic acid, succinic acid, or methyl-succinic acid. The intercalated complexed octacalcium phosphates could not be synthesized at 70 °C. Effect of pH on the synthesis of L-aspartic acid intercalated complexed octacalcium phosphates synthesized at 50 °C were examined under the synthesis conditions shown in Table III.

Fig. 6 shows the XRD results of L-aspartic acid intercalated complexed octacalcium phosphates prepared at 50 °C with various initial pH varying pH of CH_3COOH/CH_3COONa buffer solution. Although patterns of the products were in good agreement with the octacalcium phosphates phase, some of the other phases were detected. At an initial pH of 4.7, the products with L-aspartic acid composed of mainly $CaHPO_4 \cdot 2H_2O$ (DCPD) and partly octacalcium phosphate. On the other hand, the products prepared at pH of 5.5 were a mixture of octacalcium phosphate and hydroxyapatite. Over pH of 5.9, the products were only hydroxyapatite, which result is not shown in Fig. 6. Pure L-aspartic acid intercalated complexed octacalcium phosphates acid was obtained at pH of 5.1. L-aspartic acid intercalated complexed octacalcium phosphates was successfully synthesized by the present processing. However, the region of synthesizing L-aspartic acid intercalated complexed octacalcium phosphates was found to be very narrow, compared with the results of octacalcium phosphate without dicarboxylic acid abovementioned. At the same time, the main peak, $2\theta = 4.70°$, (1 0 0), was confirmed to be broad, compared to that for octacalcium phosphate without dicarboxylic acid. Nevertheless, the crystalinity of L-aspartic acid intercalated complexed octacalcium phosphates obtained in this experiment was not so high. Effect of synthetic temperature on the formation of intercalated complexed octacalcium phosphates was studied. The mono phase of intercalated complexed octacalcium phosphates could not be prepared at 70 °C due to the formation of $CaHPO_4 \cdot 2H_2O$, whereas octacalcium phosphate without dicarboxylic acid were successfully synthesized at 50–70 °C. These results agreed with the report that the pH in the region for synthesizing octacalcium phosphates lowered with the increase of hydrolysis temperature, as

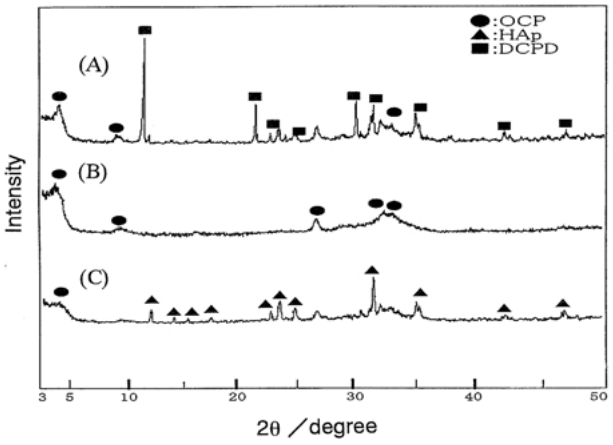

Figure 6 XRD results of L-aspartic acid intercalated complexed octacalcium phosphates prepared at 50 °C with various initial pH varying pH of CH_3COOH/CH_3COONa buffer solution. (A) pH 4.7, (B) pH 5.1 and (C) pH 5.5.

TABLE III Synthesis conditions of intercalated complexed octacalcium phosphates

Dicarboxylic acid	Time (h)	Initial pH	Final pH
L-aspartic acid	3	4.7	5.1
L-aspartic acid	3	5.1	5.7
L-aspartic acid	3	5.5	5.9
Succinic acid	3	5.5	5.9
Methyl succinic acid	3	5.5	5.8

described by Newesely [9]. In the case of L-aspartic acid as a pillar, the steric hindrance by amino group and the electrostatic interaction of amino group with HPO_4^{2-} on the surface of octacalcium phosphates inhibited the intercaration of asparlate between the A layer of octacalcium phosphate. Recently, Markovic *et al*. [12] reported that aminodicarboxylates inhibited the transformation of α-tricalcium phosphate into octacalcium phosphates and aspartate-complexed octacalcium phosphates could not be synthesized. However, in the present experiments for L-aspartic acid intercalated complexed octacalcium phosphates, peak shift of basal plane was observed and the basal spacing was expanded, regardless of the broad peak of basal plane. As L-aspartic acid possess the polar side group such as an amino group and high acid dissociation, it must strongly interact with the A-layer on surface of octacalcium phosphates. Therefore, aspartate was difficult to intercalate between the A-layers of octacalcium phosphates. The elucidation of this mechanism is in progress. The following experiments were performed by hydrolysis of α-tricalcium phosphate in presence of other dicarboxylic acids only at 50 °C.

The effect of other additives on the synthesis of complexed octacalcium phosphates was invesitigated. The products with succinic acid or methyl-succinic acid was synthesized at initial pH of 5.5. In the case of methyl-succinic acid with adding 1 N NaOH solution, the sample was prepared at initial pH of 5.5 at 50 °C. Fig. 7 shows the XRD patterns of complexed octacalcium phosphates synthesized in the presence of succinic acid or methyl-succinic acid and also contains the results of octacalcium phosphate without dicarboxylic acid and L-aspartic acid intercalated complexed octacalcium phosphate. Because the products prepared with succinic acid or methyl-succinic acid were identified to be octacalcium phosphates, complexed octacalcium phosphates were found to be successfully synthesized by the present experimental procedure. This result means the possibility that both decarboxylic acids are incorporated in the hydrated layer of octacalcium phosphates structure. The main peak of $2\theta = 4.70°$ for succinic acid complexed octacalcium phosphates was sharper than that of methyl-succinic acid complexed octacalcium phosphates. However, both products showed much sharper peaks, compared to those of L-aspartic acid intercalated complexed octacalcium phosphates.

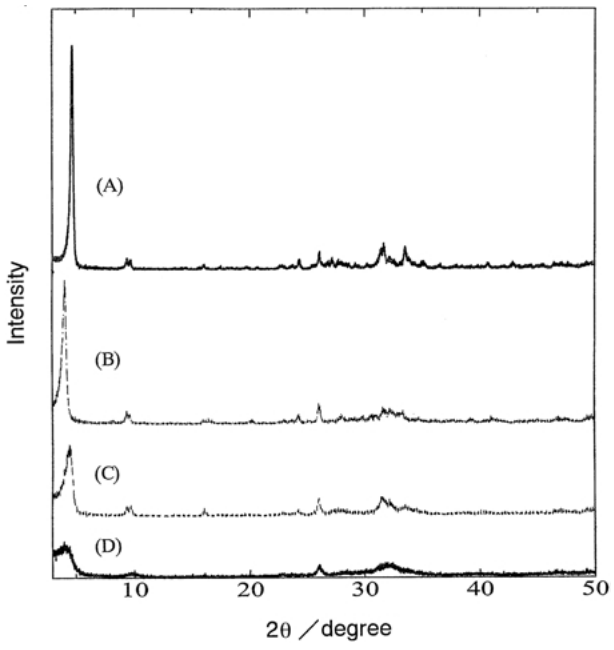

Figure 7 XRD patterns of octacalcium phosphates, succinic acid, methyl-succinic acid and L-aspartic acid intercalated complexed octacalcium phosphates. (A) OCP, (B) succ-OCP, (C) methyl succ-OCP and (D) L-asp-OCP.

Fig. 8 shows SEM photographs of succinic acid, methyl-succinic acid and L-aspartic acid intercalated complexed octacalcium phosphates. The microstructure of succinate-complexed octacalcium phosphates showed platelet and whisker-like particle as well as octacalcium phosphate without dicarboxylic. However, the morphology for products of succinic acid-complexed octacalcium phosphates were finer than that of octacalcium phosphate without dicarboxylic acid. The particle of methyl succinic-complexed octacalcium phosphates were whisker-like with small aspect ratio, never with the morphology of platelets. On the contrary, L-aspartic-complexed octacalcium phosphate was quite fine and granular, without whisker-like and platelet morphology. The results of observation for L-aspartic acid-complexed octacalcium phosphate suggest a low evolution of crystal, that is, crystallinity, compared with octacalcium phosphate without dicarboxylic acid, succinic acid and methyl-succinic acid intercalated complexed octacalcium phosphates. The features of microstructural observation by SEM were found to be in good accordance with the XRD results.

The basal spacing of various octacalcium phosphates obtained in the present experiments was evaluated from the reflection of (1 0 0). The angle of main peak, (1 0 0), shifted to lower angle for octacalcium phosphates prepared by the hydrolysis in the dicarboxylic acids, which shows an expansion in basal spacing. The basal spacings of various octacalcium phosphate in this experiment are summarized in Table IV. The interplanar spacing of succinic acid and L-aspartic acid intercalated complexed octacalcium phosphates increased, compared with that of octacalcium phosphate without dicarboxylic acid. On the other hand, methyl-succinic acid inter-

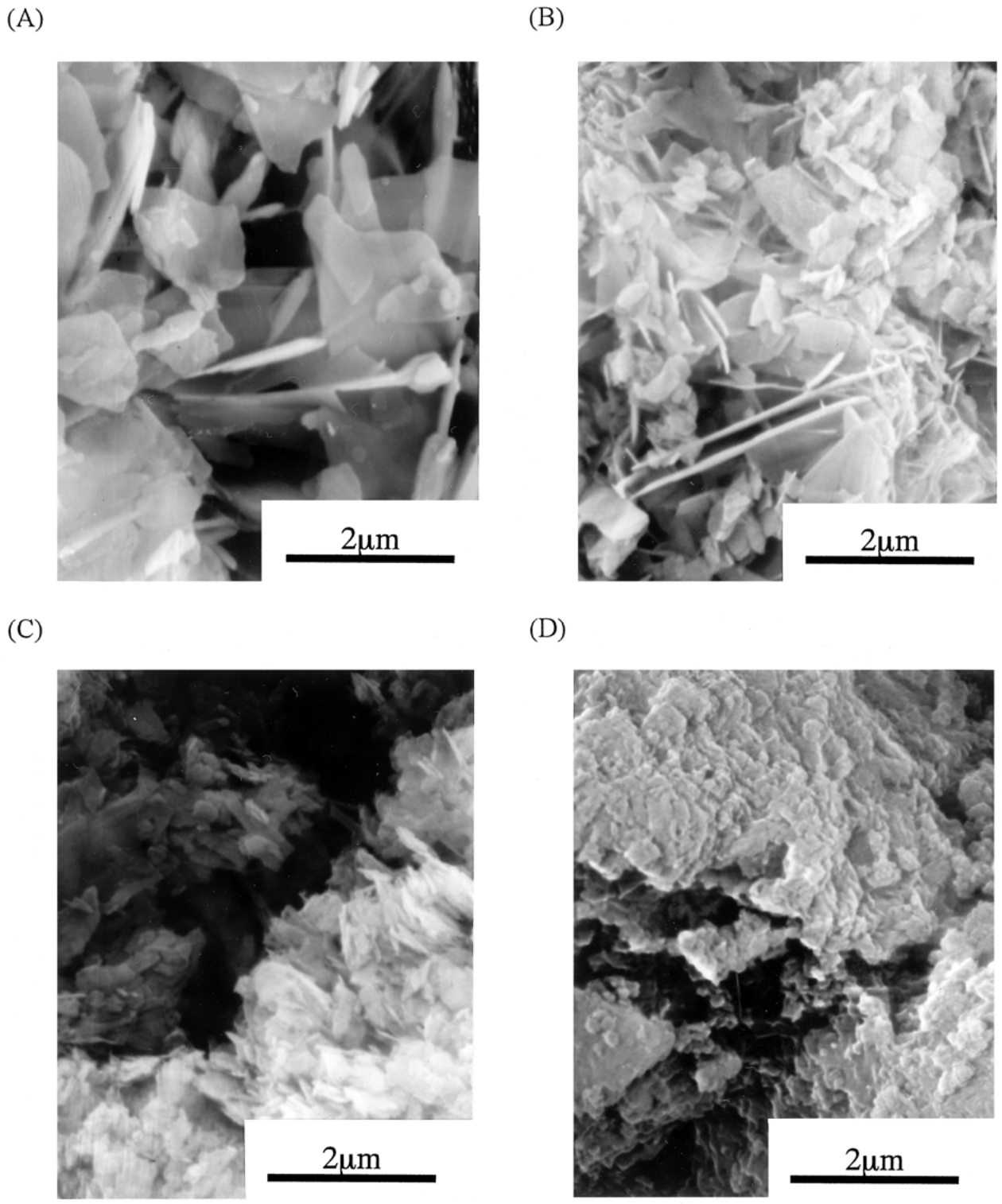

Figure 8 SEM photographs of succinic acid, methyl-succinic acid and L-aspartic acid intercalated complexed octacalcium phosphates. (A) OCP, (B) succ-OCP, (C)met-succ-OCP and (D) L-asp-OCP.

calated complexed octacalcium phosphates showed a smaller expansion of interplanar spacing. This result suggests that the presence of methyl group of dicarboxylic acid inhibited the intercalation of methyl-succinic acid into the octacalcium phosphate structure. Monma *et al*. [13] reported that the zig-zag organic group (–OOCRCOO–, R(organic group):CH_2–CH = CH–CH_2) tended to be easily intercalated into an octacalcium phosphate structure. As the presence of methyl group decreases the structural symmetry of dicarboxylic acid intercalated into octacalcium phosphates, it is thought that the increase of basal spacing of methyl-succinic acid intercalated complexed octacalcium phosphates is small. Nevertheless, these results suggested that the succinic acid, L-aspartic acid, and methyl succinic acid can be successfully intercalated into an octacalcium phosphate structure. High resolutional images of octacalcium phosphate without dicarboxylic acid and succinic acid intercalated complexed octacalcium phosphate are shown in Fig. 9(A) and (B), respectively. The lamellar

TABLE IV Interplanar spacing for intercalated complexed octacalcium phosphates

	OCP	Succ-OCP	Met-succ-OCP	L-asp-OCP
2θ	4.73°	4.07°	4.48°	4.13°
Spacing (Å)	18.7	21.7	19.7	21.4

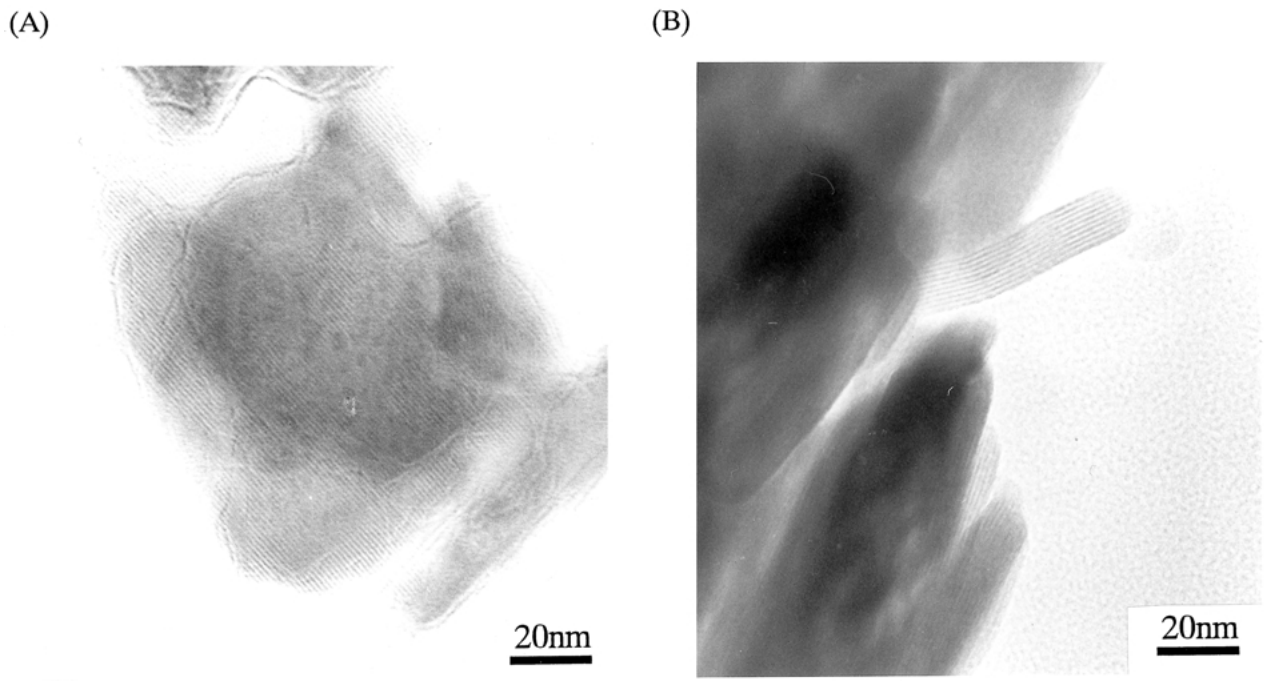

Figure 9 TEM and HREM images of octacalcium phosphate without dicarboxylic acid, L-aspartic acid and succinic acid intercalated complexed octacalcium phosphate. (A) OCP and (B) succ-OCP.

structure with approximately 2.0 nm in space was observed for octacalcium phosphate without dicarboxylic acid, which spacing was as well as the value from XRD results. Succinic acid intercalated complexed octacalcium phosphate showed also the lamellar structure with approximately 2.2 nm. Both products were relatively stable in high vacuum under the electron beam irradiation. However, L-aspartic acid intercalated complexed octacalcium was too unstable under the electron beam irradiation to allow imaging, although their lamellar structure could be observed.

Monma *et al*. [5] reported that succinic acid-complexed octacalcium phosphates can be synthesized by conducting the hydrolysis of 0.5 M α-tricalcium phosphate powder in the 0.25 M succinate ions at 40 °C and showed the expansion in basal spacing from 18.7 to 21.5 Å. The succinic acid-complexed octacalcium phosphate prepared in this experiment indicated the nearly same basal spacing as that by Monma, in spite of the different hydrolyses condition. This result shows that HPO_4^{2-} in a pure octacalcium phosphate is replaced by $C_4H_4O_4^{2-}$ of the A-layer for succinate-complexed octacalcium phosphate. However, in the case of addition of methyl succinic acid, the shift in basal plane is small and the expansion of basal spacing limited, as compared with succinate-complexed octacalcium phosphates, whose spacing was 19.7 Å. Formerly, Monma showed that the octacalcium phosphate intercalated methyl-succinate ions as a pillar and resulted in the basal spacing of 20.4 Å. However, using methyl succinic acid as a pillar the peak intensity decreased and its peak angle hardly shifted. The reason for the difficluty of replacement of HPO_4^{2-} by dicarboxylate ions with methyl group should arise from a side group such as hydrophobic methyl group which hinders the intercalation in an octacalcium phosphate structure.

4. Conclusion

Octacalcium phosphate without dicarboxylic acid was synthesized by conducting hydrolysis of α-tricalcium phosphate through a wet-chemical processing. The synthesis of some complexed octacalcium phosphates were attempted by a wet-chemical processing in presence of various dicarboxylic acids. XRD results suggested that L-aspartic acid, succinic acid or methyl-succinic intercalated complexed octacalcium phosphates were successfully synthesized by the present processing. Succinic acid or methyl-succinic intercalated complexed octacalcium phosphates showed the same crystallinity as octacalcium phosphate without dicarboxylic acid. However, the crystallinity of L-aspartic acid intercalated complexed octacalcium phosphates was lower than those of succinic acid or methyl-succinic intercalated complexed octacalcium phosphates.

The interplanar spacing of L-aspartic acid and succinic acid intercalated complexed octacalcium phosphates increased, whereas methyl-succinic acid intercalated complexed octacalcium phosphates showed a smaller expansion of interplanar spacing due to the decrease of structural symmetry by the presence of methyl group of dicarboxylic acid. In the case of L-aspartic acid

intercalated complexed octacalcium phosphates, the reason of lower crystallinity is explained by the presence of polar side groups such as an amino group and acid dissociation with a strong interaction of the A-layer on the surface of octacalcium phosphates.

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Received 15 August
and accepted 1 November 2000