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Effect of fluoride on apatite formation from $Ca_4(PO_4)_2O$ in 0.1 mol L^{-1} KH_2PO_4

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The effect of fluoride on the hydrolysis of tetracalcium phosphate (TTCP; $Ca_4(PO_4)_2O$) was investigated in 0.1 mol $l^{-1}$$KH_2PO_4$ containing 0–83 mol l^{-1} KF. Characterization of the final apatite phase formed by the hydrolysis was made with X-ray diffraction and SEM. The initial pH was between 4.5 and 5.4, depending on the solutions, and the pH rapidly increased and was kept constant between 7.3 and 6.5. An increase in KF concentration tended to lower the pH in the final stage of hydrolysis. The calcium concentration was considerably lower than the phosphorus concentration throughout the reaction. The fluoride concentration decreased shortly after the start of hydrolysis. The hydrolysis of TTCP in 0.1 mol l^{-1} KH_2PO_4 proceeded to form hydroxyapatite via DCPD when the KF concentration was low. The hydrolysis product was a calcium-deficient non-stoichiometric hydroxyapatite with a Ca/P ratio of about 1.5. With an increase in the KF concentration in the 0.1 mol l^{-1} KH_2PO_4 solution, TTCP directly transformed into hydroxyapatite containing F^- ions or fluorapatite and with improved crystallinity. The addition of fluoride in the solution initially accelerated the formation of apatite. However, the layer of newly formed apatite adhering to the TTCP particles retarded TTCP dissolution; as a result, hydrolysis was delayed. IR analysis showed that the apatite phase contained HPO_4^{2-} ions in the structure. The formula for the hydrolysis product of TTCP in the presence of fluoride can be expressed as follows: $Ca_{10-x}(HPO_4)_x(PO_4)_{10-x}(OH)_{2-x-y}F_y$.

1. Introduction

Recently, there have been many reports on calcium phosphate cements as materials for repairing hard tissue defects. In particular, a calcium phosphate cement consisting of an equimolar mixture of tetracalcium phosphate (TTCP), $Ca_4(PO_4)_2O$ and dicalcium phosphate (DCPA), $CaHPO_4$ or dicalcium phosphate dihydrate (DCPD), $CaHPO_42H_2O$, has excellent biocompatibility because it hardens to form hydroxyapatite (OHAp), $Ca_5(PO_4)\ _3OH$, without any by-product, illustrated by the equation [1–3]

$$CaHPO_4 + Ca_4(PO_4)_2O \rightarrow Ca_5(PO_4)_3OH \quad (1)$$

Several reports on the setting mechanism of the cement have been published [4–10]. It was reported that TTCP was fully consumed within 12 h in a cement mixture with a 2:1 DCPA:TTCP ratio in NaH_2PO_4 or Na_2HPO_4 solutions and that the rate of hydroxyapatite formation was governed by the dissolution rate of DCPA [8]. It was shown in a previous study [11] that DCPA was consumed within the first several hours while TTCP still remained, the TTCP hydrolysed later to form OHAp. Consequently, although the overall reaction was expressed by Equation 1, the reaction rate seemed to depend on the hydrolysis rates of both DCPA and TTCP.

There are only a few reports on the hydrolysis of TTCP [12, 13] or DCPA [14]. We have previously investigated the hydrolysis process of TTCP in a 0.01–0.1 mol l^{-1} phosphoric acid (H_3PO_4) and potassium dihydrogen phosphate (KH_2PO_4) solution [15]. In the 0.1 mol l^{-1} H_3PO_4 solution that had a low pH, TTCP rapidly converted to DCPD within a few minutes. In the KH_2PO_4 solutions, the hydrolysis of TTCP proceeded to form calcium-deficient hydroxyapatite. The hydrolysis rate was greatest in the 0.1 mol l^{-1} KH_2PO_4 solution in which the hydroxyapatite was formed through DCPD as an intermediate.

It has been reported that the formation of OHAp from the calcium-containing compounds such as DCPD or octacalcium phosphate (OCP), $Ca_8H_2(PO_4)_65H_2O$, in solution was accelerated by fluoride [16–18]. Fluoride also promoted TTCP hydrolysis to form an apatite phase [13]. Fulmer and Brown [19] showed that the kinetics of apatite formation in a 2:1 mixture of DCPA and TTCP

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depended on the liquid-to-solids ratio in the presence of fluoride. In their study, the apatite formation was accelerated at higher fluoride concentrations, but it was retarded at lower fluoride concentrations at a liquid : solid ratio of 100. However, the apatite formation was accelerated regardless of fluoride concentration at the low liquid : solid ratio of 1.

To understand these differences fully in the effects of fluoride on the setting reaction of the calcium phosphate cement, it is necessary to investigate the effect of fluoride on the hydrolysis of TTCP. In the present study, we investigated the hydrolysis of TTCP in 0.1 mol l^{-1} KH_2PO_4 solutions containing various concentrations of potassium fluoride (KF) and the effects of fluoride concentration on apatite formation. We characterized the final apatite phase formed at the various concentrations of fluoride.

2. Materials and methods

TTCP was prepared by heating an equimolar mixture of DCPA and calcium carbonate at 1500 °C for 6 h. An X-ray diffraction pattern (XRD) showed no phase other than TTCP. Particle size was measured with a particle size analyser (SA-CP3, Shimadzu, Columbia, MD). The TTCP had an average particle size of about 10 μm.

The hydrolysis experiment was done in 0.1 mol l^{-1} KH_2PO_4 solutions containing various concentrations of KF, from 0–83 mmol l^{-1}. TTCP (2 g) was placed into 100 ml solution kept at 37 °C and under constant stirring. Decarbonated nitrogen gas was passed through the solution during the experiment. The solution pH was continuously monitored with the use of glass reference electrodes connected to a pH meter (F-7ss, Hitachi-Horiba, Japan). At appropriate time intervals, 2 ml solution were extracted with a pipette and filtrated with a membrane filter (0.2 μm). Quantitative analyses of calcium, phosphorus and fluorine in the filtrate were made by atomic absorption analysis (AA-640, Shimadzu, Japan), spectrophotometry (U-best 50, JASCO, Japan) and a fluoride ion-selective electrode (Model 901, Orion Research Inc. Cambridge, MA), respectively. The solid residue was washed with distilled water and then with ethanol. X-ray diffraction (Rint 2500V, Rigaku, Japan) and infrared analyses (260-30, Hitachi, Japan) were carried out to characterize the hydrolysis product. The crystallite size, D, of OHAp was calculated based on Scherrer's equation, $D = K\lambda/\beta\cos\theta$, where λ is the wavelength of the X-ray used ($\mathrm{Cu}K_{\alpha_1}$ 0.154 05 nm), β the extent of broadening of a diffraction peak, θ the Bragg angle, and K a constant (1.05). Integral half-width, β, was used for the calculation after correction of the broadening by K_{α_2} and an instrumental factor. The lattice parameters of the apatite phase were also determined by the least-squares method using several diffraction peaks at 2θ between 20° and 55°. An external standard of polycrystalline silicon was used for the correction of 2θ to eliminate systematic error.

The product was also examined by scanning electron microscopy (JSM-5400LV, Jeol, Japan) to observe morphological changes during the hydrolysis.

3. Results and discussion

3.1. The hydrolysis process of TTCP in the presence of KF

Fig. 1 shows the change in pH during hydrolysis of TTCP in a 0.1 mol l^{-1} KH_2PO_4 solution with various KF concentrations. The initial pH was between 4.5 and 5.4, depending on the solutions, and the pH rapidly increased immediately after the addition of TTCP. Afterwards, the solution pH was kept constant between 7.3 and 6.5. An increase in KF concentration tended to cause a lower pH in the final period of hydrolysis. Fig. 2a–c show the changes in calcium, phosphorus and fluoride concentrations during hydrolysis. The calcium concentration was much lower than the phosphorus concentration throughout the reaction. With the solution containing no KF, the phosphorus concentration rapidly decreased to 60 mmol l^{-1} within 1 h, and it remained constant afterwards. The rapid decrease in phosphorus concentration was probably caused by the formation of DCPD, as reported previously [15]. With increasing KF concentration, the extent of the phosphorus concentration decrease became smaller. In solutions that contained 60 and 83 mmol l^{-1} KF, initially the phosphorus concentration increased, and the fluoride concentration decreased upon addition of TTCP, as shown in Fig. 2c.

Fig. 3 shows the changes in the solid phase during the hydrolysis reaction. In the absence of fluoride, DCPD was formed initially; the amount formed reached a maximum at 0.5 h and the DCPD disappeared after 4 h. This result is consistent with the changes in the phosphorus concentration during the hydrolysis, as shown in Fig. 2b, i.e. phosphate ions were consumed by the formation of DCPD. The conversion of TTCP to apatite was more than 90% at 8 h and 100% by 24 h. With an increasing concentration of KF, the DCPD formation was inhibited and the hydrolysis of TTCP was delayed. In the solution containing 23–83 mmol l^{-1} KF, TTCP directly converted to apatite without the intermediate DCPD formation. The phenomenon corresponded well to the change in phosphorus concentration in the solution. As pre-

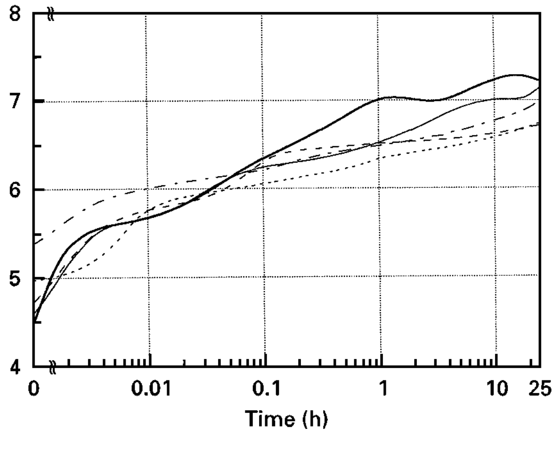

Figure 1 Change in pH during the hydrolysis of TTCP in a 0.1 mol l^{-1} KH_2PO_4 solution containing (—) 0, (—) 11, (– – –) 23, (– · –) 60 and (- - -) 83 mmol l^{-1} KF.

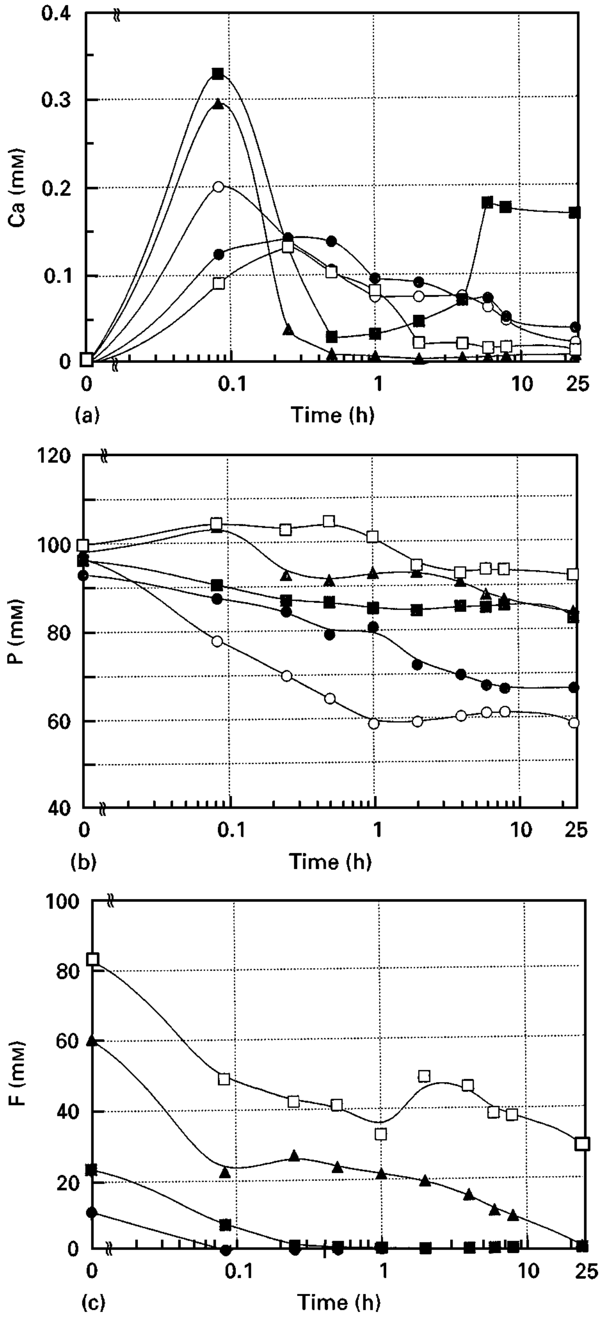

Figure 2 Changes in (a) calcium (b) phosphorus, and (c) fluoride concentration during the hydrolysis of TTCP in a 0.1 mol l^{-1} $\mathrm{KH_2PO_4}$ solution containing (○) 0 mmol l^{-1}, (●) 11 mmol l^{-1}, (■) 23 mmol l^{-1}, (▲) 60 mmol l^{-1} and (□) 83 mmol l^{-1} KF.

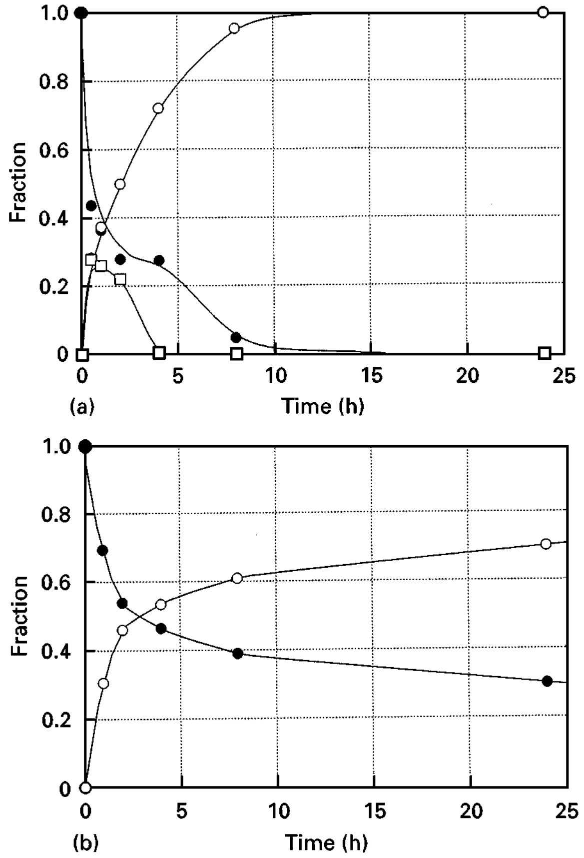

Figure 3 Change in fraction of the phases in the solid residues during the hydrolysis of TTCP in (a) 0.1 mol l^{-1} $\mathrm{KH_2PO_4}$ and (b) 0.1 mol l^{-1} $\mathrm{KH_2PO_4}$ + 83 mmol l^{-1} KF. (●) TTCP, (○) OHAp, (□) DCPD.

viously mentioned, the phosphorus concentration increased once after the start of the reaction, indicating that dissolution of TTCP occurred. The dissolution of TTCP was also presumed by the fact that the calcium concentration showed a maximum within several minutes. A decrease in fluoride concentration suggested that $\mathrm{F^-}$ ions were incorporated into the hydrolysis products [20]. It was reported that calcium phosphate compounds absorbed $\mathrm{F^-}$ ions to form fluorapatite (FAp) and/or calcium fluoride ($\mathrm{CaF_2}$), depending on the fluoride concentration [16]. The overall $\mathrm{F^-}$ ion uptake by the hydrolysis product was between 1.1 and 6 mmol l^{-1} TTCP, and it increased with KF concentration. The theoretical amount of fluoride uptake is 4.37 mmol l^{-1} when a stoichiometric FAp was formed from 2 g TTCP. Therefore, at high KF concentrations, the fluoride uptake was slightly larger than the theoretical value. This suggests that some of the $\mathrm{F^-}$ ions were incorporated to form $\mathrm{CaF_2}$. The formation of $\mathrm{CaF_2}$ was not confirmed by X-ray diffraction in this study. However, it was reported that the required fluoride concentration for $\mathrm{CaF_2}$ precipitation was 6 mmol l^{-1} at pH 7.5 and 19 mmol l^{-1} at pH 10 in the solution saturated with OHAp [21]. In this study, although the fluoride concentration decreased rapidly as soon as the reaction started, the concentration remained over 10 mmol l^{-1} during the hydrolysis reactions with high KF concentrations.

Hydrolysis of TTCP was apparently delayed in the presence of KF in the solution. However, initial apatite formation seemed to be the same as in the solution containing no KF. Fig. 4 shows scanning electron micrographs of the hydrolysis product in 0.1 mol l^{-1} $\mathrm{KH_2PO_4}$ solution with 0 and 83 mmol l^{-1} KF. According to the XRD results, the samples shown in Fig. 4c and e consisted of the apatite phase only. It was observed that thin plate-like crystals of OHAp were formed in the fluoride-free 0.1 mol l^{-1} $\mathrm{KH_2PO_4}$ solution (Fig. 4c and d), but fine granular crystals were formed on the surface of the original TTCP particles in the solution containing 83 mol l^{-1} KF (Fig. 4e and f). In the scanning electron micrograph for the samples after hydrolysis for 30 min in the fluoride-free 0.1 mol l^{-1} $\mathrm{KH_2PO_4}$ solution (Fig. 4b), many rectangular-shaped crystals with a width of

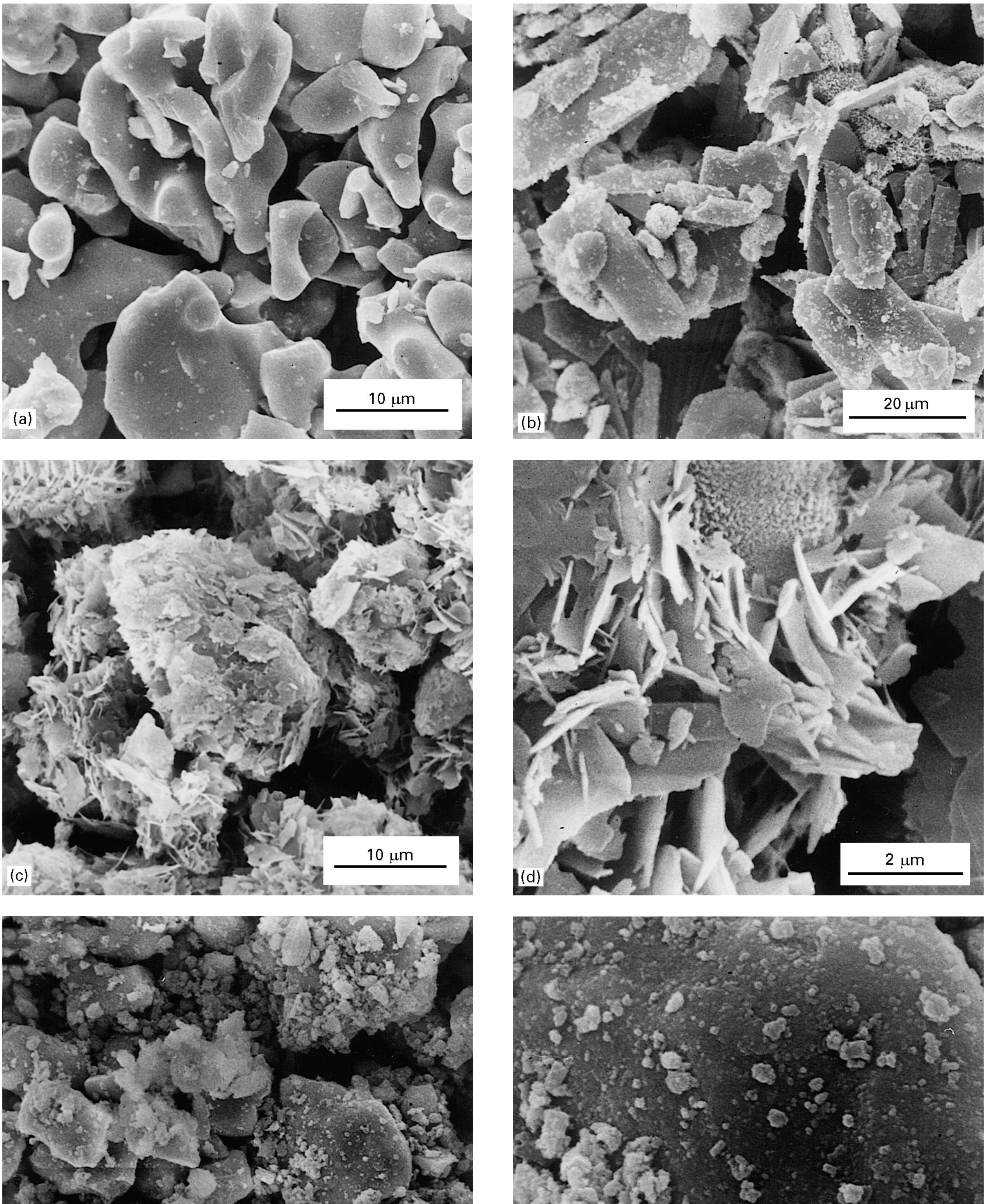

Figure 4 Scanning electron micrographs of (a) the original TTCP particles, and the product after hydrolysis in 0.1 mmol l^{-1} KH_2PO_4 for (b) 0.5 h and (c, d) 8 h, and (e, f) in 0.1 mol l^{-1} KH_2PO_4 + 83 mmol l^{-1} KF for 7 d.

10 μm or less were observed. These crystals were identified as DCPD.

As shown in Fig. 2c, the fluoride uptake by TTCP in the F^--containing solutions was nearly completed within several hours. Moreover, XRD analysis showed that about 0.4 mass fraction of TTCP still remained at that time. SEM observations showed that an apatite layer formed on the surface of TTCP particles at the initial stage of hydrolysis. Thus, dissolution of TTCP was delayed by the apatite layer. It was also reported that transformation of OCP to FAp in the NaF solution was controlled by diffusion of F^- or PO_4^{3-} ions through the FAp layer formed on the OCP particles [16]. Apparently, the delay in the hydrolysis of TTCP in the presence of F^- was also caused by the same mechanism.

3.2. Characterization of the final hydrolysis product

Fig. 5 shows XRD patterns of the final apatite phase formed in the solutions with various KF concentrations. Fig. 6 shows the lattice parameters (*a* and *c*) of the hexagonal apatite phase. The standard error of the obtained values was large with the apatite formed at lower concentrations of KF because the diffraction peaks were poorly resolved (Fig. 5). The *c*-axis length was not significantly changed with KF concentration, and it was close to the reported values of 0.6882 nm for the synthetic stoichiometric OHAp and 0.688 nm for the synthetic FAp [22]. However, the *a*-axis length significantly decreased with KF concentration. At lower KF concentrations, the *a*-axis length was around 0.944 nm, which was close to the reported value for stoichiometric OHAp ($a = 0.9438$ nm) [22]. The *a*-axis length of synthetic FAp was reported to be 0.9382 nm [22]. The apatite formed in the solution containing 83 $\text{mmol}\,l^{-1}$ KF has an *a*-axis length of 0.940 nm, which is slightly larger than that of the FAp. The *a*-axis length of synthetic apatite decreased linearly with fluoride content (ca. 0.0017 nm per 0.01 mass fraction of fluoride) [23]. The results suggested that F^- ions were incorporated into the apatite phase, but even at the highest concentration of KF, stoichiometric FAp was not formed. As discussed later, the apatite formed in this study also contained HPO_4^{2-} in its structure; the HPO_4^{2-} ions also affected the lattice parameters [24]. The *a*-axis increased and the *c*-axis decreased with the HPO_4^{2-} content. The change in the *a*-axis was larger than that in *c*-axis and was about 0.00015 nm per 0.01 mass fraction of HPO_4. Although quantitative determination of the HPO_4^{2-} content in the apatite formed was not done in this study, the HPO_4^{2-} ions would also contribute to the lattice parameters shown in Fig. 6. However, the *a*-axis of the apatite formed in the 83 $\text{mmol}\,l^{-1}$ KF solution seemed to be large for the fluoride constant calculated from the fluoride uptake shown in Fig. 2c. This fact also indicates the formation of CaF_2 during hydrolysis, as mentioned earlier. With increasing KF concentration, the diffraction peaks became sharper, indicating an improvement in the crystallinity of the apatite (Fig. 5). Fig. 7 shows the crystallite size of the *c*-direction calculated from the half-width of the 0 0 2 diffraction peak. The crystallite size increased with increasing KF concentration.

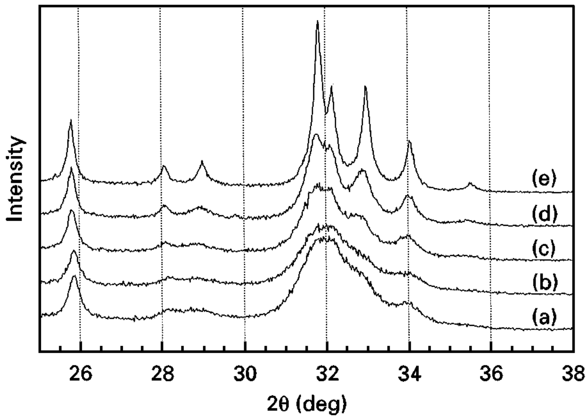

Figure 5 X-ray diffraction patterns for the apatite phase formed by the hydrolysis of TTCP in a 0.1 $\text{mol}\,l^{-1}$ KH_2PO_4 solution containing (a) 0 $\text{mmol}\,l^{-1}$ KF for 7 d, (b) 11 $\text{mmol}\,l^{-1}$ KF for 4 d, (c) 23 $\text{mmol}\,l^{-1}$ KF for 10 d, (d) 60 $\text{mmol}\,l^{-1}$ KF for 7 d, and (e) 83 $\text{mmol}\,l^{-1}$ KF for 10 d.

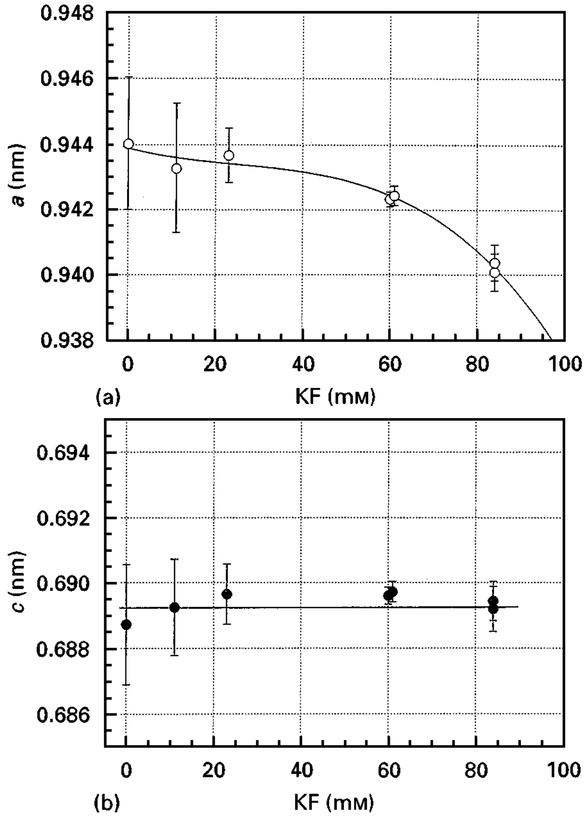

Figure 6 (a, b) Lattice parameters (*a*-and *c*-axes) of the final apatite phase formed by the hydrolysis of TTCP at various KF concentrations.

Fig. 8 shows the Ca/P molar ratio of the apatite phase. When the KF concentration was low, the ratio was about 1.5, indicating that a non-stoichiometric OHAp was formed. As the KF concentration increased, the ratio became greater than 1.6, which was close to the ratio of 1.67 for stoichiometric apatite. Fig. 9 shows IR spectra for the final apatite phase. At a low concentration of KF, a weak shoulder appears at around 640 cm^{-1}, which was assigned to an OH group in the apatite [25]. However, as the KF concentration increased, the shoulder band disappeared, suggesting the formation of FAp. The FAp formation coincided with the increase in crystallinity of the apatite phase and the increase in the Ca/P ratio with the solution containing a higher KF concentration. On the other hand, an absorption band appeared

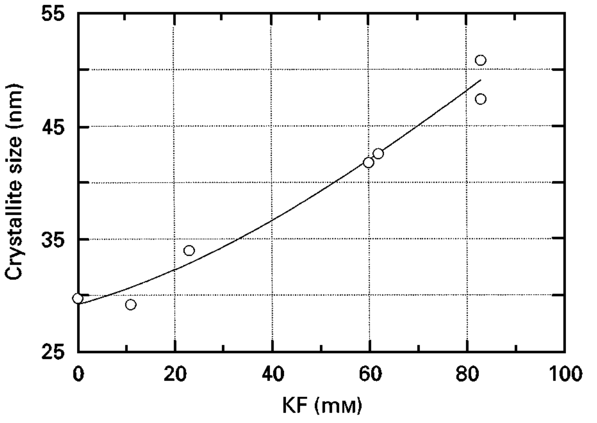

Figure 7 Crystallite size of the *c*-direction of the apatite calculated from the 0 0 2 diffraction peak.

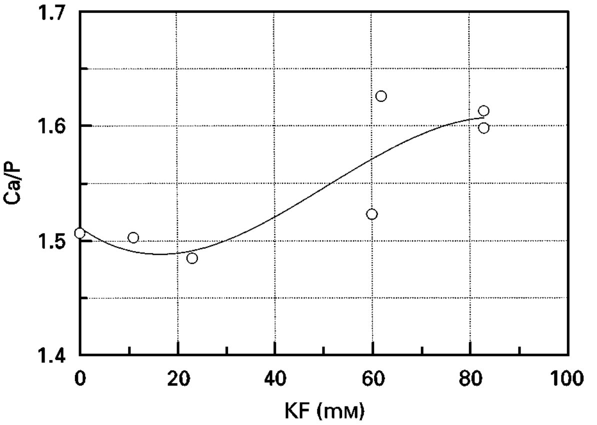

Figure 8 Ca/P molar ratio of the apatite.

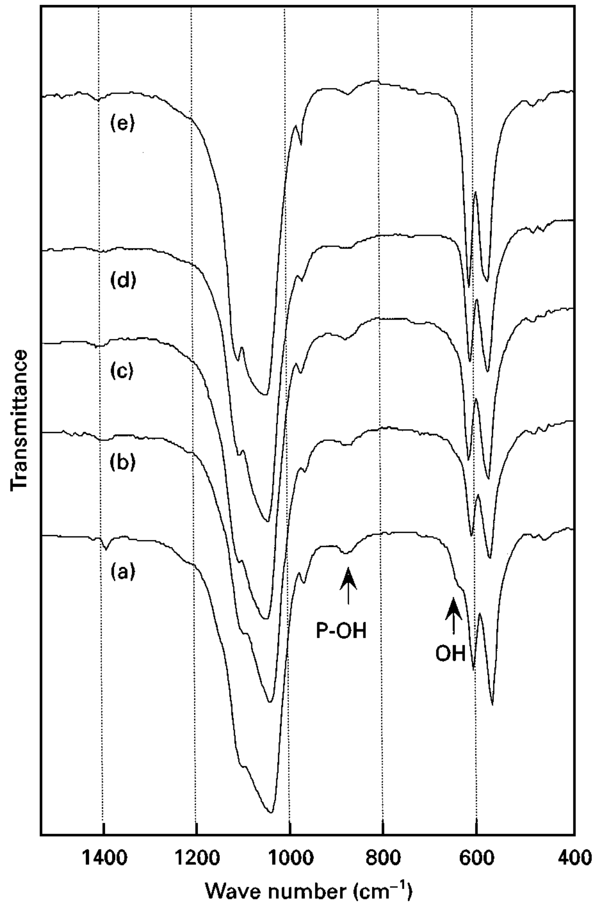

Figure 9 Infrared spectra for the apatite phase formed by the hydrolysis of TTCP in a 0.1 mol l^{-1} KH_2PO_4 solution containing (a) 0 mmol l^{-1}KF for 7 d, (b) 11 mmol l^{-1}KF for 4 d, (c) 23 mmol l^{-1} KF for 10 d, (d) 60 mmol l^{-1} KF for 7 d, and (e) 83 mmol l^{-1} KF for 10 d.

around 870 cm^{-1} in all samples. The band was assigned to the P–OH deformation vibration [25], suggesting that the apatite contained HPO_4^{2-} ions in the structure. This was why the Ca/P ratio was always lower than the stoichiometric ratio. It was reported that about 0.02 mole fraction of HPO_4^{2-} ions of the total phosphate in the synthetic apatite was adsorbed on to the crystal surface [26]. This should be taken into account in the determination of the exact composition of the lattice formula of the fluorohydroxyapatite. The substitution of HPO_4^{2-} ions for PO_4^{3-} ions in the lattice caused a calcium ion deficiency to achieve electroneutrality balance. Thus a formula of calcium-deficient apatite containing fluoride can be expressed as $Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x-y}F_y$. The values of x and y would strongly depend on the conditions of synthesis. Determination of x and y in the various conditions, warrants further study.

4. Conclusion

The hydrolysis of TTCP in 0.1 mol l^{-1} KH_2PO_4 proceeded to form OHAp via DCPD when the KF concentration was zero. The hydrolysis product was a calcium-deficient non-stoichiometric OHAp with a Ca/P ratio of about 1.5. With increasing KF concentration in the 0.1 mol l^{-1} KH_2PO_4 solution, TTCP directly transformed into a OHAp that contained F^- ions or FAp with improved crystallinity. Addition of fluoride to the solution initially accelerated the formation of apatite. However, the apatite that formed on the TTCP crystals retarded dissolution of the TTCP particles and as a result, the hydrolysis was delayed at the later stage of the hydrolysis reaction.

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