JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE **10** (1999) 99–109

Physical properties and self-setting mechanism of calcium phosphate cements from calcium bis-dihydrogenophosphate monohydrate and calcium oxide

P. BOUDEVILLE*, S. SERRAJ, J.-M. LELOUP, J. MARGERIT‡, B. PAUVERT, A. TEROL
Laboratoire de Chimie Générale et Minérale, Faculté de Pharmacie, 15 avenue Charles Flahault, and ‡Faculté d'Odontologie, 4 bis boulevard Henri IV, Université de Montpellier, 34000 Montpellier, France.

An apatitic calcium phosphate cement was developed from calcium *bis*-dihydrogenophosphate monohydrate (or monocalcium phosphate monohydrate, MCPM) and calcium oxide (CaO). The powder had a Ca/P molar ratio of 1.67, and the liquid was either pure water or 0.25 M–1 M sodium phosphate buffer, pH 7.4. The influence of the powder-to-liquid (P/L) ratio on the setting time and the mechanical strength were studied. The best results were obtained for the 1 M phosphate buffer with a P/L ratio of 1.53; the setting time was 7 min and the compressive strength was 25 MPa after 24 h and 33 MPa after 11 d. The mechanism and kinetics of the setting reaction were investigated by X-ray diffraction, differential scanning calorimetry, ^{31}P magic angle spinning–nuclear magnetic resonance and infrared spectrometry. The setting reaction was found to be biphasic: in the first step, during the mixing time, MCPM reacted with CaO immediately to give calcium hydrogenophosphate dihydrate (or dicalcium phosphate dihydrate, DCPD) which, in the second step, reacted more slowly with the remaining CaO to give hydroxyapatite. The conversion of the starting materials to hydroxyapatite was complete within 24 h when the liquid was water, but was slower and incomplete with the phosphate buffers. Of the starting materials, 30% remained after 3 d. © 1999 Kluwer Academic Publishers.

1. Introduction

A calcium phosphate cement (CPC), term introduced by Gruninger *et al.* [1], is essentially made up of calcium phosphates. CPC has attracted much attention in medicine and dentistry because of its excellent biocompatibility and bone-replacing behaviour over long periods of time [2, 3]. CPCs are obtained by an acid–base reaction in water between an acid calcium phosphate and a basic calcium phosphate, which gives a calcium phosphate with intermediate basicity. Generally, hydroxyapatite is the desired end product, because tooth and bone minerals are, in fact, impure forms of hydroxyapatite. The following compounds can be used as starting materials to produce CPCs: orthophosphoric acid (PA), monocalcium phosphate monohydrate (MCPM: $Ca(H_2PO_4)_2H_2O$) or anhydrous (MCPA: $Ca(H_2PO_4)_2$), dicalcium phosphate dihydrate (DCPD: $CaHPO_4$, $2(H_2O)$) or anhydrous (DCPA : $CaHPO_4$), octacalcium phosphate (OCP: $Ca_8(HPO_4)_2PO_4)_4$, $5(H_2O)$), α or β tricalcium phosphate (α-TCP or β-TCP: $Ca_3(PO_4)_2$), hydroxyapatite (OHAp: $Ca_{10}(PO_4)_6(OH)_2$), tetracalcium phosphate (TTCP: $Ca_4(PO_4)_2O$), calcium oxide (CaO) and calcium hydroxide ($Ca(OH)_2$). Their basicity increases in the following order: PA $<$ MCPM (or MCPA) $<$ DCPD (or DCPA) $<$ OCP $<$ α-TCP (or β-TCP) $<$ OHAp $<$ TTCP $<$ CaO $\approx$ $Ca(OH)_2$. This order is dictated by the Ca/P ratio [4], which is 0, 0.5, 1, 1.33, 1.5, 1.67, 2 and ∞, respectively. To obtain an apatitic CPC, an acid phosphate salt (Ca/P < 1.67) is mixed with a basic one (Ca/P > 1.67) in the correct amount to have a final ratio Ca/P $= 1.67$. However, as was clearly demonstrated by Brown and Chow [5], if we exclude the kinetic aspect of the reaction, from a thermodynamic standpoint, the end product obtained depends on its solubility at the final pH. Among the compounds cited above, hydroxyapatite is the most stable at pH > 4; it precipitates directly only above pH 8, but its nucleation can be initiated by the addition of a fluoride salt at lower pH. On the basis of this strategy, some CPCs were developed 10 years ago. The most studied CPC was reported by Brown

---

*Author to whom all correspondence should be addressed.

0957–4530 © *1999 Kluwer Academic Publishers*

and Chow [6–8]. The powder consisted of an equimolar mixture of TTCP and DCPA or DCPD and the liquid was water or 0.025 M H_3PO_4. Ishikawa *et al.* improved the setting time of this cement using a 0.25 M phosphate buffer (pH 7.4) as liquid [2, 9, 10] and even its setting in aqueous environment adding alginate [11] or chitosane [12] to the liquid phase and called them fast-setting CPC (FSCPC) and non-decay type FSCPC (nd-FSCPC). Other types of CPC were developed by Lemaitre *et al.* [13–19] from MCPM + β-TCP without and with CSH (calcium sulphate hemihydrate $CaSO_4$, 1/2 (H_2O)), from DCPD + β-TCP + CC (calcium carbonate $CaCO_3$) and from β-TCP + H_3PO_4; they obtained DCPD or OHAp. Note also the mixture of (i) MCPM + α-TCP + CC used by constantz *et al.* [20] to give dahllite which is a carbonated apatite; (ii) DCPA + α-TCP + OHAp as powder and pure water as liquid studied by Fernandez *et al.* [21, 22] and (iii) MCPM + β-TCP + TTCP as powder and 4% H_3PO_4 with sodium glycerophosphate as liquid proposed by Lacout *et al.* [23, 24]: in the first step, MCPM reacts with β-TCP to give DCPD which reacts, in the second step, with TTCP to give OHAp just like Brown's cement. Potential formulations to obtain CPC from calcium orthophosphates and other related materials were screened by Driessens *et al.* [4, 25], and some of them were developed [26–30].

In this paper, we report a CPC obtained from MCPM as the acid phosphate salt and CaO as the basic compound.

2. Materials and methods

2.1. Chemicals

All chemicals were analytical reagent grade from Aldrich (CaO, OHAp), Fluka (MCPM, DCPD, DCPA, NaH_2PO_4, Na_2HPO_4 12(H_2O), $Ca(OH)_2$) or Prolabo (H_3PO_4). Commercial CaO was heated at 900 °C for 2 h to remove H_2O and CO_2 and stored in a vacuum desiccator. The CaO particle size was around 7 μm (2–40 μm; specific area, 1.3 $m^2\,g^{-1}$, Mastersizer, Malvern Instruments). Commercial MCPM contained 2% moisture (determined by thermogravimetry) and 4% free H_3PO_4 (determined by acidimetry); the particle size was around 230 μm (50–700 μm; specific area, 0.06 $m^2\,g^{-1}$). The commercial powder was pulverized for 5 h in a rotating micromill (Retsch Instruments) before use, to obtain a final particle size of around 20 μm (5–130 μm; specific area, 0.60 $m^2\,g^{-1}$) and was used without further treatment. Water was doubly distilled on quartz after deionization on an ion-exchange resin.

2.2. Preparation of calcium phosphate cement (CPC)

Cement powder was prepared by weighing the two components in a stoichiometric ratio according to Equation 1, and mixing just before use by crushing in an agate mortar

$$3Ca(H_2PO_4)_2 \cdot H_2O + 7CaO \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 8H_2O \qquad (1)$$

The liquid phase was either pure water, 0.1 M or 1 M H_3PO_4 or 0.25 M, 0.45 M, 0.75 M or 1 M phosphate buffers (pH 7.4) prepared from NaH_2PO_4 and $Na_2HPO_4 \cdot 12(H_2O)$. The powder was generally incorporated into the liquid by successive fractions as for dental zinc phosphate cements (one-sixth of the powder was added every 15 s) and kneaded with the aid of a spatula between each addition to produce a paste of workable consistency. After a mixing time of 2 min, carried out on a glass plate at 20 ± 1 °C, the paste was loaded into the moulds. The different powder-to-liquid (P/L) ratios tested ranged from 1–2.

2.3. Setting time measurements

The setting time of the CPC samples was measured according to the method set out in International Standard ISO 1566 for dental zinc phosphate cements. In this method, the cement is considered set when a 400 g weight loaded on to a Vicat needle with a tip diameter of 1 mm; fails to make a perceptible circular indentation on the surface of the cement. The standard requires that the cement be maintained at a temperature of 37 °C and relative humidity (RH) at least 37%. In the present investigation, the conditions were 37 °C and over 80% RH.

2.4. Mechanical strength measurements

After mixing for 2 min, the paste was loaded into Teflon moulds (4 mm diameter × 6 mm high) by spatulation, with periodic packing by means of a stainless steel rod. The top and bottom surfaces of the moulds were then covered tightly with two Plexiglas plates, clamped and stored in a 37 °C, 100% RH box for 24 h. The hardened CPC specimens were then removed from the moulds, after polishing their top and bottom planes, and the compressive strength (CS) was measured. At least five specimens were used for each determination. The diameter and length of each specimen were first measured at ± 0.02 mm. The CS was determined on an Erweka TBH 28 testing machine when the force applied was lower than 32 kg (loading rate of 2 $mm\,s^{-1}$) or on an Instron when it was greater (loading rate 1 $mm\,min^{-1}$).

2.5. Mechanism and kinetics of the CPC setting reaction

The setting reaction was investigated by powder X-ray diffraction (XRD), infrared absorption spectrometry (IR), ^{31}P magic angle spinning – nuclear magnetic resonance spectroscopy (MAS-NMR), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

Powder X-ray diffraction patterns were obtained with an automatic Phillips diffractometer controlled by an IBM PC (36 acquisitions, 3°–35 °θ, 3200 points, acquisition delay 500 ms) using an anticathode CuK_α (0.1542 nm) with a nickel filter.

Infrared absorption spectra were recorded on a Perkin–Elmer 983 in the 4000–400 cm^{-1} range. Samples were diluted (1% wt/wt) in vacuum-dried KBr (Aldrich Chemicals, spectroscopic grade) and pellets were made 13 mm diameter, 0.2 mm thick, under 9 $\mathrm{kN\,cm}^{-2}$ pressure.

Solid-state high-resolution ^{31}P nuclear magnetic resonance spectra were obtained using magic angle spinning (^{31}P MAS–NMR). A Bruker AM 300 7.04 spectrometer was used, operating at 121.4 MHz and ambient probe temperature. Samples were used as powder. Other experimental conditions were spinning speed 4.35 kHz, scanning domain 30 kHz, pulses emitted at 90°, pulse width 5 μs, delay between pulses 5 s. All spectra were recorded with 64 accumulations. Chemical shifts are reported with respect to the signal of orthophosphoric acid (85% H_3PO_4) as external reference.

Thermogravimetric analyses were performed using a Setaram thermobalance with continuous registering by means of a B 601 Ugine-Eyrand system and temperature controller RT 64. The heating rate was 2.5 °C min^{-1}.

Differential scanning calorimetry was performed using a DSC4 Perkin–Elmer computer-managed calorimeter. The calorimetric and thermometric reference was indium. All experiments were performed under a nitrogen flow, on 2–3 mg samples in closed aluminium pellets. The heating rate was 20 °C min^{-1}.

For these investigations, five CPC specimens were removed from the moulds at a given time, crushed and immediately placed in a tube which was cooled to − 195 °C in liquid nitrogen for 10 min and freeze dried. In this way, the cement setting reaction could be stopped at a specific period. The freeze-dried samples were ground to fine powder and were studied by XRD, DSC, IR, TGA and ^{31}P MAS-NMR for characterization of final products and reaction extent. TGA, DSC and XRD measurements on MCPM, DCPD and calcium hydroxide wet powder, before and after the freeze-drying operations, showed that only the trapped water was (completely) eliminated whereas the water of crystallization or hydroxyl groups remained.

3. Results

3.1. Influence of the powder-to-liquid mixing procedure on the compressive strength

To determine the best powder-to-liquid mixing procedure, we varied both the number of powder fractions added into the liquid at 15 s intervals and the total mixing time (Table I). The experimental conditions were: powder with Ca/P = 1.67 and P/L = 1.53 g ml^{-1}. Compressive strength was determined after 24 h at 37 °C, 100% RH on five samples (Table I). The best results were obtained with procedure (d) which was systematically used.

3.2. Setting times and compressive strengths

The setting times were measured using a powder containing MCPM and CaO with a Ca/P ratio of 1.67 according to Equation 1, when the liquid was water, and a Ca/P ratio of 1.76, when the liquid was a phosphate buffer. Under these conditions, the final Ca/P ratio was about 1.67 according to the liquid amount and concentration (third column in Table II). Different powder-to-liquid ratios were tested from 1–2 depending on the liquid used: pure water or 0.25 M, 0.45 M, 0.75 M and 1 M sodium phosphate buffer pH 7.4. These results are summarized in Table II (the indicated molarity represents the overall phosphate content).

The compressive strengths (CS) were determined on five samples prepared under the same conditions as those used for the setting times (Table II, last column).

Attempts were also made with 0.1 M and 1 M orthophosphoric acid as liquid; under these conditions, the setting time was shorter than with pure water (≈ 7 min) but the specimens were brittle and presented a weak compressive strength (≈ 2.2 MPa). Consequently, we did not carry out further investigations using this liquid.

In some papers, mechanical strength is represented by the diametral tensile strength (DTS). For comparison, we only determined the DTS on specimens (9 mm diameter × 5 mm high) obtained for P/L ratios that gave the best compressive strengths. The values found (2–2.5 MPa) were surprisingly weak. The CS/DTS ratios were around 10, whereas they are generally around 4 [25]. At present we do not have an explanation for this difference.

3.3. Mechanism and kinetics of the CPC setting reaction

3.3.1. With pure water as liquid

XRD, DSC and IR (Figs 1–3, respectively) spectra showed that the setting reaction was biphasic. In the

TABLE I Influence of powder-to-liquid mixing procedure on the compressive strength. Powder: Ca/P = 1.67, liquid; water or 0.45 sodium phosphate buffer, P/L = 1.53. Values in parentheses denote standard errors on five measurements

Procedure	Number of powder fractions	Time between each addition (s)	Total mixing time (s)	Compressive strength (MPa)	
				Water	0.45 M sodium phosphate buffer
(a)	1		30	3.0 (0.5)	12.8 (0.7)
(b)	2	15	60	3.5 (0.3)	14.4 (0.8)
(c)	4	15	90	4.8 (0.5)	15.1 (1.2)
(d)	6	15	120	6.0 (1.0)	18.1 (1.5)

TABLE II Setting times and compressive strengths (CS) values of CPCs obtained with water and different sodium phosphate buffers as liquid and different powder-to-liquid ratios (P/L). Values in parentheses denote standard errors on n measurements ($n = 3$ for setting times, $n \geq 5$ for CS).

Sodium phosphate buffer (M)	P/L ratio (g ml^{-1})	Ca/P molar ratio	Setting time (min)	CS (MPa)
0	1.40	1.67	12.0 (0.4)	2.6 (0.5)
	1.53	1.67	11.5 (1.0)	6.1 (1.1)
	1.65	1.67	8.3 (0.7)	5.0 (0.4)
0.25	1.40	1.70	11.5 (0.5)	14.0 (0.8)
	1.53	1.71	9.2 (0.3)	15.8 (0.7)
	1.65	1.71	8.7 (0.3)	15.7 (1.3)
	1.80	1.71	8.2 (0.3)	14.5 (0.6)
	2.00	1.72	7.5 (0.5)	13.7 (0.6)
0.45	1.40	1.66	9.5 (0.5)	14.6 (0.8)
	1.53	1.67	8.3 (0.3)	17.9 (1.4)
	1.65	1.67	7.5 (0.5)	18.3 (0.3)
	1.80	1.68	7.6 (0.3)	18.4 (0.7)
	2.00	1.69	6.7 (0.3)	18.0 (0.9)
0.75	1.40	1.59	9.2 (0.3)	13.2 (0.7)
	1.53	1.61	8.7 (0.3)	19.7 (2.4)
	1.65	1.62	7.3 (0.3)	21.3 (2.4)
	1.80	1.63	6.6 (0.2)	19.8 (2.2)
	2.00	1.64	5.3 (0.4)	16.8 (0.9)
1	1.00	1.47	16.5 (0.5)	13.5 (0.7)
	1.20	1.51	12.5 (0.5)	14.8 (1.2)
	1.30	1.53	11.2 (0.3)	17.5 (1.2)
	1.40	1.55	9.2 (0.3)	21.8 (1.3)
	1.53	1.57	7.3 (0.3)	24.8 (1.4)
				27.2 (5 days)
				33.0 (11 days)
				31.0 (45 days)
	1.65	1.58	6.7 (0.3)	17.9 (1.5)
	1.80	1.59	6.2 (0.3)	10.3 (0.9)
	2.00	1.60	4.7 (0.3)	7.9 (1.0)

first step, during the mixing, MCPM reacted with CaO immediately to give DCPD (Fig. 1a, b) according to Equation 2, then in the second step, DCPD reacted more slowly with the remaining CaO to give hydroxyapatite (Fig. 1b–e) according to Equation 3

$$3Ca(H_2PO_4)_2H_2O + 3CaO + 6H_2O \rightarrow 6CaHPO_4 \cdot 2(H_2O) \quad (2)$$

$$6CaHPO_4 \cdot 2(H_2O) + 4CaO \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 14H_2O \quad (3)$$

The XRD and IR spectra showed that hydration of CaO to give $Ca(OH)_2$ was low. It was estimated to be about 10% by (i) comparison of the 0 0 1 ($\theta = 9.07°$) $Ca(OH)_2$ XRD peak intensity with the 2 0 0 ($\theta = 18.75°$) or 3 1 1 ($\theta = 32.18°$) CaO peak intensity, and (ii) the very low IR absorption band intensity at 3640 cm^{-1} corresponding to free hydroxyls of $Ca(OH)_2$.

Figs 1–4 show that after 24 h there was only OHAp; no starting materials remain. The kinetics of conversion of the CPC starting materials to OHAp can be estimated by powder X-ray diffraction analysis [8, 9], but the results are not always very accurate because of the lack of reproducibility of peak intensities, a possible overlap of peaks and the lack of crystallinity particularly for the OHAp formed during the setting reaction [9]. Therefore, in this study we tested the possibilities offered by three other techniques, namely DSC, ^{31}P MAS–NMR and IR for which the signal intensity is less dependent on the crystallinity and the powder particle size than in XRD.

DSC curves of freeze-dried specimens showed a single endotherm at $T_{max} = 190 \pm 1$ °C, corresponding to the transformation of DCPD in DCPA (Fig. 2). The energy calculated from the peak integration is directly proportional to the amount of DCPD in the freeze-dried cement. This allows the quantitative determination of the remaining DCPD at each time and, consequently, the extent of the setting reaction.

The ^{31}P MAS–NMR spectrum of hydroxyapatite showed a main line at $\delta_{iso} = 2.82 \pm 0.03$ p.p.m. and two low-spinning side bands at -33.0 ± 0.3 and $+38.5 \pm 0.3$ p.p.m. (Fig. 4e). The DCPD spectrum also exhibited a main line at $\delta_{iso} = 1.43 \pm 0.03$ p.p.m. and two low-spinning side bands at -34.4 ± 0.3 and 37.2 ± 0.3 p.p.m. (Fig. 4a) as reported by Rothwell *et al.* [31]. The two main lines overlap, but the visible deformations of the overall peak all along the setting reaction give a qualitative estimation of its extent (Fig. 4a–e). The quantitative determination of OHAp and DCPD at each time was carried out by solving the following system of two equations with two unknowns: Equation 4, which corresponds to the DCPD and OHAp contribution to the total area, A_t, of the

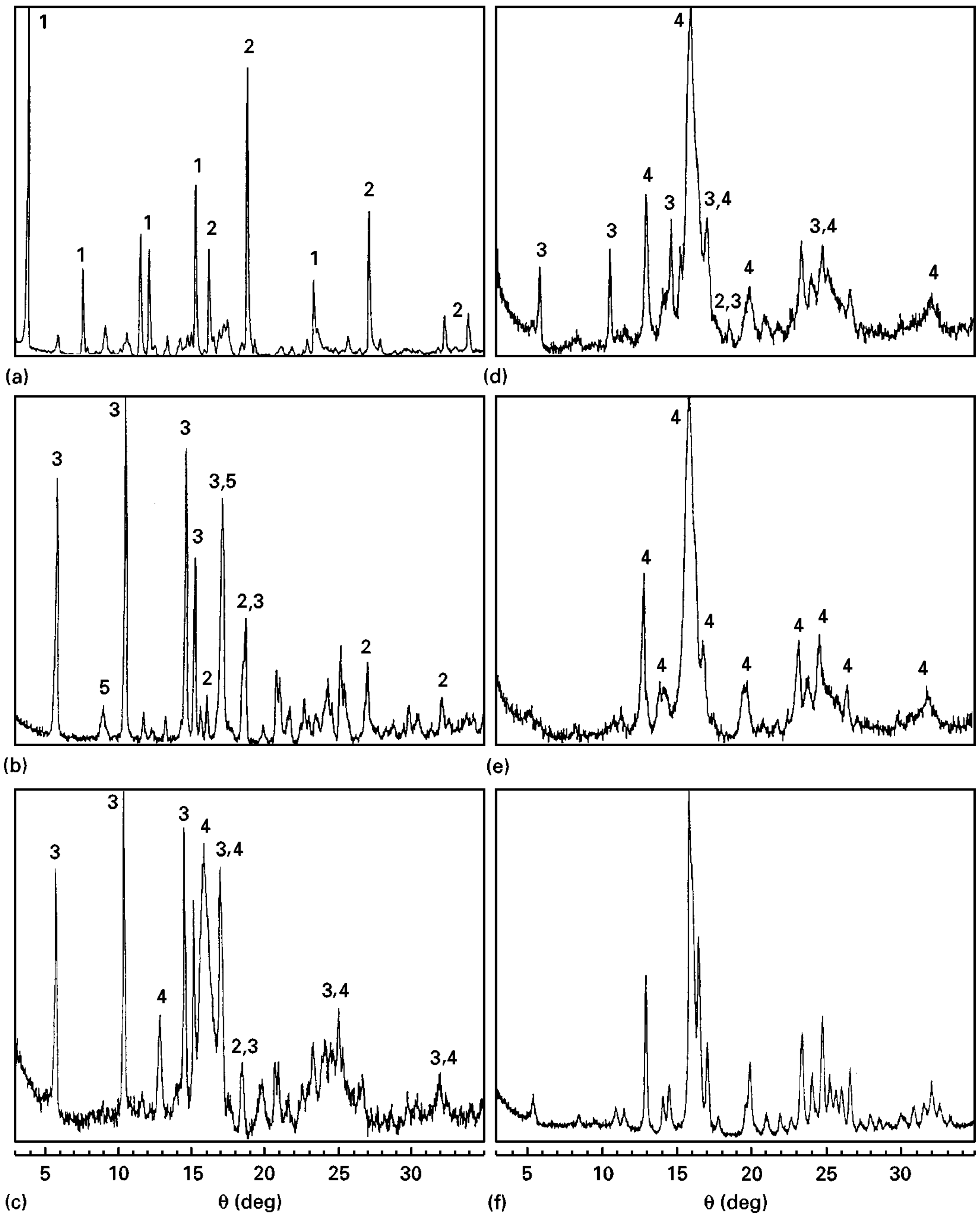

Figure 1 XRD patterns of the freeze-dried CPC specimens with water as liquid at various intervals: (a) starting materials (MCPM + CaO), (b) 5 min, (c) 40 min, (d) 4 h, (e) 24 h, (f) hydroxyapatite. 1 = MCPM, 2 = CaO, 3 = DCPD, 4 = OHAp, 5 = $Ca(OH)_2$.

main peak, and Equation 5, which corresponds to the mass conservation (subscript $i = 1$ for DCPD and 2 for OHAp, n_i = number of moles of DCPD or OHAp per gram of powder or freeze-dried cement, A_i = area per gram for the main line of pure substances, molar masses = 172, 56 and 1004 for DCPD, CaO and OHAp, respectively)

$$172\ n_1 A_1 + 1004\ n_2 A_2 = A_t \qquad (4)$$

$$(172 + 2 \times 56/3) n_1 + 1004\ n_2 = 1 \qquad (5)$$

The DSC and MAS–NMR procedures used to obtain quantitative data on the extent of the setting reaction were tested by analysing mixtures prepared with different amounts of DCPD, CaO and OHAp according to Equation 3. The results in Table III were satisfactory; the error was estimated to be below 5%).

The IR spectra of the freeze-dried cement specimens (Fig. 3a–f) showed with time a continuous change in their profile from the quasi-starting materials (DCPD + CaO) (Fig. 3a) up to OHAp (Fig. 3f). It seemed interesting to obtain a quantitative evaluation of reactants and product by comparing the spectrum of freeze-dried cement obtained at each time with a set of spectra corresponding to different ratios of (6 DCPD + 4CaO)/OHAp according to Equation 3. Using 14 spectra covering a range of 0–1 OHAp, we obtained amounts of DCPD and OHAp with a maximum error about 7%.

Finally, the XRD spectra for each time were treated according to the method used by Fusake *et al.* [8] from the sum of the 0 2 0 (θ = 5.82°) and 0 2 1 (θ = 10.46°) DCPD peak intensities and from the 0 0 2

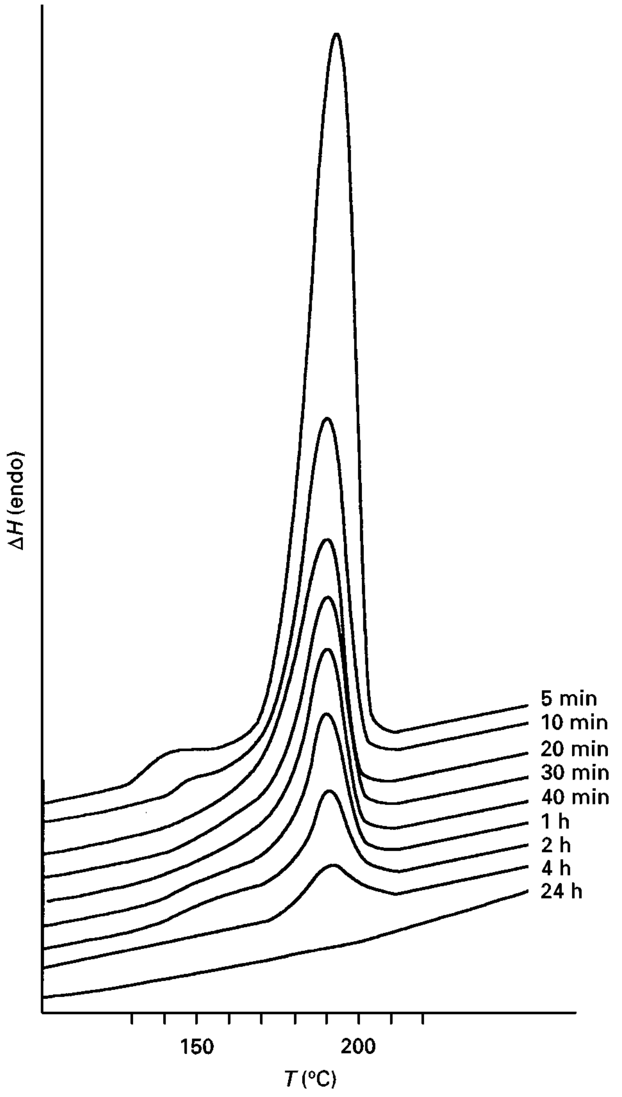

Figure 2 DSC curves of the freeze-dried CPC specimens with water as liquid at various intervals noted on the figure. Endotherms correspond to DCPD.

($\theta = 12.96^\circ$) OHAp peak intensity for which there was no overlap.

The disappearance of DCPD and the concomitant appearance of OHAp with time are represented in Figs. 5 and 6.

3.3.2. With pH 7.4 sodium phosphate buffer as liquid

As for pure water, MCPM disappeared to give DCPD during mixing, but DCPD reacted more slowly with the remaining CaO to give hydroxyapatite. Approximately 30% DCPD remained after 72 h (Figs 7 (0.45 M phosphate buffer) and 8 (1 M phosphate buffer)) whatever the phosphate concentration, but after 45 d, DCPD had completely disappeared, while a small fraction of the calcium hydroxide remained. The XRD pattern at 45 d had an apatitic profile, suggesting that the end product was probably a calcium-deficient hydroxypatite (CDOHAp). The percentage of OHAp formed at each time was calculated from the 0 0 2 ($\theta = 12.96^\circ$) OHAp peak intensity measured for pure water as liquid after 24 h.

Owing to the comparatively long reaction time with pure water, CaO was progressively hydrated to give calcium hydroxide; hydration was complete after 4 h.

4. Discussion

4.1. Setting times and mechanical strengths

CPCs obtained from MCPM and CaO set in a reasonable time (Table I), neither too long nor too short, in the range recommended for clinical applications, where rapid hardening of the cement is important. The best compromise (7 min setting time and 25 MPa compressive strength after 24 h and 33 MPa after 11 d at 37 °C and 100% RH) is obtained with a 1 M phosphate buffer as liquid and a powder-to-liquid ratio of 1.53. The replacement of pure water by phosphate buffer reduces the setting time as expected [9, 22, 32, 33] but has a paradoxical effect on the conversion kinetics of starting materials to OHAp and on the final compressive strength in comparison with the results already published [9, 22, 33]. Indeed, with phosphate buffer, we observe an increase of the final compressive strength and a decrease of the rate of OHAp formation in contrast to the reported effects on CPCs that consisted of (i) DCPA and TTCP for which the rate of OHAp formation was enhanced [9, 33] without variation of the final mechanical strength [9]; (ii) α-TCP or α-TCP and DCPA for which the mechanical strength was lowered [22]. An increase in the powder-to-liquid ratio (Table I) reduced the setting time and raised, in the first instance, the compressive strength, then decreased it. This is probably due to the fact that, with the high P/L ratios, the paste dries out and is not very easily workable, which affects the mechanical strength of the hardened cement.

We observed an approximately linear correlation between compressive strength and the percentage of OHAp formed: $\mathrm{CS} = 0.36\% + 3.7$ ($r = 0.90$) with 0.45 M and $\mathrm{CS} = 0.32\% + 4.5$ ($r = 0.88$) with 1 M phosphate buffer. A quadratic correlation gives a higher correlation coefficient ($r = 0.96$) because the DCPD formed at the beginning of the setting reaction leads to a certain degree of hardness of the cement, which is improved later by its conversion to OHAp. It is known that the rate of OHAp formation is dependent on the solubility of the starting materials in the interstitial liquid [5]. Furthermore, the solubility is itself dependent on the pH of the liquid: therefore pH measurements carried out all along the setting reaction and with the different phosphate buffers should lead to a better understanding of this behavior, in particular, why the OHAp conversion is not dependent on the phosphate buffer concentration, whereas the final compressive strength is.

CPCs from MCPM and CaO [34] or MCPM, CaO and α-TCP [28] were already developed by Bernudez *et al.* Using MCPM and CaO with a Ca/P of 1.67 and a 1.66 powder-to-water ratio, they obtained a setting time around 40 min and a compressive strength of 0.5 MPa, values very different from those that we obtained under the same conditions. This is probably due to the powder-to-liquid mixing procedure which we showed to be crucial (Table I). Therefore, from

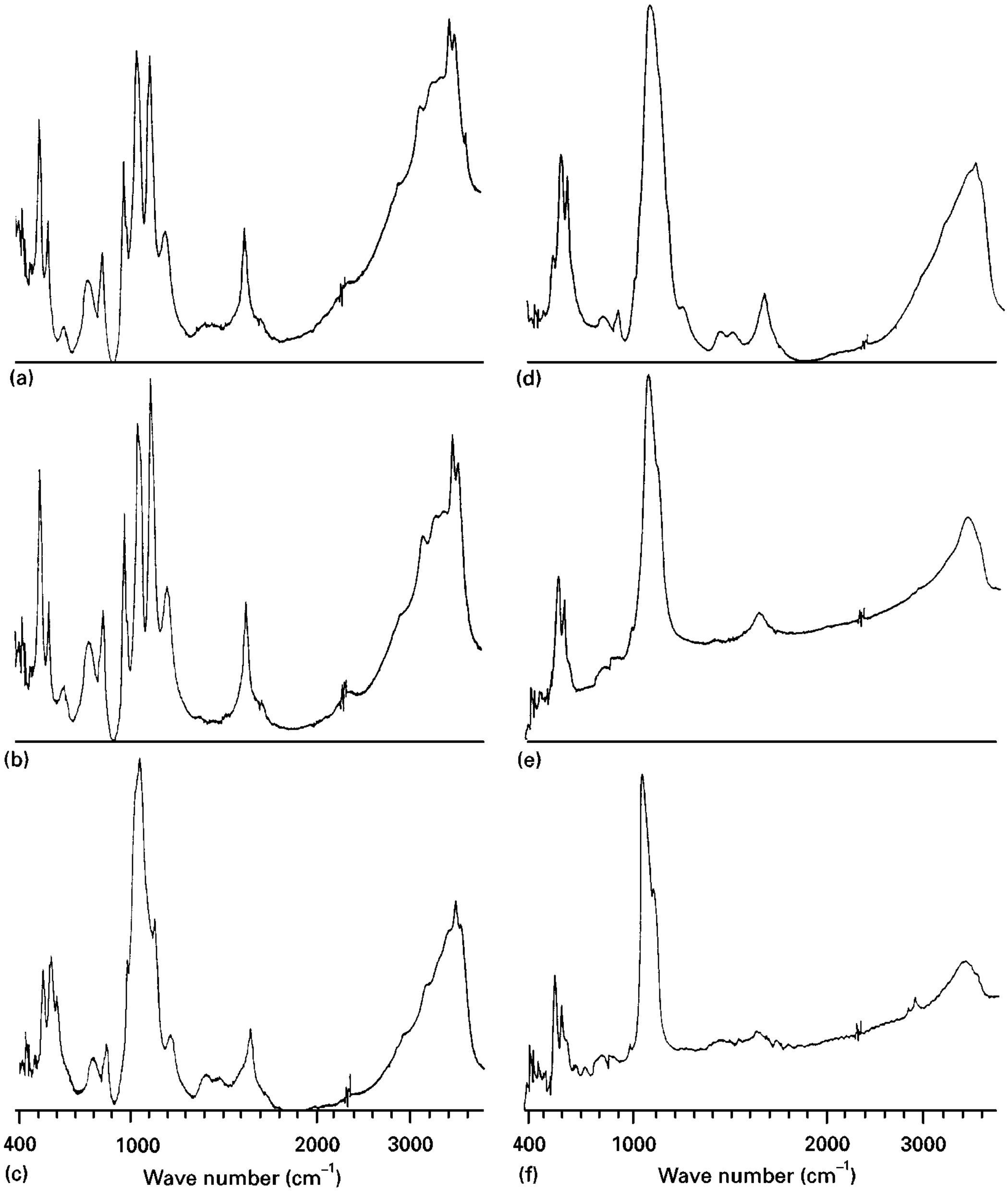

Figure 3 IR spectra of the freeze-dried CPC specimens with water as liquid at various intervals. (a) Pseudo-zero time (physical mixture of 6 DCPD + 4CaO), (b) 5 min, (c) 30 min, (d) 2 h, (e) 24 h, (f) hydroxyapatite.

TABLE III Validation of DSC and ^{31}P MAS-NMR procedures for quantitative determination of OHAp and/or DCPD in freeze-fried cement specimens

DCPD			OHAp	
Taken	Found		Taken	Found
	NMR	DSC		NMR
0.820	0.821	0.820	0	0
0.649	0.644	0.647	0.210	0.216
0.457	0.455	0.479	0.444	0.446
0.242	0.248	0.247	0.706	0.698
0	0	0	1	1

these starting materials, they found that an octacalcium phosphate cement (Ca/P = 1.35 and P/L = 1.9) gave better results than an apatitic one (CS of 5.2 MPa and setting time around 17 min). The addition of α-TCP improved the compressive strength but the highest value (25 MPa [28]) was observed with 0% (MCPM + CaO). They did not investigate the mechanism of the setting reaction.

4.2. Mechanism and kinetics of the CPC setting reaction

The results obtained from the DSC, XRD, MAS–NMR and IR measurements for DCPD disappearance (Fig. 5) and OHAp appearance (Fig. 6) with pure water as liquid, were practically identical. However, DSC and XRD gave lower values than MAS–NMR and IR for DCPD, whereas XRD, NMR and IR gave the same values for OHAp considering the experimental errors. With DSC, only DCPD was measured and with XRD, the OHAp and DCPD determinations were independent. With NMR and IR the OHAp and DCPD determinations were dependent and the

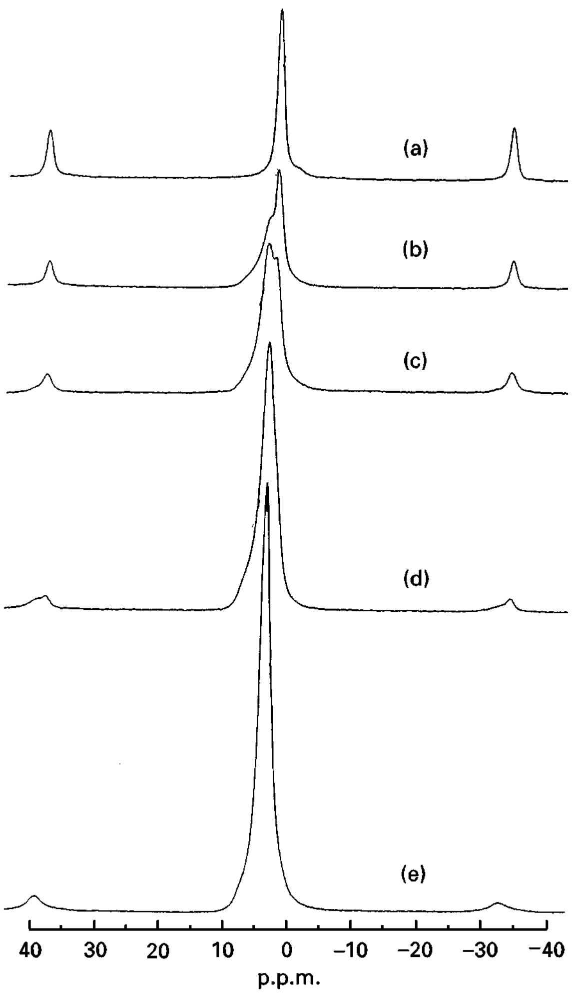

Figure 4 ^{31}P MAS–NMR spectra of the freeze-dried CPC specimens with water as liquid at various intervals. (a) Pseudo-zero time (physical mixture of 6 DCPD + 4 CaO), (b) 10 min, (c) 30 min, (d) 1 h, (e) 24 h.

OHAp signal was predominant. Consequently, the estimation of the amount of OHAp was more accurate than that of DCPD and a small lack of OHAp led to a higher estimation of the amount of DCPD. Indeed, whatever the type of liquid used, from the XRD measurements, we never obtained 100% by adding the percentages of DCPD remaining and OHAp formed. The sum was generally between 80% and 92%, although the XRD patterns did not reveal the presence of any other products. Some explanations are possible: (i) the yield of the reaction is below 100%; (ii) the signal intensities corresponding to pure products used to calculate their percentage at each time were inaccurate in particular for OHAp, because of a variation with time in its degree of crystallinity when the liquid used was water, (iii) the CDOHAp signal was not exactly the same as that of pure OHAp when the liquid used was a phosphate buffer.

However that may be, to study the setting reaction kinetics of a CPC, the profile of the curve that represents the variations with time of the amount of reactants or product(s) is as important as their individual values. In this aim, XRD remains the best analytical technique, for it gives both unambiguous qualitative and quantitative information; its major drawback is the long experiment time. DSC requires the presence of a hydrated compound as reactant or product, but under this condition it is a fast technique. NMR and IR can be used to confirm accurately XRD measurements.

Lastly, because the first step of the setting reaction is the formation of DCPD from MCPM and CaO reaction, it was logical to mix DCPD and CaO to form a CPC. Our first attempts were not encouraging, i.e. a setting time around 20 min and compressive strength of 0.4 MPa; therefore this approach has been abandoned.

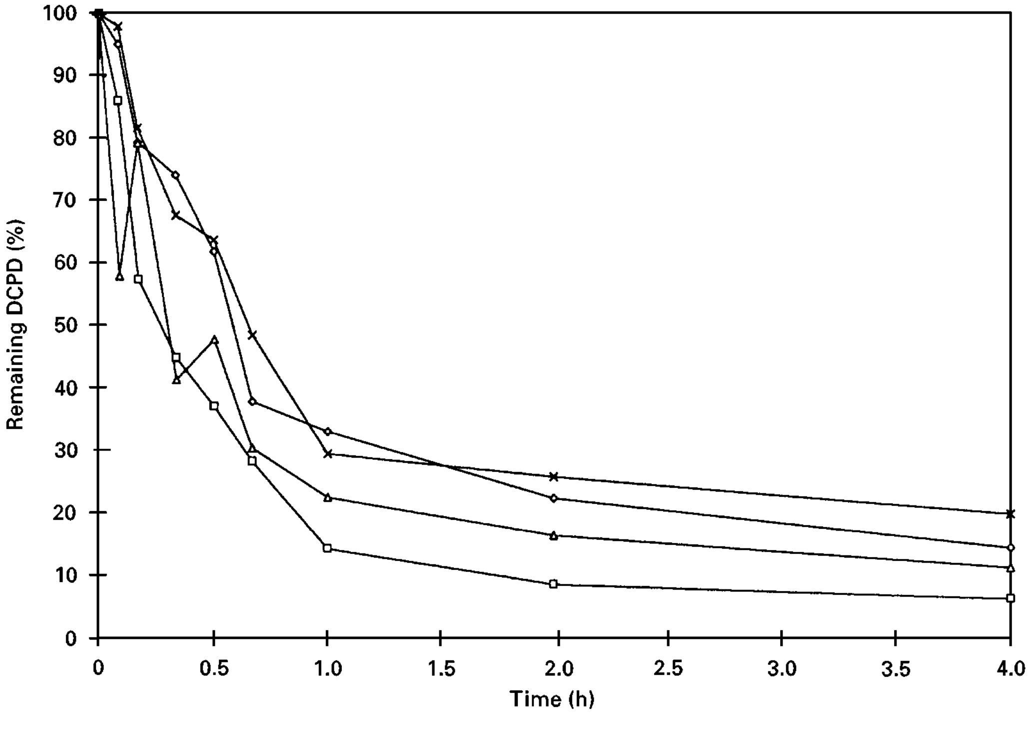

Figure 5 Variations of the remaining DCPD percentage, in the freeze-dried CPC specimens with water as liquid at various intervals, obtained with the different analytical techniques. (◇) RMN, (□) DSC, (△) XRD, (×) IR.

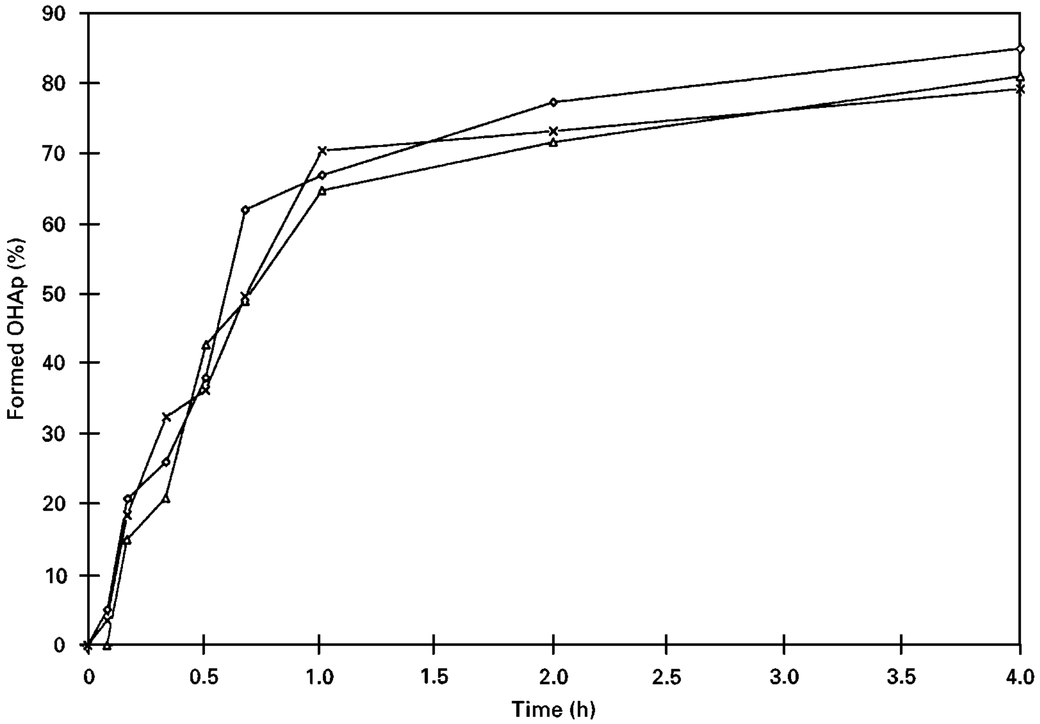

Figure 6 Variations of the formed OHAp percentage, in the freeze-dried CPC specimens with water as liquid at various intervals, obtained with the different analytical techniques. (◇) RMN, (△) XRD, (×) IR.

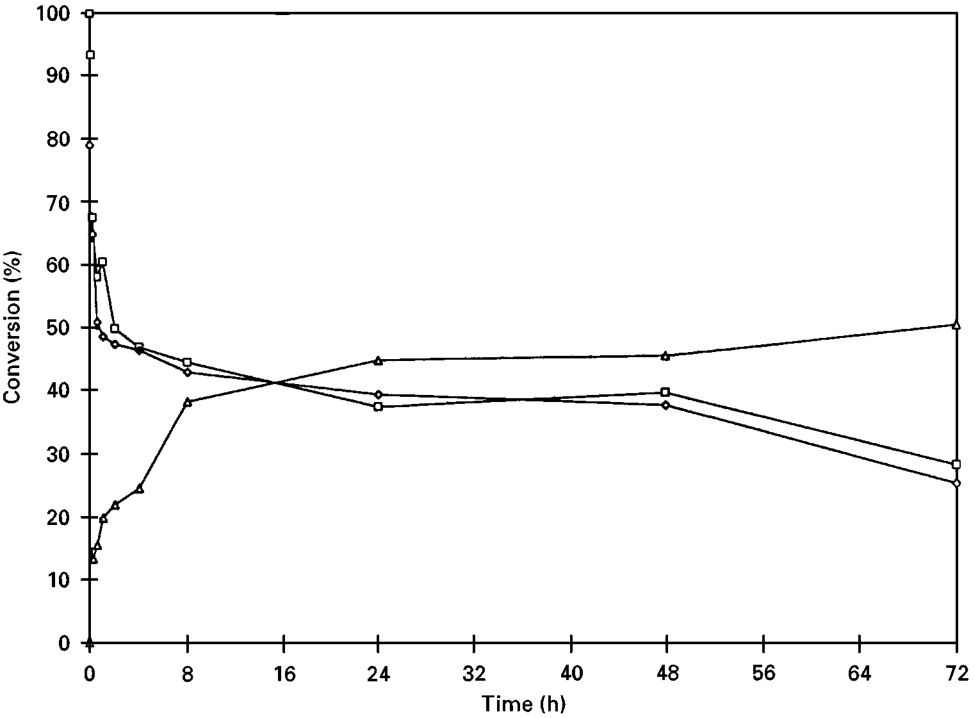

Figure 7 Variations of (◇, □) the remaining DCPD percentage and of (△) the formed OHAp percentage, in the freeze-dried CPC specimens with 0.45M phosphate buffer as liquid at various intervals, obtained with the (□, △) XRD and (◇) DSC measurements.

Our first results on a calcium phosphate cement made from MCPM and CaO are promising. The fact that we could not rapidly obtain hydroxyapatite with phosphate buffers as liquid is not a major obstacle for clinical applications of these cements, because DCPD and CDOHAp seem to be more easily bioresorable than pure hydroxyapatite [3]. Work remains to be carried out for a better understanding of the setting reaction and to optimize the mechanical properties.

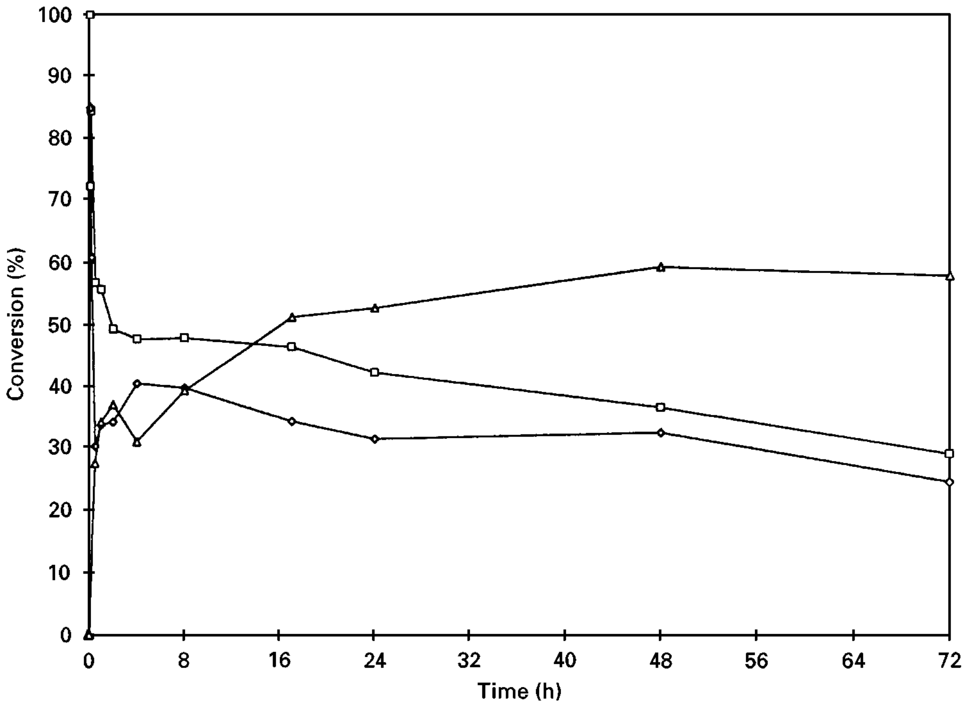

Figure 8 Variations of (◇, □) the remaining DCPD percentage and of (△) the formed OHAp percentage, in the freeze-dried CPC specimens with 1M phosphate buffer as liquid at various intervals, obtained with the (□, △) XRD and (◇) DSC measurements.

Acknowledgements

The authors thank C. Gauffier, University of Montpellier II, for the ^{31}P MAS–NMR spectra, S. Bovis for the IR study and Dr S.L. Salhi for help in preparing the manuscript.

References

1. S. E. GRUNINGER, C. SIEW, L. C. CHOW, A. O'YOUNG, N. K. TS'AO and W. E. BROWN, *J. Dent. Res.* **63** (1984) 200.
2. K. ISHIKAWA and K. ASAOKA, *Biomaterials.* **16** (1995) 527, and references 1–11 therein.
3. F. C. M. DRIESSENS, M. G. BOLTONG, M. I. ZAPATERO, R. M. H. VERBEECK, W. BONFIELD, O. BERNUDEZ, E. FERNANDEZ, M. P. GINEBRA and J. A. PLANELL, *J. Mater. Sci. Mater. Med.* **6** (1995) 272, and references 3–35 therein.
4. F. C. M. DRIESSENS, M. G. BOLTONG, O. BERMUDEZ and J. A. PLANELL, *ibid.* **4** (1993) 503.
5. W. E. BROWN and L. C. CHOW, US Pat. 4518 430 (1985).
6. *idem*, in "Cement Research Progress", edited by P. W. Brown (American Ceramic Society, Westerville, OH, 1986) p. 352.
7. *idem*, *US Pat.* 4612 053 (1986).
8. Y. FUSAKE, E. D. EANES, S. TAKAGI, W. E. BROWN and L. C. CHOW, *J. Dent. Res.* **69** (1990) 1852.
9. K. ISHIKAWA, S. TAKAGI, L. C. CHOW and Y. ISHIKAWA, *J. Mater. Sci. Mater Med.* **6** (1995) 528.
10. Y. MIYAMOTA, K. ISHIKAWA, H. FUKAO, M. SAWADA, M. NAGAYAMA, M. KON and K. ASAOKA, *Biomaterials* **16** (1995) 855.
11. K. ISHIKAWA, Y. MIYAMOTO, M. KON, M. NAGAYAMA and K. ASAOKA, *ibid.* **16** (1995) 527.
12. M. TAKECHI, Y. MIYAMOTO, K. ISHIKAWA, M. YUASA, M. NAGAYAMA, M. KON and K. ASAOKA, *J. Mater. Sci. Mater Med.* **7** (1995) 317.
13. J. LEMAITRE, A. MIRTCHI and A. MORTIER, *Sil. Ind. Ceram. Sci. Technol.* **52** (1987) 141.
14. A. MIRTCHI, J. LEMAITRE and N. TERAO, *Biomaterials* **10** (1989) 475.
15. A. MIRTCHI, J. LEMAITRE and E. MUNTING, *ibid.* **10** (1989) 634.
16. *Idem, ibid.* **11** (1990) 83.
17. E. MUNTING, A. MIRTCHI and J. LEMAITRE, *J. Mater. Sci. Mater Med.* **4** (1993) 337.
18. K. OHURA, M. BOHNER, P. HARDOUIN, J. LEMAITRE, G. PASQUIER and B. FLAUTRE, *J. Biomed. Mater. Res.* **30** (1996) 193.
19. H. ADRIANJATOVO, F. JOSE and J. LEMAITRE, *J. Mater. Sci. Mater Med.* **7** (1996) 34.
20. B. R. CONSTANTZ, I. C. ISON, M. T. FULMER, R. D. POSER, S. T. SMITH, M. VANWAGONER, J. ROSS, S. A. GOLDSTEIN, J. B. JUPITER and D. I. ROSENTHAL, *Science* **267** (1995) 1796.
21. E. FERNANDEZ, M. P. GINEBRA, M. G. BOLTONG, F. C. M. DRIESSENS, J. GINEBRA, E. A. P. DEMAEYER, R. M. H. VERBEECK and J. A. PLANELL, *J. Biomed. Mater. Res.* **32** (1996) 367.
22. E. FERNANDEZ, M. G. BOLTONG, M. P. GINEBRA, O. BERNUDEZ and J. A. PLANELL, *Clin. Mater.* **16** (1994) 99.
23. J. L. LACOUT, E. MEDJOUBI and M. HAMAD, *J. Mater. Sci. Mater Med.* **7** (1996) 371.
24. E. MEDJOUBI, J. L. LACOUT, P. MICHAUD and F. RODRIGUEZ, in "Hydroxypatite and related materials", edited by P. W. Brown and B. Constandtz (CRC Press, Boca Raton, FL, 1994) p. 209.
25. O. BERNUDEZ, M. G. BOLTONG, F. C. M. DRIESSENS and J. A. PLANELL, *J. Mater. Sci. Mater Med.* **4** (1993) 389.
26. M. P. GINEBRA, M. G. BOLTONG, F. C. M. DRIESSENS, O. BERNUDEZ, E. FERNANDEZ and J. A. PLANELL, *ibid.* **5** (1994) 103.
27. O. BERNUDEZ, M. G. BOLTONG, F. C. M. DRIESSENS and J. A. PLANELL, *ibid.* **5** (1994) 144.
28. *idem, ibid.* **5** (1994) 160.
29. F. C. M. DRIESSENS, M. G. BOLTONG, O. BERNUDEZ, J. A. PLANELL, M. P. GINEBRA and E. FERNANDEZ, *ibid.* **5** (1994) 164.
30. M. P. GINEBRA, M. G. BOLTONG, E. FERNANDEZ, J. A. PLANELL and F. C. M. DRIESSENS, *ibid.* **6** (1995) 612.
31. W. P. ROTHWELL, J. S. WAUGH and J. P. YESINOWSKI, *J. Am. Chem. Soc.* **102** (1980) 2637.

32. F. C. M. DRIESSENS, M. G. BOLTONG, J. A. PLANELL, O. BERNUDEZ, M. P. GINEBRA and E. FERNANDEZ, in "Bioceramics", Vol. **6**, edited by P. Ducheyne and D. Christiansen (Butterworth-Heinemann, Oxford, 1993) p. 469.
33. L. C. CHOW, S. TAGAKI and K. ISHIKAWA, in "Hydroxyapatite and related materials", edited by P.W. Brown and B. Constantz (CRC Press, Boca Raton, FL, 1994) p. 127.
34. O. BERNUDEZ, M. G. BOLTONG, F. C. M. DRIESSENS and J. A. PLANELL, *J. Mater. Sci. Mater Med.* **5** (1994) 67.

Received 18 July
and accepted 16 September 1997