High early strength calcium phosphate bone cement: Effects of dicalcium phosphate dihydrate and absorbable fibers

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Abstract: Calcium phosphate cement (CPC) sets *in situ* to form resorbable hydroxyapatite with chemical and crystallographic similarity to the apatite in human bones, hence it is highly promising for clinical applications. The objective of the present study was to develop a CPC that is fast setting and has high strength in the early stages of implantation. Two approaches were combined to impart high early strength to the cement: the use of dicalcium phosphate dihydrate with a high solubility (which formed the cement CPC_D) instead of anhydrous dicalcium phosphate (which formed the conventional cement CPC_A), and the incorporation of absorbable fibers. A 2×8 design was tested with two materials (CPC_A and CPC_D) and eight levels of cement reaction time: 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 8 h, and 24 h. An absorbable suture fiber was incorporated into cements at 25% volume fraction. The Gilmore needle method measured a hardening time of 15.8 min for CPC_D, five-fold faster than 81.5 min for CPC_A, at a powder:liquid ratio of 3:1. Scanning electron microscopy revealed the formation of nanosized rod-like hydroxyapatite crystals and platelet crystals in the cements. At 30 min, the flexural strength (mean $\pm$ standard deviation; $n = 5$) was 0 MPa for CPC_A (the paste did not set), (4.2 ± 0.3) MPa for CPC_D, and (10.7 ± 2.4) MPa for CPC_D-fiber specimens, significantly different from each other (Tukey's at 0.95). The work of fracture (toughness) was increased by two orders of magnitude for the CPC_D-fiber cement. The high early strength matched the reported strength for cancellous bone and sintered porous hydroxyapatite implants. The composite strength S_c was correlated to the matrix strength S_m: $S_c = 2.16S_m$. In summary, substantial early strength was imparted to a moldable, self-hardening and resorbable hydroxyapatite via two synergistic approaches: dicalcium phosphate dihydrate, and absorbable fibers. The new fast-setting and strong cement may help prevent catastrophic fracture or disintegration in moderate stress-bearing bone repairs. © 2005 Wiley Periodicals, Inc. J Biomed Mater Res 75A: 966–975, 2005

Key words: calcium phosphate cement; hydroxyapatite; early strength; fast setting; absorbable fibers; bone repair

INTRODUCTION

Calcium phosphate cements can be molded and self-harden in the prepared bone site to form resorbable hydroxyapatite.[1] The first self-setting calcium phosphate cement, referred to as CPC, was developed in 1986.[1] Since then, many compositions of calcium phosphate cements have been formulated and tested.[2–6] CPC is comprised of a mixture of fine particles of tetracalcium phosphate [TTCP: $Ca_4(PO_4)_2O$] and dicalcium phosphate anhydrous [DCPA: $CaHPO_4$].[1] Because the hydroxyapatite from CPC is formed in an aqueous environment at body temperature, it is more similar to biological apatites than sintered hydroxyapatite formed at high temperatures.[7–11] Due to its self-setting ability, excellent osteoconductivity, and bone replacement capability, CPC is highly promising for a wide range of clinical applications.[7–11]

However, the low strength of CPC has limited its use to only nonstress applications,[8] and clinical usage has been severely hindered by its brittleness.[10] One clinical study on the repair of periodontal bone defects demonstrated that the brittle nature of CPC caused early exfoliation of all or pieces of the implant.[12] An-

Certain commercial materials and equipment are identified in this article to specify experimental procedures. In no instance does such identification imply recommendation by NIST or the ADA Foundation, or that the material identified is necessarily the best available for the purpose.

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other major shortcoming is that it takes a relatively long time for the CPC paste to set. A long setting time can result in the crumbling of CPC when the paste comes in contact with physiological fluids, or if bleeding occurs due to the difficulty in some cases to achieve complete hemostasis.[4,13,14] Low strength in the early postoperative stage (low early strength) can result in the cement to fail or disintegrate under even moderate stresses. Studies were carried out to overcome these disadvantages of CPC.[14–17] Hydroxypropyl methylcellulose and other gelling agents were incorporated into CPC to render the paste more cohesive and resistant to washout.[14,15] Chitosan, a biopolymer, imparted nonrigidity, high toughness, and fast-setting to CPC.[16,17] In a more recent study,[18] dicalcium phosphate dihydrate (DCPD, $CaHPO_4 \cdot 2H_2O$), a calcium phosphate compound known to possess a relatively high solubility and resorbability,[19,20] was used to replace the DCPA component in CPC. The high solubility of DCPD resulted in the fast setting of the cement, yielding a hardening time of about 15 min with water used as the cement liquid and 6 min with the use of a phosphate solution, although the phosphate solution resulted in a lower cement strength.[18]

The objective of the present study was to develop a hydroxyapatite cement that can quickly develop high strength shortly after paste placement. Two approaches were tested: the use of DCPD in the place of DCPA to form the cement, and the incorporation of absorbable fibers. The fibers would provide the needed early strength and then be dissolved to create long cylindrical macropores for cell infiltration and bone ingrowth. It was hypothesized that combining the two approaches synergistically would substantially increase the early strength, elastic modulus, and work of fracture (toughness) for the cement compared to using a single approach. It was further hypothesized that these properties would significantly depend on the cement reaction time (or incubation time).

MATERIALS AND METHODS

Preparation of CPC_A and CPC_D

The tetracalcium phosphate (TTCP) powder was synthesized from a solid-state reaction between $CaHPO_4$ (dicalcium phosphate anhydrous, DCPA) and $CaCO_3$ (Baker Analyzed Reagents, J. T. Baker Chemical, Phillipsburg, NJ), which were mixed and heated at 1500°C for 6 h in a furnace (Model 51333, Lindberg, Watertown, WI). The heated mixture was quenched to room temperature, ground, and sieved to obtain TTCP particles with sizes ranging from about 1 to 60 μm, with a median particle size of 20 μm. The DCPA powder was ground in 95% ethanol for 24 h to obtain particles with sizes ranging from 0.4 μm to 6 μm, with a median particle size of 1.2 μm. The TTCP and DCPA powders were then mixed in a micromill (Bel-Alert Products, Pequannock, NJ) in equimolar amounts to form the powder for the cement designated as CPC_A.

Preliminary studies using commercial dicalcium phosphate dihydrate (DCPD) powders yielded long setting times of greater than 1 h for the TTCP-DCPD paste, likely due to certain unidentified impurities in the commercial powders.[18] Therefore, the DCPD powder used in the present study was prepared in the laboratory. The pH was slowly raised via the addition of $CaCO_3$ for a DCPD–monocalcium phosphate monohydrate singular point solution at a pH of 1.9 and a temperature of 4°C. DCPD that precipitated before the pH reached about 3.5, which is significantly below the hydroxyapatite-DCPD singular point of 4.2, was collected to avoid possible contamination of the DCPD by hydroxyapatite. The DCPD was washed, first with distilled water, and then with ethanol of 95%, and then dried in air. The DCPD was ground in water with a ball mill to obtain particles with size ranging from approximately 0.5 to 4 μm and a median particle size of 1.3 μm. The DCPD powder was mixed with the TTCP powder at a molar ratio of 1:1 to form the powder for the cement referred to as CPC_D.

Measurement of cement setting time

The CPC powder and liquid were manually mixed with a spatula to form a paste that was filled into a stainless steel mold of 6-mm diameter and 3-mm depth.[21] Distilled water was used as the cement liquid. Each specimen in the mold was sandwiched between two glass slides, and the assembly was incubated in a humidor with 100% relative humidity at 37°C. The hardening time was measured using the Gilmore needle method with a load of 453.5 g and a flat tip diameter of 1.06 mm.[22] A cement specimen was considered set when the needle loaded onto the specimen surface failed to leave a perceptible indentation. The time measured from the paste being mixed to this point was used as the setting time. A 2×5 full-factorial design was tested with two materials (CPC_A and CPC_D) and five powder:liquid mass ratios (4.5:1, 4:1, 3.5:1, 3:1, and 2.5:1).

Fabrication of CPC_A and CPC_D specimens

To investigate the early strength of CPC and its dependence on cement incubation time, a 2×8 full-factorial design was tested with two materials (CPC_A and CPC_D) and eight levels of incubation time: 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 8 h, and 24 h. The incubation time was defined as the time from the paste being mixed to the specimen being tested in three-point flexure. An intermediate powder:liquid mass ratio of 3:1 was selected because the paste was relatively flowable and cohesive. The paste at 4.5:1 was quite dry, and that at 2.5:1 resulted in a lower strength for the set cement. The CPC powder and water were mixed with a spatula to form a paste that was filled into a stainless steel mold of $3 \times 4 \times 25$ mm. The paste in each mold was

sandwiched between two glass slides, and set in a humidor with 100% relative humidity at 37°C. For incubation times of 4 h or less, the specimen was demolded and tested in flexure as described in the following section. For incubation times of greater than 4 h, the specimen was demolded at 4 h, then immersed in distilled water in the humidor for the remainder of the prescribed incubation time.

Mechanical testing

A three-point flexural test with a span of 20 mm was used to fracture the specimens at a crosshead speed of 1 mm/min on a computer-controlled universal testing machine (model 5500R, Instron, Canton, MA). Flexural strength, elastic modulus, and work of fracture were measured.

Conversion to hydroxyapatite

Powder X-ray diffraction (XRD) analysis was used to examine the CPC conversion to hydroxyapatite.[17,23] The halves from the flexural specimens were dried and milled into a powder by mortar and pestle to characterize the hydroxyapatite formation for CPC_A and CPC_D. The XRD patterns were recorded with a powder X-ray diffractometer (Rigaku, Danvers, MA) with the use of graphite-monochromatized copper K_α radiation ($\lambda = 0.154$ nm) generated at 40 kV and 40 mA. The 002 peak intensity of hydroxyapatite was used to measure the percentage of conversion to hydroxyapatite. All data were collected in a continuous scan mode (1° 2θ min^{-1}, step time 0.6 s, step size 0.01°).

Fiber reinforcement

An absorbable suture fiber (Vicryl polyglactin 910, Ethicon, Somerville, NJ) was used. This suture consisted of individual fibers braided into a bundle with a bundle diameter of about 322 μm that provided substantial strength and toughness for about 4 weeks, and then dissolved and produced macropores in CPC as shown in a previous study.[24] As in the previous study, the suture was cut to filaments 8 mm in length. The CPC powder was mixed with distilled water at a powder:liquid mass ratio of 3:1. The filaments were mixed with the CPC paste randomly to form a composite paste, which was placed into the 3 × 4 × 25 mm molds and set in the humidor. During three-point flexural testing, most of the fiber-reinforced specimens were still intact after the matrix had cracked, due to fibers bridging the cracks. The test was stopped at a displacement of 2.0 mm for a consistent calculation of work of fracture.[25]

Microscopy and statistics

The fracture surfaces of specimens at various incubation times were sputter coated with gold and examined with a scanning electron microscope (SEM, JEOL 5300, Peabody, MA). Two-way and one-way analysis of variance (ANOVA) was performed to detect significant effects. Tukey's multiple comparison was used to compare the data at a family confidence coefficient of 0.95. One standard deviation was used as the estimated standard uncertainty of the measurements. These values should not be compared with data obtained in other laboratories under different conditions.

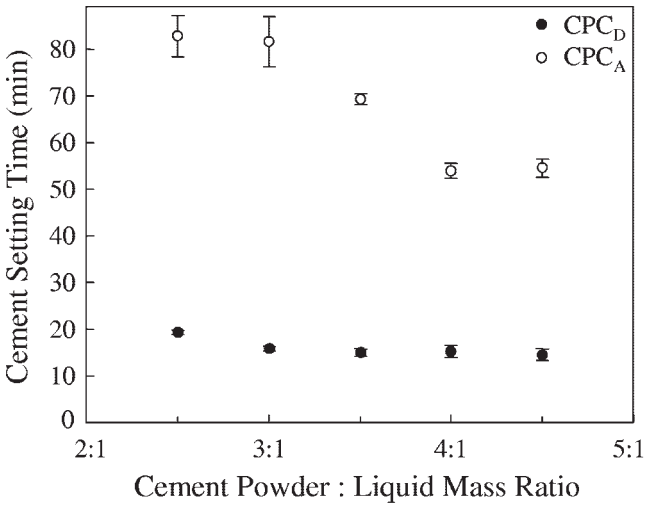

Figure 1. Cement setting time versus powder:water ratio. Each value is the mean of four measurements with the error bar showing one standard deviation (mean ± standard deviation; $n = 4$). CPC_D, using dicalcium phosphate dihydrate, was much faster setting than the conventional cement CPC_A, with anhydrous dicalcium phosphate.

RESULTS

Setting time

Figure 1 shows the cement setting time as a function of powder:liquid ratio. Each value is the mean of four measurements, with the error bar showing one standard deviation (mean ± standard deviation; $n = 4$). Two-way ANOVA identified significant effects ($p < 0.001$) of powder:liquid ratio and cement composition. CPC_A had a setting time ranging from 82.8 ± 4.4 min to 54.5 ± 1.9 min. The setting time for CPC_D was much shorter, ranging from 19.3 ± 0.5 min to 14.5 ± 1.3 min. At a powder:liquid mass ratio of 3:1, the setting time was 15.8 ± 0.5 min for CPC_D, significantly faster than 81.5 ± 5.3 min for CPC_A (Tukey's multiple-comparison test; family confidence coefficient = 0.95).

Mechanical properties

Figure 2 is a plot of the flexural strength, elastic modulus, and work of fracture for CPC_A and CPC_D

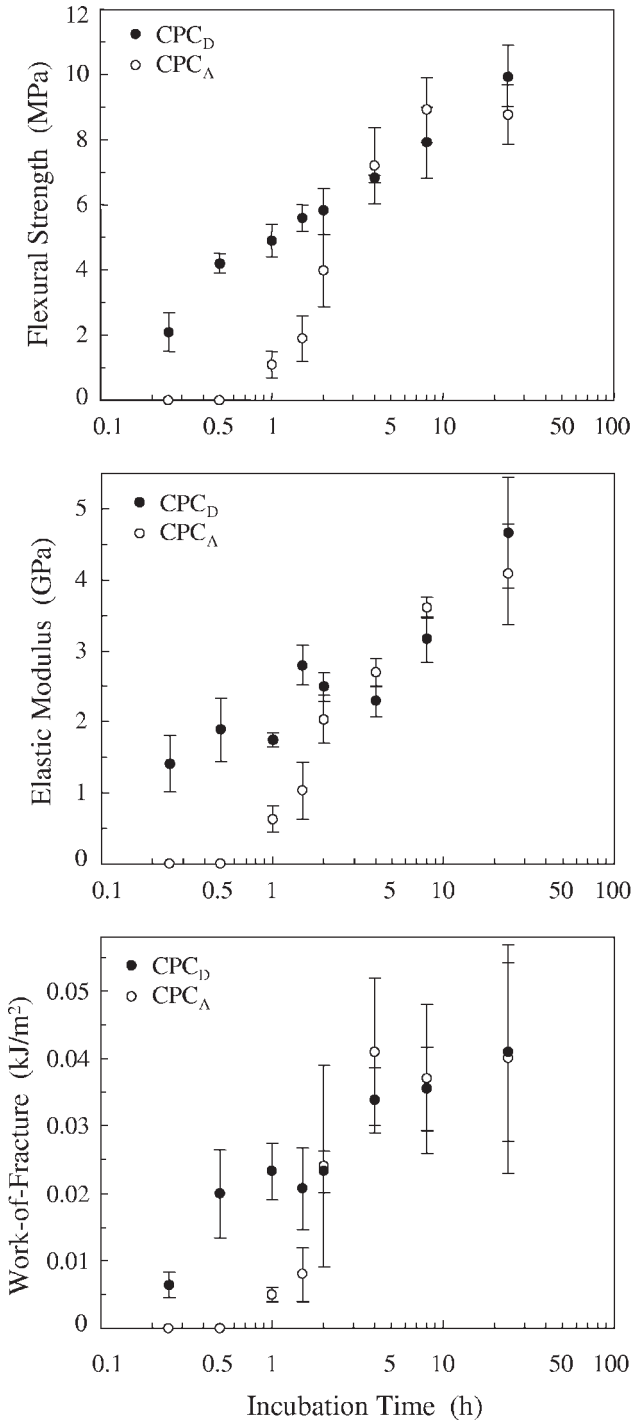

Figure 2. Flexural strength, elastic modulus, and work of fracture versus incubation time. Each value was the mean of five measurements, with the error bar showing one standard deviation (mean ± standard deviation; $n = 5$). For both CPC_D and CPC_A mechanical properties increased with increasing incubation time. However, in the early stage after paste mixing, CPC_D had much higher mechanical properties than CPC_A. CPC_A failed to set at incubation times up to 30 min. CPC_D achieved high early properties (15 min to 2 h) without compromising later-stage properties from 2 to 24 h.

without fibers. Two-way ANOVA of the 2 × 8 design showed significant effects of composition and incubation time, with a significant interaction between the two variables ($p < 0.001$). For CPC_A, the paste failed to set at incubation time up to 30 min. This was radically different from CPC_D, which produced well-set, smooth, strong specimens. CPC_D had flexural strengths (mean ± standard deviation; $n = 5$) of 2.1 ± 0.6 MPa and 4.2 ± 0.3 MPa, at incubation times of 15 min and 30 min, respectively.

At 1 h, CPC_A started to set, exhibiting a flexural strength of 1.1 ± 0.4 MPa. It then monotonically increased to 1.9 ± 0.7 MPa at 1.5 h and 8.9 ± 1.5 MPa at 8 h, after which it plateaued. In comparison, CPC_D possessed strengths of 4.9 ± 0.5 MPa at 1 h and 5.6 ± 0.4 MPa at 1.5 h, three–four times higher than their CPC_A counterparts. The strengths of CPC_A and CPC_D became statistically similar after 2 h (Tukey's at family confidence coefficient of 0.95). Similarly, the elastic modulus and work of fracture of CPC_D were in general several times higher than those of CPC_A at incubation times from 15 min to 1.5 h, then became statistically similar after 2 h.

Conversion to hydroxyapatite

XRD analysis showed that the conversion of the cement components to hydroxyapatite occurred for both CPC_A and CPC_D. The percentage (%) of CPC converted to hydroxyapatite is listed in Table I. From 1–2 h of incubation, a small amount of hydroxyapatite was formed in CPC_A. A relatively large amount of hydroxyapatite was formed in CPC_D as early as 15 min. After incubation time of 2 h, the hydroxyapatite formation accelerated in CPC_A at a faster rate than in CPC_D.

SEM micrographs of fracture surfaces of CPC_D specimens are shown in Figure 3(A,B) at 15-min incubation time and in Figure 3(C,D) at 30-min incubation time.

TABLE I
Percentage of CPC conversion to Hydroxyapatite (HA) as a Function of Incubation Time (Mean ± Standard Deviation; $n = 3$) Obtained from Powder X-Ray Diffraction Analysis

Incubation Time (h)	% HA Conversion in CPC_A	% HA Conversion in CPC_D
0.25	Paste did not set	13.4 ± 0.0
0.5	Paste did not set	18.1 ± 2.1
1	6.2 ± 0.0	19.3 ± 2.1
1.5	6.2 ± 0.0	26.4 ± 2.1
2	8.6 ± 4.1	27.6 ± 0.0
4	45.4 ± 3.6	34.7 ± 0.0
8	79.8 ± 2.1	46.6 ± 5.4
24	85.7 ± 2.1	53.7 ± 4.1

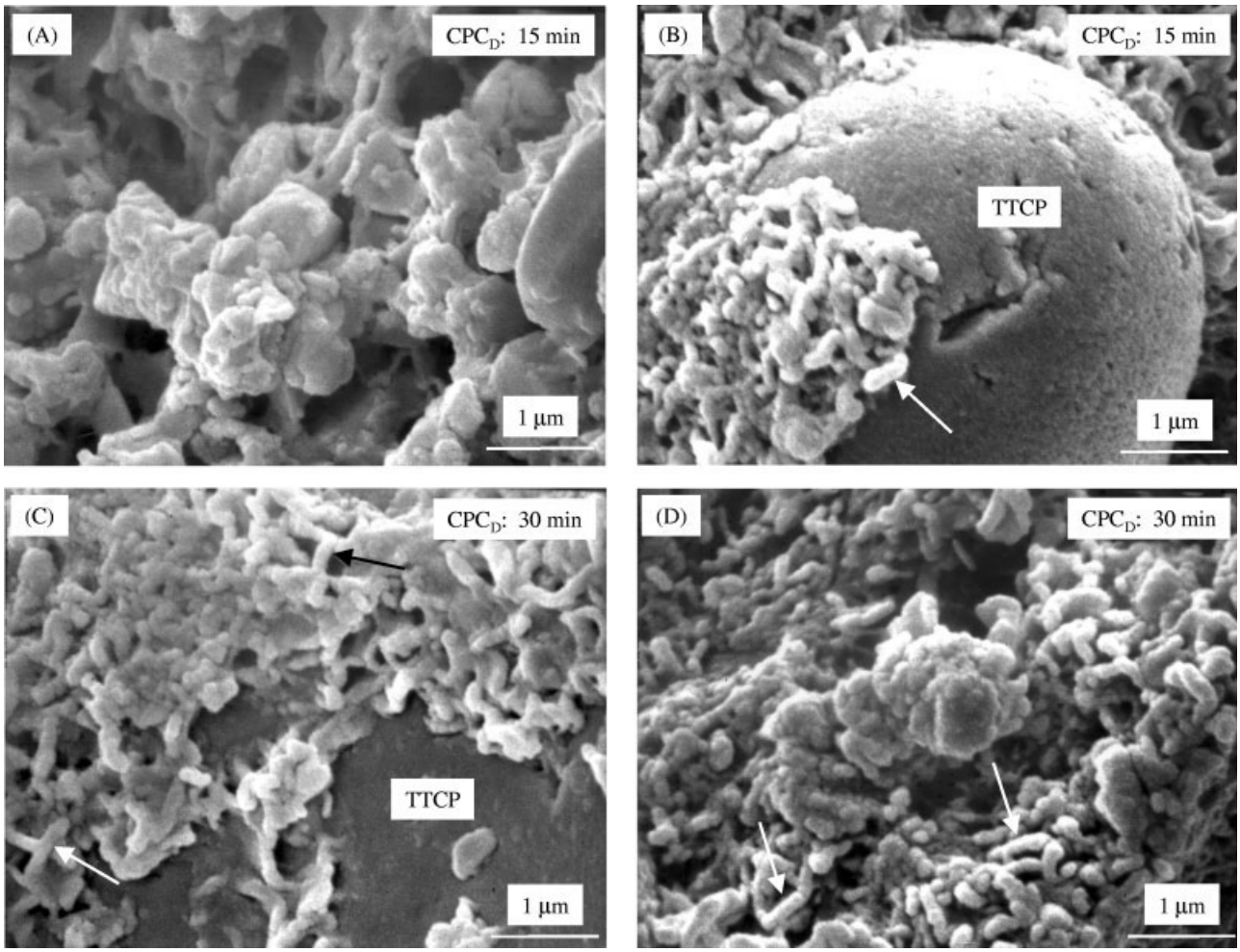

Figure 3. SEM at 15 and 30 min for CPC_D. (A) At 15 min, DCPD particles were still visible. These particles were similar to the starting DCPD particles with a median particle size of 1.3 μm. (B) Small crystals formed on the surfaces of TTCP particles at 15 min. These small crystals are hydroxyapatite crystals because they were not present in the starting powder, and XRD detected the formation of hydroxyapatite. (C) At 30 min, some TTCP particles were covered with the elongated hydroxyapatite crystals, and (D) hydroxyapatite crystals were also observed away from TTCP.

CPC_A is not shown here because it did not set. At 15 min [Fig. 3(A)], some areas of CPC_D consisted of DCPD particles that were not yet consumed in the setting reaction (earlier, the starting powder had a DCPD median particle size of 1.3 μm and a TTCP median particle size of 17 μm). Other areas of the CPC_D fracture surfaces showed small crystals forming on the surfaces of TTCP particles [Fig. 3(B)]. These small, elongated crystals had a diameter of about 0.1 μm and a length of 0.3–0.5 μm [arrows in (B–D)]. They are believed to be hydroxyapatite crystals because they were not present in the starting powder, and XRD detected the formation of hydroxyapatite in these specimens. At 30 min, some TTCP particles were nearly entirely covered with the elongated hydroxyapatite crystals [arrows in Fig. 3(C)], and hydroxyapatite crystals were also observed away from the TTCP particles [arrows in Fig. 3(D)].

Figure 4 shows that at 1 h, hydroxyapatite crystals were observed in both CPC_D and CPC_A. Some areas of the fracture surfaces of CPC_D showed a mixture of small crystals and platelet crystals [Fig. 4(A)]. Larger platelet crystals of a size of a few micrometers were occasionally observed in CPC_D [Fig. 4(B)]. Submicron, elongated crystals were observed in the fractured surfaces of CPC_A [Fig. 4(C)], but no platelets were observed. In addition, DCPD particles similar to Figure 3(A) and TTCP particles similar to Figure 3(B) were still observed, indicating that the setting reaction was ongoing.

At 24 h, submicron crystals were frequently observed in the fracture surfaces of CPC_D, as shown in Figure 5(A), whereas larger platelets were occasionally found [Fig. 5(B)]. The platelets had a wide dimension on the order of 2 μm and a thickness of about 0.1 μm. CPC_A consisted of numerous rod-like hydroxyapatite crystals with a diameter of about 0.1 μm and a length of up to 0.5 μm [Fig. 5(C)].

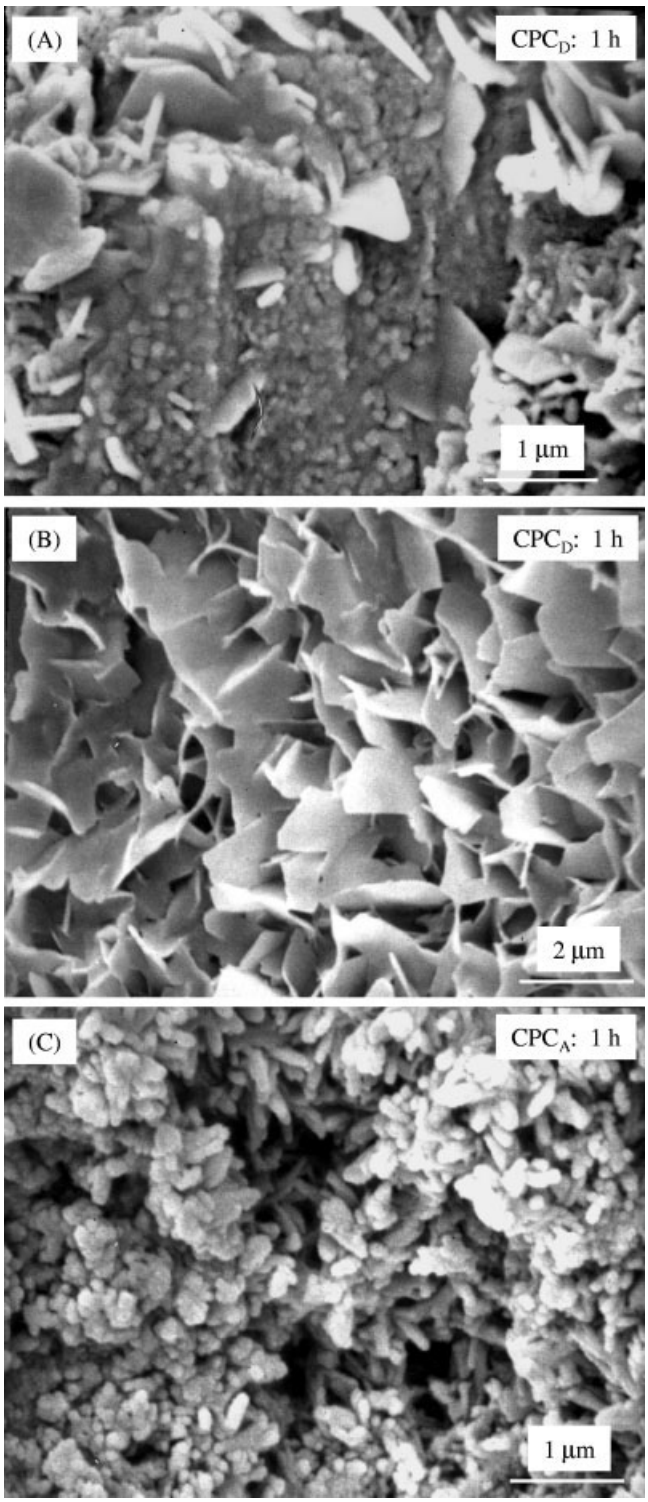

Figure 4. SEM at 1 h for (A) and (B) CPC_D and (C) CPC_A. (A) Some areas of the fractured surfaces of CPC_D showed a mixture of small crystals and platelet crystals. (B) Larger platelet crystals were occasionally observed. (C) Small elongated crystals were observed in CPC_A.

Fiber reinforcement

To further increase the early strength of the hydroxyapatite cements, absorbable fibers were incorporated into the pastes. Figure 6 shows flexural strength, elastic modulus, and work of fracture versus incubation time. Both CPC_D and CPC_A contained 25% volume fraction of fibers. At incubation times of 15 and 30

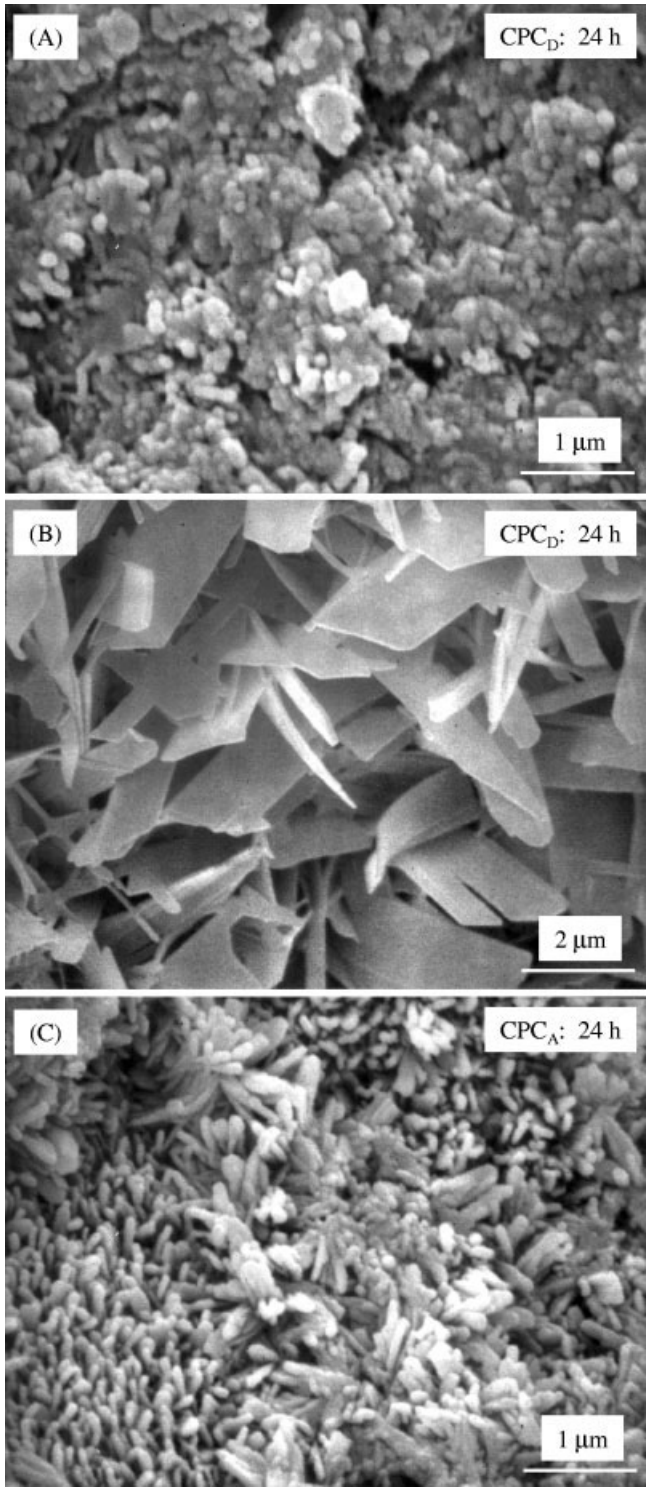

Figure 5. SEM at 24 h for (A) and (B) CPC_D and (C) CPC_A. (A) Small crystals were frequently observed in the fractured surfaces. (B) Large platelets were occasionally observed. (C) Rod-like hydroxyapatite crystals were observed in CPC_A.

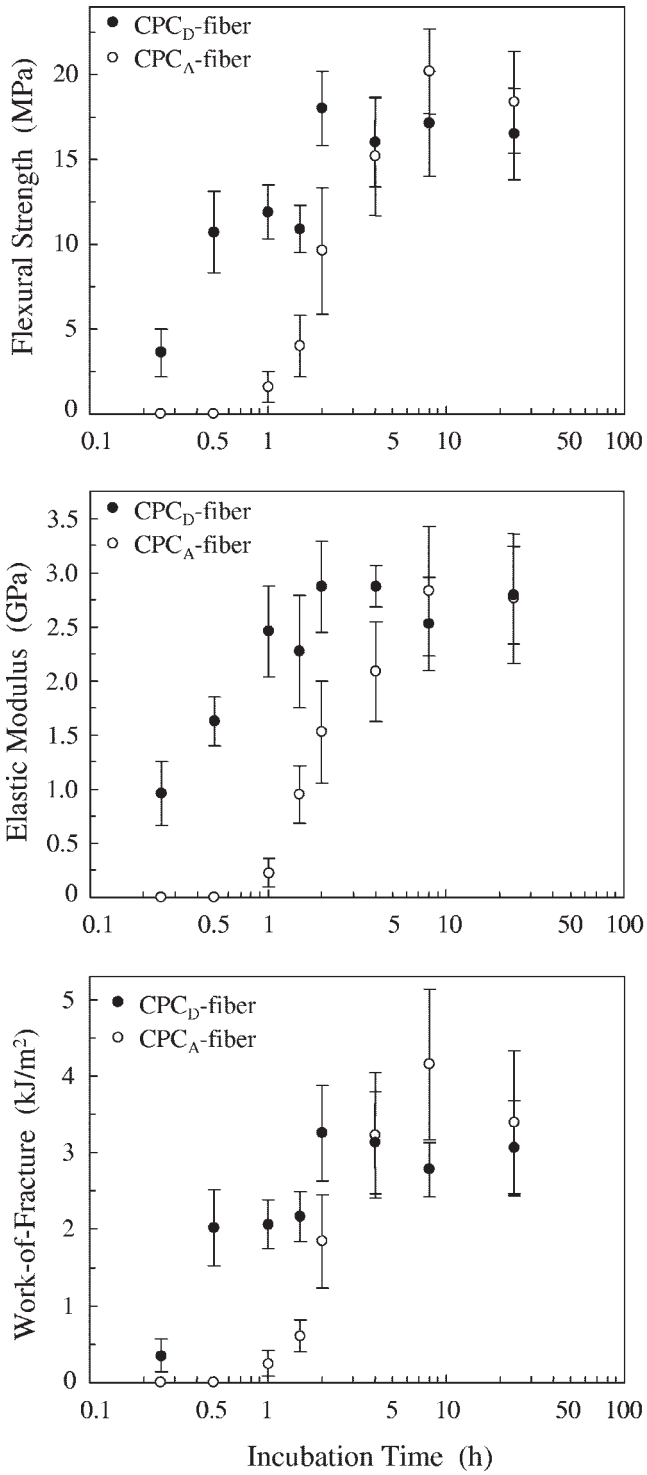

Figure 6. Fiber reinforcement. Flexural strength, elastic modulus, and work of fracture were higher for CPC_D than for CPC_A at incubation times of 15 min to 2 h. For both materials, properties first increased with incubation time, then started to plateau after 8 h. Compared to specimens without fibers (Fig. 2), the strengths of CPC_D and CPC_A fibers were generally about two times higher, the modulus values were slightly lower due to the fibers being less stiff than CPC, and the work of fracture was increased by two orders of magnitude because of fiber reinforcement. Each value was the mean of five measurements with the error bar showing one standard deviation (mean ± standard deviation; $n = 5$).

min, CPC_D-fiber specimens had strengths (mean ± standard deviation; $n = 5$) of 3.6 ± 1.4 MPa and 10.7 ± 2.4 MPa, respectively, while CPC_A failed to set. At 1 h, CPC_D-fiber specimens reached a strength of 11.9 ± 1.6 MPa, whereas that of CPC_A fiber was only 1.6 ± 0.9 MPa. For both materials, the strength, elastic modulus, and work of fracture first increased with incubation time, then plateaued after 8 h. Compared to specimens without fibers (Fig. 2), the strengths of CPC_D and CPC_A fibers were generally about two times higher, the modulus values were slightly lower due to the polymer fibers being less stiff than CPC, and the work of fracture was increased by two orders of magnitude because of fiber reinforcement.

DISCUSSION

Hydroxyapatite cement with substantially improved early strength, elastic modulus, and toughness was developed in the present study via two approaches: (1) use of DCPD instead of DCPA in the cement, and (2) incorporation of absorbable fibers. The first approach resulted in a fast-setting cement, with hardening time reduced by a factor of four (Fig. 1). In the clinical situation, the surgeon needs to place a CPC paste into the prepared bone site and then wait for the paste to sufficiently harden before closing the wound. Otherwise the soft paste could be deformed easily to lose its geometrical shape by the stresses generated in closing the wound, or even be disintegrated and fail to set into a cohesive implant. A long setting time could cause problems because of the cement's inability to support stresses within this time period.[14,26] A severe inflammatory response was observed when CPC failed to set and disintegrated, likely due to a low initial mechanical strength.[13] Another study revealed a transient inflammatory response without foreign-body reaction.[27] The surgeon needs to touch or palpate the cement, or tap the cement lightly, to make sure that the cement has sufficiently set. Only after that can the surgeon close the wound by suturing together the muscle, fascia, and the skin. A hardening time of 15 min for CPC_D (powder:liquid = 3:1) would save valuable time clinically, compared to 80 min for the conventional CPC_A.

The TTCP-DCPD cement set faster than the TTCP-DCPA cement, possibly because the DCPD particles have a faster dissolution rate than DCPA.[18–20] The same faster dissolution of DCPD was likely responsible for the higher hydroxyapatite formation for CPC_D than CPC_A in the first 2 h of cement reaction (Table I). CPC_A had a rapid increase in hydroxyapatite formation after 4 h. This was probably because once DCPA started to significantly dissolve, numerous DCPA particles started dissolving simultaneously. In examining

hydroxyapatite formation, the gold coating on the SEM specimen surfaces prevented charging, but it may have also had some influence on the sharpness of the edges of the hydroxyapatite crystals. This is because some hydroxyapatite crystals in several previous studies[23,28] appeared to have slightly sharper edges. Figures 3–5 showed the formation of hydroxyapatite crystals in CPC_D as early as 15 min, consistent with its fast setting time, and the presence of platelets [Figs. 4(B) and 5(B)] in CPC_D that were generally absent in CPC_A. However, fast setting did not occur with the TTCP-DCPD cement in the pilot study, when commercial DCPD powders were used.[18] This was possibly due to unidentified impurities in the commercial powders.[18] Later, the DCPD powders were processed in the laboratory, as described in the Materials and Methods section, which resulted in much faster setting of the cement. Several previous studies developed novel cements based on DCPD that were self-setting and bioactive, and useful for orthopedic, dental, and drug-delivery applications.[29–32] Compared to the DCPD cements in the previous studies, the cement in the present study had a much shorter hardening time (15 min vs. $>$ 1 h) and higher mechanical strength,[18] without the use of hydroxyapatite seeds. Although a higher purity of the DCPD in the present study may have contributed to the faster setting and higher strength, further studies are needed to examine other processing factors. Previous studies have reported a range of CPC setting times from about 20 min to more than 100 min,[33] suggesting the dependence of setting on microstructural and processing parameters. Hence it is possible that the setting time of both CPC_D and CPC_A could be further shortened by optimizing the particle size and size distribution, which warrants further study.

Early strength was dramatically increased via the two approaches. At 30 min after paste mixing, the conventional CPC (CPC_A) was still a paste and had no measurable strength. The first approach resulted in the setting of solid CPC_D specimens with a flexural strength 4.2 MPa. The second approach resulted in the CPC_D-fiber specimens possessing an even higher strength of 10.7 MPa. In comparison, the flexural strength of available sintered porous hydroxyapatite implants ranged from 2–11 MPa.[34] Cancellous bone has a tensile strength of about 3.5 MPa.[35] The CPC_D-fiber paste could harden in 15 min to develop a strength of 3.6 MPa, similar to that of cancellous bone. At 30 min after implantation, it further developed a strength similar to sintered porous hydroxyapatite implants. Sintered hydroxyapatite implants require machining to fit to a prepared bony defect, and are usually not resorbable or replaceable by new bone.[36,37] Histologic analyses showed that nonresorbable hydroxyapatite induced little new bone fill, and very limited, if any, periodontal bone regeneration.[37] In contrast, the CPC_D-fiber paste can harden *in situ* in the bone cavity, resulting in intimate contact with neighboring bone, and both CPC and the fiber can be resorbed and replaced by new bone. The elastic modulus of CPC_D-fiber specimens reached 1.63 GPa at 30 min, compared to an elastic modulus measured in flexure of about 12.8 GPa for cortical bone[38] and 0.3 GPa for cancellous bone.[39] The work of fracture at 30 min for CPC_D fiber was 2.0 kJ/m^2, compared to a work of fracture of about 1.5 kJ/m^2 for cortical bone.[40] Such improvements in mechanical properties in the early stage immediately after paste placement, imparted by the two approaches, should help protect the CPC implant from catastrophic fracture or disintegration under stresses. Animal and clinical studies are needed to investigate the use of the CPC_D-fiber hydroxyapatite cement in moderate stress-bearing bone repairs. In addition, the cyclic fatigue properties of the CPC_D-fiber composite also need to be investigated to simulate the cyclic loading in clinical applications.

In a previous study on fiber reinforcement of CPC, a semiempirical equation was obtained that relates the CPC-fiber composite strength, S_c, to the fiber strength, S_f[28]

$$S_c = S_m + \alpha S_f \quad (1)$$

where S_m is the strength of the matrix, and α is a coefficient. Fitting the experimental data to Eq. (1) yielded $S_c = 12.5 + 0.0082S_f$ for the compositions used in the previous study.[28] In that study, the matrix was held constant, and S_f was varied by using different types of fibers.[28] In the present study, S_f was kept constant, and the CPC matrix was varied by changing the incubation time. The coefficient α in Eq. (1) should be proportional to S_m, because when the CPC paste did not set, $S_m = 0$ and $S_c = 0$, thus requiring that $\alpha = 0$. This is because there was no matrix holding and supporting the fibers. Although the fibers are strong, without a matrix there is no composite nor composite strength. Hence it is assumed that $\alpha = \beta S_m$ to satisfy the condition that in Eq. (1), when $S_m = 0$, so should S_c, even when S_f is not zero. Therefore, $S_c = S_m + \beta S_m S_f = S_m (1 + \beta S_f)$, and finally

$$S_c = \gamma S_m \quad (2)$$

where $\gamma = 1 + \beta S_f$. Figure 7 plots the measured composite strength S_c from Figure 6 versus the corresponding S_m from Figure 2. The straight line in Figure 7 is a linear best fit through the origin with a correlation coefficient $R = 0.93$, yielding

$$S_c = 2.16\ S_m \quad (3)$$

This suggests that

1. When the fiber type, fiber length, and fiber volume fraction were kept constant, the composite

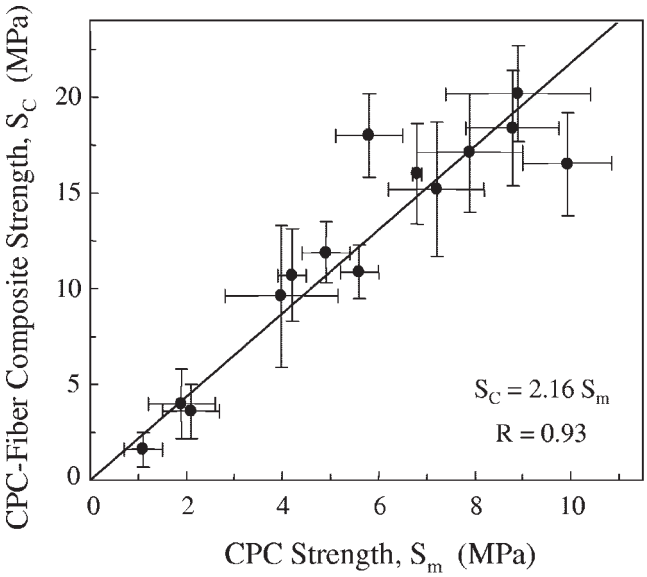

Figure 7. Experimentally measured data on composite strength, S_c, and CPC matrix strength, S_m, were fitted to Eq. (2) by linear regression, resulting in the establishment of Eq. (3): $S_c = 2.16S_m$, with a correlation coefficient $R = 0.93$. Each value was the mean of five measurements, with the error bar showing one standard deviation (mean ± SD; $n = 5$).

strength increased linearly when the matrix strength was increased.

2. The CPC composite strength was, in general, 2.16 times higher than the strength of CPC without fibers, when the suture fibers at 25% volume fraction and 8-mm length were randomly mixed into the CPC paste.

Although this study focused on the development of early strength for the implant, previous studies investigated the longer-term properties of absorbable fiber-reinforced CPC.[14,24,41] The suture fibers were chosen because a previous clinical study showed that these fibers had significant potential as an absorbable dural substitute with minimal inflammatory reaction.[42] These large-diameter fibers provided significant strength and toughness to the implant for several weeks.[24] Then, long cylindrical macropores of 293 ± 46 μm in diameter were created in CPC after fiber dissolution.[24,43] When implanted *in vivo*, the fibers should degrade to expose macropores for bony ingrowth. The strengthening of the graft from bony ingrowth and the deposition of new bone[34,44] should help offset the weakening of the graft due to fiber degradation. The CPC-fiber composite was shown in a previous study to support osteoblast cell adhesion, proliferation, and viability.[43] The method of using large-diameter absorbable fibers in bone graft for mechanical strengthening and formation of long cylindrical macropores for bone ingrowth may be applicable to other tissue-engineering materials.

SUMMARY

Substantial early strength and toughness were imparted to a moldable, self-hardening, and resorbable hydroxyapatite bone repair material via two approaches: the use of DCPD instead of DCPA, and the incorporation of absorbable fibers. As a result, the paste hardening time was reduced from about 80 min to 15 min, which should significantly shorten the surgical time. SEM revealed the progressive formation of nanosized rod-like hydroxyapatite crystals and platelet crystals in the cements. The flexural strength quickly reached 10.7 MPa for the CPC_D-fiber cement in 30 min, compared to 0 MPa for the conventional CPC_A, which did not set. Such a high early strength matched the reported strength for cancellous bone and sintered porous hydroxyapatite implants. The work of fracture (toughness) was increased by two orders of magnitude for CPC_D-fiber specimens. A previous study observed disintegration of the conventional CPC implant, "possibly due to lower initial mechanical strength, resulting in severe foreign-body response."[4] Therefore, the high early strength and toughness of the new CPC_D-fiber formulation, developed in the present study, should help protect the implant from catastrophic fracture or disintegration under stresses. The composite strength was correlated to the matrix strength by $S_c = 2.16S_m$, suggesting that the development of a strong matrix was as important as the incorporation of a strong reinforcing agent. The method of synergistic use of a strong matrix (CPC_D) and a reinforcing agent (absorbable fibers) in a bone graft may be applicable to other tissue-engineering materials.

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