Injectable and Rapid-Setting Calcium Phosphate Bone Cement with Dicalcium Phosphate Dihydrate

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Abstract: Calcium phosphate cement (CPC) sets *in situ* with intimate adaptation to the contours of defect surfaces, and forms an implant having a structure and composition similar to hydroxyapatite, the putative mineral in teeth and bones. The objective of the present study was to develop an injectable CPC using dicalcium phosphate dihydrate (DCPD) with a high solubility for rapid setting. Two agents were incorporated to impart injectability and fast-hardening to the cement: a hardening accelerator (sodium phosphate) and a gelling agent (hydroxypropyl methylcellulose, HPMC). The cement with DCPD was designated as CPC_D, and the conventional cement was referred to as CPC_A. Using water without sodium phosphate, CPC_A had a setting time of 82 ± 6 min. In contrast, CPC_D exhibited rapid setting with a time of 17 ± 1 min. At 0.2 mol/L sodium phosphate, setting time for CPC_D was 15 ± 1 min, significantly faster than 40 ± 2 min for CPC_A (Tukey's at 0.95). Sodium phosphate decreased the paste injectability (measured as the paste mass extruded from the syringe divided by the original paste mass inside the syringe). However, the addition of HPMC dramatically increased the paste injectability. For CPC_D, the injectability was increased from 65% ± 12% without HPMC to 98% ± 1% with 1% HPMC. Injectability of CPC_A was also doubled to 99% ± 1%. The injectable and rapid-setting CPC_D possessed flexural strength and elastic modulus values overlapping the reported values for sintered porous hydroxyapatite implants and cancellous bone. In summary, the rapid setting and relatively high strength and elastic modulus of CPC_D should help the graft to quickly attain strength and geometrical integrity within a short period of time postoperatively. Furthermore, the injectability of CPC_D may have potential for procedures involving defects with limited accessibility or narrow cavities, when there is a need for precise placement of the paste, and when using minimally invasive surgical techniques. © 2005 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 77B: 126–134, 2006

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INTRODUCTION

Approximately one million bone grafts are performed each year in the United States to treat osseous defects.[1,2] This need is increasing dramatically as the world population ages.[3] Autograft, the gold standard in bone repair, is restricted by bone availability, donor site morbidity, and contouring difficulty. Allografts and xenografts raise concerns of immunorejection and disease transmission. These factors are providing much of the driving force for the development of synthetic biomaterials. Calcium phosphate biomaterials have gained clinical acceptance for bone substitution and augmentation.[4–11] Porous calcium phosphate scaffolds have been developed to facilitate tissue ingrowth[12–14] by using controlled pore architectures[15] and three-dimensional fabrication techniques.[16]

Calcium phosphate cements can be easily manipulated and shaped, provide intimate adaptation to the contours of defect surfaces, and set *in situ* in the bone cavity to form a solid restoration.[17] The concept of calcium phosphates as possible cement materials was first introduced in 1982.[18] The first calcium phosphate cement (CPC) was reported in 1987.[17] Since then, many compositions have been formulated.[17,19–22]

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CPC is comprised of a mixture of tetracalcium phosphate [TTCP: $Ca_4(PO_4)_2O$] and dicalcium phosphate anhydrous (DCPA: $CaHPO_4$).[17] The CPC powder can be mixed with an aqueous liquid to form a paste[23–26] where the water provides a vehicle for the dissolution of the reactants and the precipitation of the product. The set cement has a structure and composition similar to hydroxyapatite, the putative mineral in teeth and bones: $2Ca_4(PO_4)_2O + 2CaHPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2$.[17,26] Due to its excellent osteoconductivity and bone replacement capability, CPC is highly promising for a wide variety of clinical applications.[17,23–26]

In other *in vitro* studies, dicalcium phosphate dihydrate (DCPD, $CaHPO_4 \cdot 2H_2O$), a compound with a relatively high solubility, was used to replace the DCPA component in CPC to form hydroxyapatite [27,28]: $2Ca_4(PO_4)_2O + 2CaHPO_4 \cdot 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 4H_2O$. The conventional cement from DCPA–TTCP was referred to as CPC_A, and the cement from DCPD–TTCP was termed CPC_D.[28] The high solubility of DCPD resulted in faster setting and higher early strength for CPC_D.[28] Thirty minutes after powder and liquid mixing, CPC_D developed a flexural strength of 4.2 MPa, while CPC_A was not set and consequently had no strength.[28] Fast setting is desirable because a long setting time can result in the crumbling of the inserted paste when it comes in early contact with physiological fluids, or when bleeding occurs due to the difficulty to achieve complete hemostasis in some cases.[21,29,30] High early strength is needed to prevent early-stage implant failure or disintegration.[28]

In addition to rapid setting and early strength, the injectability of a CPC paste is also an important property. This is especially true in procedures involving defects with limited accessibility or narrow cavities, when there is a need for precise placement of the paste to conform to a defect area, and when using minimally invasive surgical techniques.[31–37] Several factors affecting the injectability of a number of calcium phosphate cements have been examined.[31–37] However, the injectability of the high early-strength CPC_D[27,28] remains to be investigated.

The objective of the present study was to investigate the injectability of CPC_D in comparison with the conventional CPC_A, and to examine the effects of incorporating a hardening accelerator and a gelling agent. The tested hypotheses were: (1) incorporating sodium phosphate into the cement liquid would impart rapid setting to the cement, but would decrease the paste's injectability; (2) incorporating hydroxypropyl methylcellulose would improve the paste's injectability, without compromising the mechanical strength; and (3) the use of DCPD with its high solubility for rapid setting would not reduce the paste's injectability compared to DCPA.

MATERIALS AND METHODS

Synthesis of Cement Powders

TTCP was synthesized from a solid-state reaction between $CaHPO_4$ and $CaCO_3$ (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).[17] The heated mixture was quenched to room temperature and ground dry in a ball mill (Retsch PM4, Brinkman, NY). The TTCP powder was then sieved using a standard testing sieve (W. S. Tyler Inc., Mentor, OH) with openings of 38 μm to remove the large particles. The TTCP powder that went through the sieve was collected and analyzed. The particle size distribution was measured by a sedimentation method with the use of a centrifugal particle analyzer (SA-CP3, Shimazu, Kyoto, Japan), which yielded a TTCP particle size range of about 1 μm to 60 μm and a median particle size of 20 μm. The commercial DCPA powder was ground and then analyzed using the same particle size analyzer, which reported a particle size range of 0.4 μm to 6 μm and a median particle size of 1.2 μm. The TTCP and DCPA powders were mixed in a micromill (Bel-Alert Products, Pequannock, NJ) in equimolar amounts to form the powder for the cement designated as CPC_A.

Commercial DCPD powders were first used in our pilot studies,[27] but the resulting TTCP–DCPD pastes exhibited undesirable long setting times of > 1 h. This was likely due to unidentified impurities in the commercial powders.[27] Hence DCPD in the present study was prepared in our laboratory. To synthesize DCPD, the pH of a DCPD–monocalcium phosphate monohydrate singular point solution (pH = 1.9, 4°C) was slowly raised via the addition of $CaCO_3$.[27,28] DCPD that precipitated before the pH reached 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.[27,28] The DCPD was ground and then analyzed using the same particle size analyzer that showed a particle size range of 0.5 μm to 4 μm and a median particle size of 1.3 μm. The DCPD powder was then mixed with the TTCP powder at a molar ratio of 1:1 to form the powder for the cement referred to as CPC_D.

Cement Liquids

Two types of liquid were used: (1) aqueous sodium phosphate solution and (2) aqueous sodium phosphate–hydroxypropyl methylcellulose solution. The sodium phosphate solutions were prepared by diluting a 3 mol/L phosphate solution (Na_2HPO_4 and NaH_2PO_4, Abbott Laboratories, North Chicago, IL) with distilled water at the following sodium phosphate concentrations: 0 mol/L (distilled water without sodium phosphate), 0.1 mol/L, 0.2 mol/L, 0.3 mol/L, 0.4 mol/L, and 0.5 mol/L. In a previous study,[30] sodium phosphate imparted fast setting to CPC_A. But the very fast-setting property might exert adverse effects on the paste injectability because of paste thickening and stiffening caused by the rapid setting. Hence, the purpose here was to examine the effect of sodium phosphate on setting time as well as injectability for both CPC_A and CPC_D.

For the second type of liquid, hydroxypropyl methylcellulose (HPMC, Sigma, St. Louis, MO) was added to the liquid containing 0.2 mol/L sodium phosphate because this

concentration imparted rapid setting while only moderately reducing the paste's injectability. HPMC mass fractions in the liquid were: 0 % (without HPMC), 0.5 %, 1 %, 2 %, and 3 %. HPMC was used here as a gelling agent because previous studies showed that it improved paste cohesiveness.[30,38,39]

Setting Time Measurement

Two groups of specimens were tested. The first group had a 2 × 6 full factorial design, with two cements (CPC_D and CPC_A) and the sodium phosphate solution having the six concentrations described above.

The second group had a 2 × 5 full factorial design, with two cements (CPC_D and CPC_A) and five liquids having the five HPMC mass fractions described above.

Each powder and liquid were manually mixed with a spatula at a powder:liquid mass ratio of 2:1, slightly lower than the 2.5:1 used in a previous study on injection.[32] The purpose of the lower ratio was to form a flowable paste while providing room for additions of macropore forming particles[40] and reinforcing fibers[41,42] to the paste in future studies. The paste was filled into a stainless-steel mold of 6 mm diameter and 3 mm depth.[39] Each specimen was incubated in a humidor with 100% relative humidity at 37°C. Following the method used in previous studies,[30,38,39] when the powder component of the specimen did not come off when scrubbed gently with fingers, the setting reaction had occurred enough to hold the specimen together. The time measured from the powder and liquid mixing to this point was used as the setting time.[30,38,39]

Injectability Testing

The same factorial designs as in the Setting Time Measurement were subjected to an injectability test. A 10-mL syringe (Free-Flo, Kerr, Romulus, MI) with a diameter of 10 mm and an opening of 2.8 mm was used. The syringe was similar to those used in previous studies on calcium phosphate injection while the opening was slightly larger than the 2 mm used earlier.[31,32] This was because we planned to add strengthening fibers[28,41,42] of possibly 3-mm length to the injectable paste in future studies. Each cement powder of 2 g was mixed with 1 g of the corresponding liquid and placed into the syringe. The syringe was placed between the compression plates of a computer-controlled Universal Testing Machine (5500R, MTS Systems Corp., Cary, NC). At 1.5 min from the mixing, compression was started and the cement was extruded from the syringe at a crosshead speed of 15 mm/min until a maximum force of 100*N* was achieved, following the methods reported in previous studies.[31,32] Injectability was determined as the mass of the paste extruded from the syringe divided by the original mass of the paste inside the syringe.[31,32,36] The force of 100*N* was selected because it could be applied in clinical applications.[31,32]

Specimen Fabrication

To compare mechanical properties of injectable CPC_D and CPC_A and to investigate the effect of incorporating HPMC, a 2 × 5 full factorial design was tested with two materials (CPC_A and CPC_D) and five liquids with the five HPMC fractions described in Cement Liquids. Steel molds of 3 mm × 4 mm × 25 mm were used to make flexural specimens.[28,41,42] Each specimen was allowed to set in the humidor for 4 h, then demolded and immersed in distilled water at 37°C for 20 h.[30,40] The CPC conversion to hydroxyapatite was shown to be largely complete during the 24 h incubation.[17,26,40]

Mechanical Testing

Specimens were fractured using a three-point flexural test with 20-mm span at a crosshead speed of 1 mm/min on the same Universal Testing Machine.[40,41] Four-point flexure is a preferred test because it samples a volume of the specimen,[43,44] while three-point flexure samples a thin plane in the specimen. When the loading was started in four-point flexure, usually one of the two upper pins of the four-point fixture touched the specimen first. After preloading, the two loading pins then both touched the specimen and shared the applied load. Some of the relatively weak CPC specimens broke under the first touching pin, instead of breaking somewhere between the two loading pins. A flexural strength of 3 MPa to 5 MPa (Figure 3) is much lower than, for example, 60 MPa of a dental composite[43] and 200 MPa of a dental glass–ceramic.[44] Therefore, three-point flexure was used in the present study. The flexural strength was calculated by $S = 3P_{max}L/(2bh^2)$, where P_{max} is the maximum load on the load-displacement (*P-d*) curve, L is the span, b is specimen width, and h is specimen thickness. The elastic modulus $E = (P/d)(L^3/[4bh^3])$, where P divided by the corresponding d is the slope of the *P-d* curve in the linear elastic region. The work-of-fracture (toughness) was calculated by $WOF = A/(bh)$, where A is the area under the *P-d* curve, which is the work done to deform and fracture the specimen.[40,41]

Microscopy and Statistics

The fracture surfaces of selected specimens were sputter coated with gold and examined with a scanning electron microscope (SEM, JEOL 5300, Peabody, MA). Two-way and one-way analyses of variance (ANOVA) were performed to detect significant effects of sodium phosphate concentration and HMPC mass fraction on setting time, injectability, and mechanical properties. Tukey's multiple comparison was used to compare the data at a family confidence coefficient of 0.95. Linear and nonlinear regressions were used to analyze the data. 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.

RESULTS

Effects of Sodium Phosphate

Figure 1 plots setting time T and injectability I versus sodium phosphate concentration, C. Two-way ANOVA identified

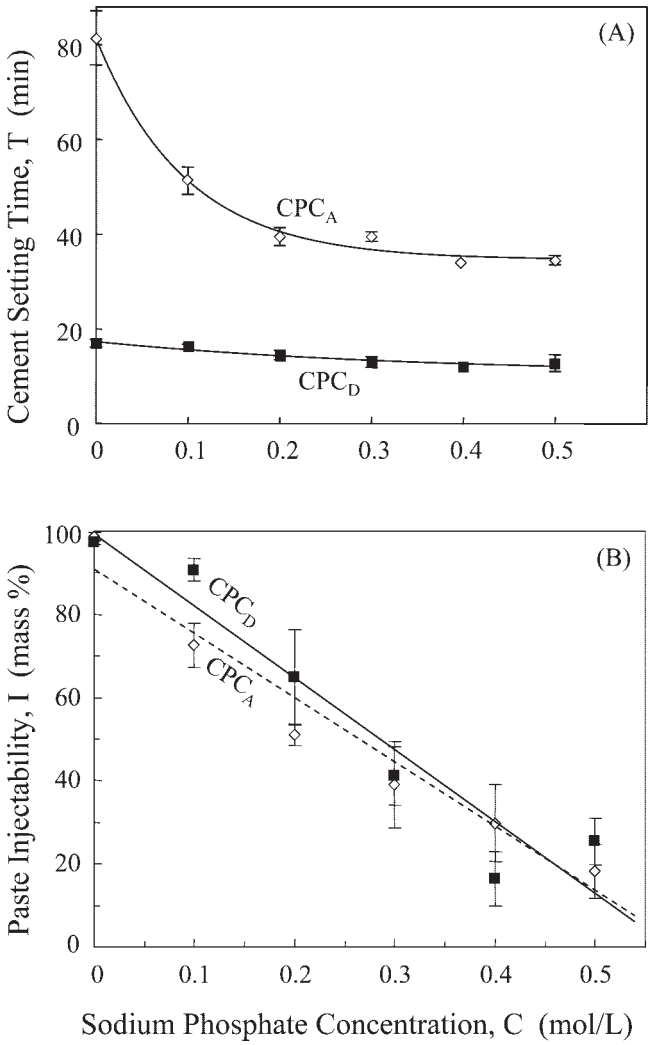

Figure 1. (A) Cement setting time and (B) injectability versus sodium phosphate concentration. The cement liquid contained no hydroxypropyl methylcellulose (HPMC). Each value is the mean of four measurements with the error bar showing one standard deviation (mean ± SD; $n = 4$). The conventional CPC_A had a long setting time with water, while adding sodium phosphate significantly decreased the setting time. The new CPC_D exhibited much faster setting than CPC_A. Increasing the sodium phosphate concentration decreased the injectability.

significant effects ($p < 0.001$) of C and cement composition (CPC_D vs. CPC_A), with a significant interaction between the two factors ($p < 0.001$). Adding sodium phosphate to the liquid resulted in faster setting. The curves in Figure 1(A) were best fits using a three-parameter exponential decay model.[45] This yielded $T = 35 + 47e^{-10C}$ (correlation coefficient, $R^2 = 0.99$) for CPC_A, and $T = 11 + 7e^{-3C}$ ($R^2 = 0.92$) for CPC_D. They show that T decreased at a higher power of 10 for CPC_A than the 3 for CPC_D. As C increased, T approached 35 min for CPC_A and 11 min for CPC_D. At each sodium phosphate concentration, CPC_D had a shorter setting time than CPC_A (Tukey's multiple comparison at family confidence coefficient of 0.95).

Increasing sodium phosphate concentration significantly decreased the paste injectability, I [Figure 1(B)]. The lines in Figure 1(B) are linear best fits to the experimental data, yielding $I = 99–173C$ for CPC_D with $R^2 = 0.92$, and $I = 90–155C$ for CPC_A with $R^2 = 0.95$. The two materials exhibited a similar trend of rapidly decreasing injectability, with I at 0.5 mol/L sodium phosphate being about 1/5 of the injectability at 0 mol/L sodium phosphate.

Effects of Hydroxypropyl Methylcellulose (HPMC)

The above experiment showed that the addition of sodium phosphate imparted rapid setting, but also decreased the paste injectability. Hence, HPMC was added to the liquid containing an intermediate concentration of 0.2 mol/L sodium phosphate to improve the paste's injectability. Figure 2(A) shows that HPMC did not adversely prolong the setting time. Actually, both CPC_D and CPC_A exhibited shorter setting times at intermediate HPMC concentrations. For CPC_A, setting

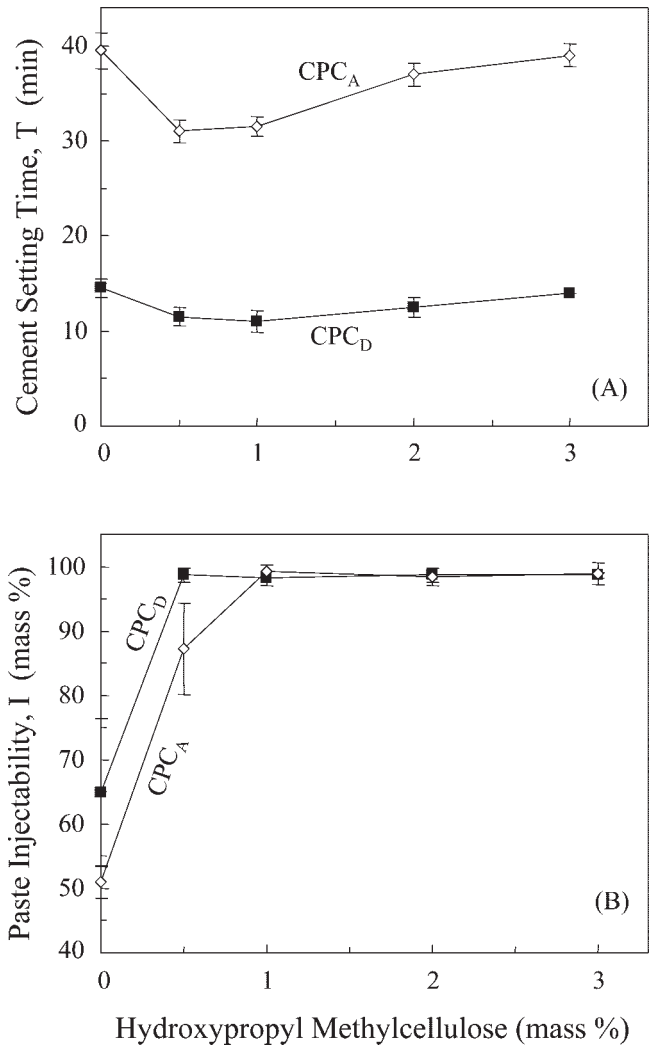

Figure 2. (A) Setting time and (B) injectability versus HPMC. The cement liquid contained 0.2 mol/L sodium phosphate. Adding HPMC to the liquid did not prolong the setting time; in fact, the setting time was reduced at HPMC fractions of 0.5% and 1%. The addition of HPMC dramatically increased the paste injectability. Each value is mean ± SD; $n = 4$.

time (mean ± SD; $n = 4$) was 32 ± 1 min at 1% HPMC, significantly faster than 40 ± 2 min at 0% HPMC and 39 ± 1 min at 3% HPMC ($p < 0.05$). Setting time of CPC_D was about three times faster than CPC_A, and reached 11 ± 1 min at 1% HPMC.

HPMC addition dramatically increased the paste injectability [Figure 2(B)]. For CPC_D, injectability was increased from 65% ± 12% without HPMC to the maximum measurable 98% ± 1% with 0.5% HPMC. For CPC_A, injectability achieved the maximum measurable 99% ± 1% with 1% HPMC. Both CPCs remained at the maximum injectability as the HPMC concentration was increased to 2% and 3%.

Mechanical Properties

HPMC improved paste injectability. To examine whether HPMC adversely affects mechanical properties, the flexural strength, elastic modulus, and work-of-fracture were measured (Figure 3). Both CPC_D and CPC_A showed no decrease in strength with increasing HPMC fraction. CPC_D had significantly higher strengths than CPC_A at 0%, 1%, and 2% of HPMC ($p < 0.05$). CPC_D had significantly ($p < 0.05$) higher work-of-fracture than CPC_A at all HPMC fractions except 3%. For elastic modulus, two-way ANOVA showed no significant effect for HPMC ($p = 0.073$) or cement composition (CPC_D vs. CPC_A) ($p = 0.756$).

Fracture Surfaces

SEM micrographs of fracture surfaces are shown in Figure 4 for CPC_A. CPC_A had small crystals that appeared to be needle-shaped (arrow), with a thickness of approximately 100 nm and a length of 300 nm. No significant differences were found between fracture surfaces with or without HPMC.

In Figure 5(A), CPC_D consisted of a mixture of needle-shaped nanocrystals and platelets. Occasionally, relatively larger platelet crystals were also observed in the fracture surfaces of CPC_D [Figure 5(B)]. The features in Figure 5(A,B) were observed in CPC_D without HPMC or with HPMC. The relatively large platelets were not observed in CPC_A. As reported in previous studies, crystals of such shapes and sizes were not present in the starting powder of the cement, and X-ray diffraction analysis showed that the set cement had converted to hydroxyapatite.[28]

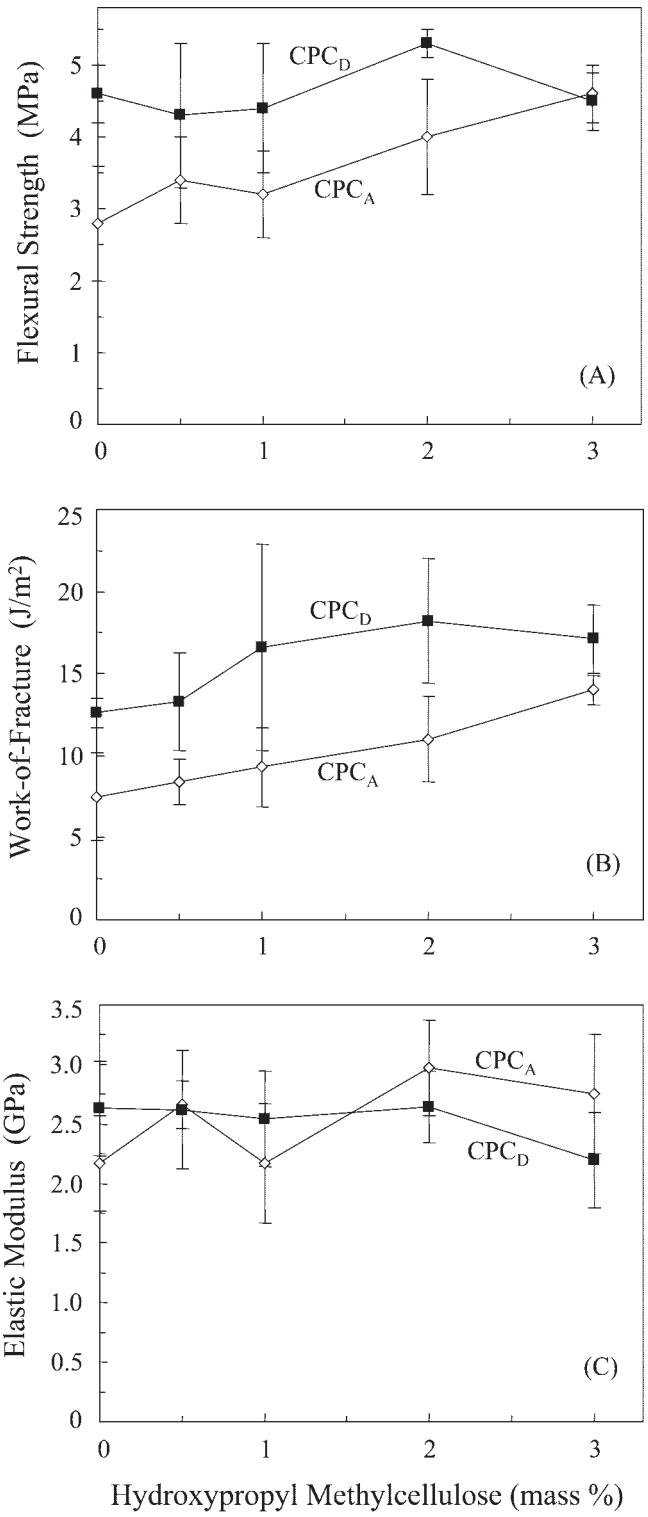

Figure 3. (A) Flexural strength, (B) work-of-fracture (toughness), and (C) elastic modulus versus hydroxypropyl methylcellulose (HPMC) mass fraction. The liquid contained 0.2 mol/L sodium phosphate. Each value is the mean ± SD; $n = 6$.

DISCUSSION

Injectable calcium phosphate cements can be placed easily in surgery and have potential for minimally invasive techniques. This may widen the applications of CPC to surgical sites that are not freely accessible by open surgery and areas that involve narrow defects and *in situ* fracture fixation. It has been reported by surgeons that calcium phosphate cements are poorly injectable.[35,37] This is because when a calcium phosphate powder and water are mixed into a paste and delivered through a wide bore needle or cannula, a filter-pressing phenomenon can occur in which the liquid is pushed out but a major portion of the powder remains inside the syringe, leading to the phase separation of liquid and solid.[36] Previous studies on calcium phosphate cements have investigated the dependence of injectability on powder-to-liquid

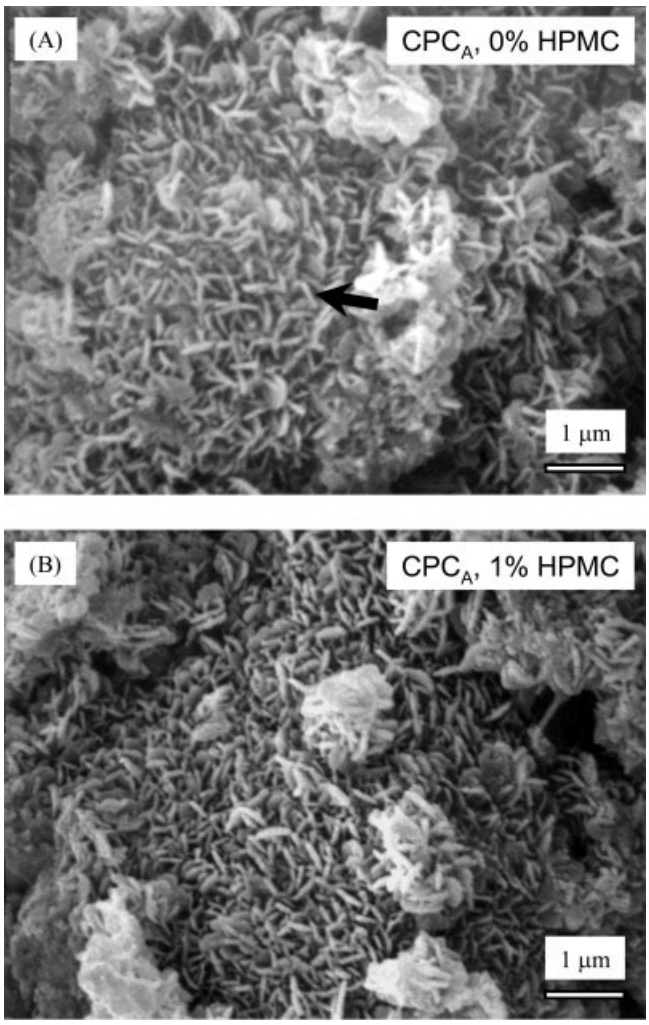

Figure 4. SEM of specimen fracture surfaces showing the *in situ* formation of nanohydroxyapatite crystals at body temperature (37°C). CPC_A had nanosized hydroxyapatite crystals that were elongated (arrow). The cement liquid contained 0.2 mol/L sodium phosphate. No significant differences were observed in fracture surfaces of specimens with or without HPMC.

ratio and time after mixing,[31] particle shape,[35] and particle size.[37] The effects of adding a polymeric drug,[32] incorporation of citric acid,[33] use of oscillatory mixing,[46] and ion modification[36] have also been shown to influence the injectability.

Injectability and rapid setting can be opposing properties because a rapid setting paste may start setting in the syringe thus increasing the paste thickness and rigidity, and reducing its injectability. Improvements in injectability via powder or liquid modifications may inadvertently result in slow setting. Therefore, any enhancement in paste injectability should not compromise other critical properties, such as setting time. For example, the addition of glycerol improved the injectability of a calcium phosphate cement, but greatly increased its setting time.[47] A long setting time could cause problems because of the cement's inability to support stresses during this time period.[21,29,30] For example, a severe inflammatory response was observed when CPC failed to set and disintegrated, likely due to low initial mechanical strength.[21,29]

In the present study, using dicalcium phosphate dihydrate prepared in our laboratory, a gelling agent, and a hardening accelerator, a unique cement was developed that was not only injectable but also rapid setting. CPC_D with 0.2 mol/L sodium phosphate and 1% HPMC achieved a setting time of 11 min together with 99% of paste injectability under the specified experimental conditions. In comparison, the conventional CPC_A was injectable but had a long setting time of 32 mm with 0.2 mol/L sodium phosphate and 1% HPMC. The rapid setting of the injectable CPC_D should yield a graft that can attain early strength and geometrical integrity.

Sodium phosphate concentration had a significant effect on setting time [Figure 1(A)]. TTCP [$Ca_4(PO_4)_2O$], DCPD ($CaHPO_4 \cdot 2H_2O$), and DCPA ($CaHPO_4$) dissolved in water

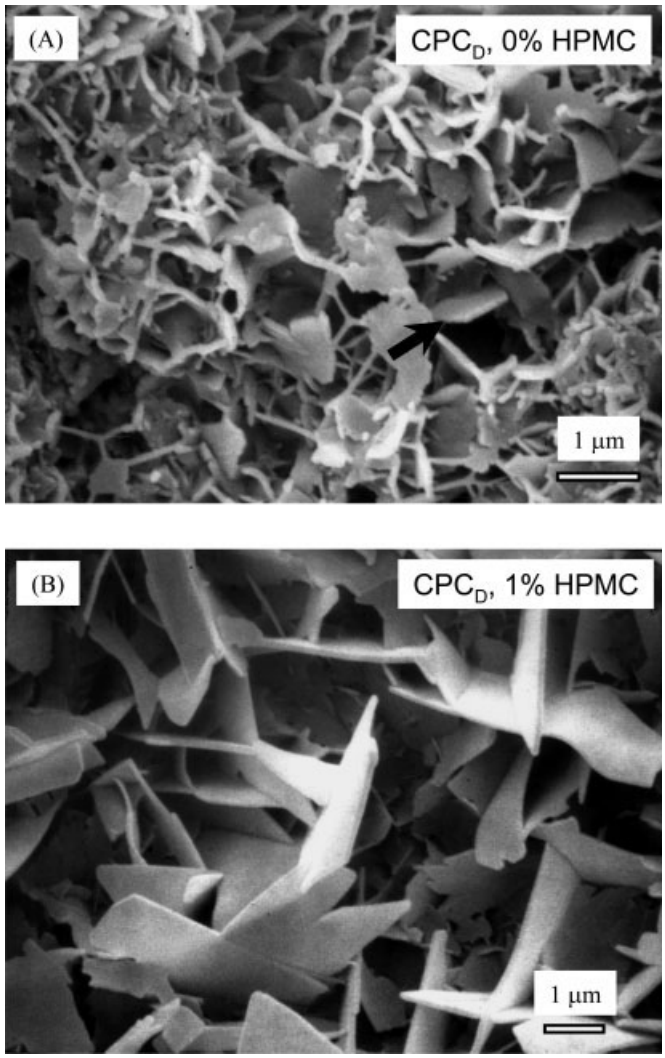

Figure 5. SEM of fracture surfaces of CPC_D showing *in situ* formation of hydroxyapatite crystals at body temperature (37°C). (A) CPC_D consisted of nanosized crystals and platelets. Arrow indicates a platelet. (B) Larger platelet hydroxyapatite crystals were occasionally observed. No significant differences were observed with or without HPMC.

as Ca^{2+}, PO_4^{3-} and OH^- ions, which then reprecipitated to form hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$. The Na_2HPO_4 in the liquid increased the phosphate concentration, which in turn accelerated the setting reaction to form hydroxyapatite. However, such rapid setting adversely and dramatically decreased the paste's injectability [Figure 1(B)]. This drawback was overcome via the addition of HPMC [Figure 2(B)].

HPMC is a derivative of cellulose, which is one of the most commonly occurring polysaccharides, and it is noncytotoxic.[30,38,39] It was used in this study as a gelling agent because of its ability to hydrogen bond to water keeping it in the solution, thereby forming a viscous solution that improves CPC's washout resistance.[30,38,39] The mechanism via which HPMC improved the injectability was likely that HPMC improved the paste cohesiveness and made it more difficult for the solid phase and the liquid phase to separate. The presence of HPMC probably also provided lubrication that allowed the solid particles in the paste to slide over each other, making the paste easier to move during injection. In Figure 2(B), the pastes with HPMC concentrations of 1% to 3% had all passed the injectability test. The injectability test of the present study did not further identify the differences between all the pastes above the "pass" level. It should be noted that the injectability of a paste is not an absolute value; it depends on the test conditions including the orifice size and the injection force. When these parameters change (which is to be experimented in further studies), the paste injectability values may vary.

The mechanism via which HPMC reduced the setting time at intermediate fractions [Figure 2(A)] was likely that HPMC improved the distribution of the particles in the paste. TTCP particles had a median size of 20 μm. DCPD and DCPA particles are much smaller, with median sizes of 1.3 μm and 1.2 μm, respectively. Due to their high surface areas, the smaller particles tend to stick together and form agglomerates (Figure 2 in Ref. 27). It is possible that a thin HPMC film coated the individual particles, thus separating the particles from each other and thus preventing the particles from forming agglomerates, resulting in a more homogeneous particle distribution in the paste. In the case of CPC_D, instead of DCPD particles contacting other DCPD particles in an agglomerate, a more homogeneous distribution may enhance the reaction between the acidic DCPD particles and the basic TTCP. The same applies to CPC_A. The setting time was shortened for both CPC_D and CPC_A at 1% of HPMC (Figure 3). However, when the HPMC content was increased to 3%, the setting time increased. The liquid with 3% HPMC became quite viscous, which likely retarded the movement of Ca^{2+}, PO_4^{3-} and OH^- ions to form hydroxyapatite. Indeed a previous study showed that the CPC conversion to hydroxyapatite was slowed when the content of another gelling agent chitosan was increased in the cement liquid.[48] Further studies are needed to examine these mechanisms, the distribution of particles in the paste, and the effects of particle size[37] and shape[35] on injectability and cement setting.

Improvement in calcium phosphate injectability via HPMC did not adversely affect the mechanical properties (Figure 3). Flexural strength of sintered porous hydroxyapatite implants was reported to range from 2 MPa to 11 MPa.[10] Cancellous bone had a tensile strength of about 3.5 MPa.[49] The rapid-setting and injectable CPC_D, developed in the present study, possessed a flexural strength of approximately 5 MPa. While the measurement methods may differ and the strengths may not be directly comparable, the strength of CPC_D appeared to overlap the strengths of sintered porous hydroxyapatite and cancellous bone. Sintered hydroxyapatite implants require machining to fit a prepared bony defect, and are usually not resorbable or replaceable by new bone.[50,51] Histologic analyses showed that nonresorbable hydroxyapatite implants had induced little new bone fill, and very limited, if any, periodontal bone regeneration.[51] In comparison, the injectable CPC_D of the present study can be placed and shaped easily with intimate contacts to neighboring bone, and harden *in situ* to form hydroxyapatite. While animal studies are needed to examine the bioresorbability of the injectable CPC_D, hydroxyapatite from CPC is in general biocompatible and resorbable.[23–26] This is because the latter is formed in an aqueous environment at body temperature, hence is more similar to biological apatites than sintered hydroxyapatite formed at high temperatures.[52] The elastic modulus of the injectable CPC_D was approximately 2.5 GPa. This compares to an elastic modulus measured in flexure of 12.8 GPa for cortical bone[53] and 0.3 GPa for cancellous bone.[54]

SUMMARY

A rapid-setting and fully injectable calcium phosphate cement was developed via the use of tetracalcium phosphate, dicalcium phosphate dihydrate, and the combined incorporation of a hardening accelerator and a gelling agent. The hardened cement possessed strength and elastic modulus values overlapping those of sintered porous hydroxyapatite implants and cancellous bone. The rapid setting ability and a relatively high strength should help protect the implant from catastrophic fracture or disintegration under stresses. SEM revealed the formation of nanosized rodlike hydroxyapatite crystals and slightly larger platelet crystals in the cement. Compared to sintered hydroxyapatite, the new calcium phosphate cement has advantages including complete injectability, *in situ* hardening, formation of hydroxyapatite, and close contact with neighboring bone. It has the potential to be delivered through needles and applicators for practices that involve minimally invasive methods, narrow defects, and sites of limited accessibility for open surgeries, while still providing mechanical strength and elastic modulus matching those for sintered porous hydroxyapatite implants and cancellous bone.

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cedures. 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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