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Injectable Calcium Phosphate Cement: Effects of Powder-to-Liquid Ratio and Needle Size

Elena F. Burguera, Hockin H. K. Xu, and Limin Sun

Paffenbarger Research Center, American Dental Association Foundation, National Institute of Standards and Technology, Gaithersburg, Maryland 20899-8546

Abstract

Calcium phosphate cement (CPC) sets *in situ* and forms apatite with excellent osteoconductivity and bone-replacement capability. The objectives of this study were to formulate an injectable tetracalcium phosphate-dicalcium phosphate cement (CPC_D), and investigate the powder/liquid ratio and needle-size effects. The injection force (mean $\pm$ SD; $n = 4$) to extrude the paste increased from (8 ± 2) N using a 10-gauge needle to (144 ± 17) N using a 21-gauge needle ($p < 0.05$). With the 10-gauge needle, the mass percentage of extruded paste was $(95 \pm 4)\%$ at a powder/liquid ratio of 3; it decreased to $(70 \pm 12)\%$ at powder/liquid = 3.5 ($p < 0.05$). A relationship was established between injection force, F , and needle lumen cross-sectional area, A : $F = 5.0 + 38.7/A^{0.8}$. Flexural strength, S , (mean $\pm$ SD; $n = 5$) increased from (5.3 ± 0.8) MPa at powder/liquid = 2 to (11.0 ± 0.8) MPa at powder/liquid = 3.5 ($p < 0.05$). Pore volume fraction, P , ranged from 62.4% to 47.9%. A relationship was established: $S = 47.7 \times (1 - P)^{2.3}$. The strength of the injectable CPC_D matched/exceeded the reported strengths of sintered porous hydroxyapatite implants that required machining. The novel injectable CPC_D with a relatively high strength may be useful in filling defects with limited accessibility such as periodontal repair and tooth root-canal fillings, and in minimally-invasive techniques such as percutaneous vertebroplasty to fill the lesions and to strengthen the osteoporotic bone.

Keywords

calcium phosphate cement; nano apatite; injectability; strength; needle size; bone repair

INTRODUCTION

Approximately 1.5 million bone fractures occur annually resulting from osteoporosis alone, costing \$5-10 billion per year in the U.S.¹ The need to treat osseous defects is increasing dramatically as the population ages.^{2,3} Fractures in the elderly have recently seen a marked increase in frequency and severity.⁴ Calcium phosphate biomaterials have been studied as bone replacement materials.⁵⁻¹¹ For sintered hydroxyapatite to fit into a bone cavity, the surgeon needs to machine the graft to the desired shape or carve the surgical site around the implant. This leads to increases in bone loss, trauma, and surgical time.³ In contrast, calcium phosphate cements (CPC) can be molded and set *in situ* to provide intimate adaptation to the contours of defect surfaces.¹²⁻¹⁸ One CPC is comprised of a mixture of tetracalcium phosphate (TTCP:

Correspondence to: Hockin H. K. Xu.

Correspondence to: H. H. K. Xu (e-mail: hockin.xu@nist.gov).

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. Certain commercial materials and equipment are identified in this paper 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.

$\text{Ca}_4[\text{PO}_4]_2\text{O}$) and dicalcium phosphate anhydrous (DCPA: CaHPO_4).¹³ Because of its excellent osteoconductivity and bone replacement capability, CPC is highly promising for a wide range of clinical applications.¹⁹⁻²¹ However, one important drawback of CPC has been its poor injectability.^{22,23}

The injectability of CPC is important for minimally invasive surgical techniques such as percutaneous vertebroplasty to fill bone lesions and cracks to strengthen the bone.²⁴⁻²⁹ Vertebral fractures occur at a rate of 700,000 per year in the U. S. alone,¹ and an injectable and bioactive bone cement like CPC has the potential to fill the lesions and stabilize the osteoporotic bone at risk for fracture. Furthermore, the injectability is also important for applications that involve defects with limited accessibility and narrow cavities, and when there is a need for precise placement of the paste to conform to a defect area, such as periodontal bone repair and tooth root canal fillings.³⁰

Previous studies investigated the injectability of CPCs.²⁴⁻²⁹ One study improved the injectability with the addition of a polysaccharide xanthan, likely due to a lubricating effect.²³ The addition of a polymeric drug also increased the cement injectability.²⁶ In another study, the addition of glycerol improved the injectability, but greatly increased the time for the cement to harden.³¹ A long setting time could cause problems because of the cement's inability to support stresses within this time period.³² Indeed, a severe inflammatory response occurred *in vivo* when the CPC failed to set and disintegrated.³² The dilemma was that a paste capable of setting rapidly could start setting in the syringe, thereby increasing the paste rigidity and reducing its injectability.

This problem was overcome in a previous study that formulated a cement to be fully injectable while still having a rapid-setting ability.³³ This was achieved by using a TTCP-DCPD (dicalcium phosphate dihydrate, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) cement (referred to as CPC_D),³⁴ instead of the TTCP-DCPA cement (referred to as CPC_A), to impart fast-setting. A recent study used hydroxypropyl methylcellulose (HPMC) to greatly improve the paste cohesiveness and injectability.³³ Another study used mannitol porogen and absorbable fibers to develop an injectable, strong, macroporous CPC_D scaffold.³⁵

However, in these previous studies,^{33,35} a single needle size was used, and a single cement powder/liquid ratio was used. The effects of cement powder/liquid ratio, and the influence of needle size, on the injectability of CPC_D had not been investigated.

The aim of this study, therefore, was to investigate the effects of powder/liquid ratio and needle size on the injectability of CPC. The powder/liquid mass ratio of CPC_D was gradually varied from 2/1 to 4/1. The needle size was varied from 10-gauge (inner diameter = 2.68 mm) to 25-gauge (inner diameter = 0.26 mm). These sizes were selected because gauge sizes of 10-16 would be useful for orthopedic procedures,²⁴⁻²⁶ and gauge sizes of 16-25 would be useful for dental uses such as filling root canals and sealing furcation perforation in endodontics.³⁰

MATERIALS AND METHODS

Cement Powder and Liquid

The CPC_D powder consisted of an equimolar mixture of TTCP and DCPD.³⁴ TTCP was synthesized from a solid state reaction between CaHPO_4 and CaCO_3 (J.T. Baker Chemical, Phillipsburg, NJ) at 1500°C for 6 h. The TTCP was then ground and sieved to obtain particles with sizes ranging from about 1-60 μm , with a median size of 20 μm .

Attempts using commercial DCPD resulted in cements with long setting times; therefore, DCPD was synthesized in our laboratory.³⁴ Briefly, DCPD was precipitated by increasing the

pH of a DCPD-monocalcium phosphate monohydrate solution from 1.90 to 3.5 via CaCO_3 addition. The end pH was below the DCPD-hydroxyapatite singular point of 4.2 to prevent hydroxyapatite precipitation. The collected DCPD was washed and dried in air. The DCPD was ground to obtain a particle size range of 0.5–4 μm , with a median size of 1.3 μm . The DCPD powder was then mixed with TTCP at a molar ratio of 1:1 to form the powder for CPC_D .³⁴

The cement liquid contained sodium phosphate as a hardening accelerator and hydroxypropyl methylcellulose (HPMC) as a gelling agent, following previous studies.^{33,35,36} A sodium phosphate solution (a mixture of Na_2HPO_4 and NaH_2PO_4 with a total ionic PO_4 concentration of 3 mol/L; Abbott, North Chicago, IL) was diluted with distilled water to obtain a sodium phosphate concentration of 0.2 mol/L.³⁵ Then HPMC (Sigma-Aldrich, St. Louis, MO; viscosity = 100,000 centipoises at 2% by mass in water) was added to the solution at a HPMC mass fraction of 1% following a previous study.³⁵

Injectability Testing

The injectability testing was done in two parts. The first part investigated the effect of needle size on injection. The second part examined the effect of powder/liquid ratio.

For the first part, seven needle gauge sizes were used as follows: 10, 12, 14, 16, 21, 23, and 25. They corresponded to needle lumen inner diameters of 2.69, 2.16, 1.60, 1.19, 0.51, 0.34, and 0.26 mm, respectively. The CPC_D powder-to-liquid mass ratio was 2/1 following a previous study.³³ In this article, a ratio of 2:1 is used interchangeably as 2/1, which is equal to 2 (i.e., mass of powder/mass of liquid = 2/1 = 2). These needle sizes were selected for two reasons. First, they provided a wide range for a systematic study of the needle size effect on injection. Second, gauge sizes of 10–16 would be useful for orthopedic procedures,^{24–26} whereas gauge sizes of 16–25 would be suitable for dental applications.³⁰

A 10-mL syringe (Free-Flo, Kerr, Romulus, MI) with an internal diameter of 10 mm, similar to those in previous studies,^{33,35} was used with the needles (Fisher Scientific, Suwanee, GA). Cement paste of 3 g was used for each injection test.³³ The paste was mixed using an automatic mixer (Maxi Mix, Thermolyne, Dubuque, IA) for 15 s and then placed into the syringe.³⁵ The syringe was placed between the compression plates of a computer-controlled Universal Testing Machine (5500R, MTS, Cary, NC). Following a previous study,³⁵ 1.5 min after the start of mixing, the compression was started and the cement was extruded at a crosshead speed of 15 mm/min. This was continued until either the entire paste was extruded, or a maximum force of 300 N was reached (at which point the test was stopped). A previous study showed that it took about 15 min for the paste to undergo significant setting.³⁵ In the present study, it took 1 min or less to finish injecting each paste, hence setting in the syringe was minimal. The force of 300 N was selected because it could be readily delivered using manually-operated injection guns and it was within the range used in previous studies, which ranged from 100 N²⁴ to 250 N²³ and to 1000 N.³⁰

Two parameters were measured. First, the percentage of paste extruded was determined as the mass of the extruded paste/the original mass of the paste inside the syringe.³³ Second, the injection force was continuously recorded.³³

In the second part of injection testing, the powder/liquid ratio was varied using two needle sizes: 10-gauge and 21-gauge. They were selected because 10-gauge was similar to spinal needles used in the augmentation of osteoporotic vertebrae and the management of vertebral compression fractures,²⁵ whereas 21-gauge was suitable for dental applications.³⁰ For 10-gauge, the cement powder/liquid mass ratios were as follows: 2, 2.5, 3, 3.5, and 4. Ratios of

less than 2 were not tested because the specimens were too weak mechanically. Ratios of larger than 4 were not tested because the paste was too dry.

For gauge 21, the powder/liquid ratios were as follows: 2, 2.25, 2.5, 2.75, and 3. Ratios larger than 3 were not tested because the paste could not be injected using the 21-gauge needle.

Mechanical Testing

The aforementioned powder/liquid ratios for the injectable pastes were used in the measurement of mechanical properties. Specimens were prepared in stainless steel molds of 3 mm × 4 mm × 25 mm and clamped between two glass slides.³⁷ The specimens were left to set in a humidior at 37°C for 4 h,³⁸ then demolded and immersed in distilled water at 37°C for 20 h.³⁹ The specimens were fractured using a three-point flexural test with a 20 mm span at a crosshead speed of 1 mm/min on the Universal Testing Machine.⁴⁰ The flexural strength was calculated by $S = 3La/(2bh^2)$, where L is the maximum load on the load-displacement curve, a is the span, b is specimen width, and h is specimen thickness.⁴¹ Elastic modulus $E = (L/c) \times a^3/(4bh^3)$, where c is specimen displacement.⁴²

Density and Porosity

The broken halves from the mechanical testing were used for density and porosity measurements. The sides and ends of each specimen were polished with 600-grit silicon carbide paper to render them flat and approximately parallel. The specimens were dried in a desiccator under vacuum, and the density was measured as the specimen mass/volume. The volume was calculated by the specimen dimensions measured with a micrometer, with each linear dimension being the average of three locations along the specimen. Six specimens were thus measured for each powder/liquid ratio. A previous study showed that this simple method yielded density nearly identical to those measured via a mercury intrusion porosimetry method.⁴⁰ The standard uncertainty for the density measurement was estimated to be 0.01 g/cm³. The measured density, d , yields the porosity, P : $P = (d_{HA} - d)/d_{HA}$, where d_{HA} is the density of fully-dense hydroxyapatite which is 3.14 g/cm³.⁴⁰

Microscopy and Statistics

The fracture surfaces of selected specimens were sputtercoated with gold and examined with a scanning electron microscope (SEM, JEOL 5300, Peabody, MA). One-way and two-way analyses of variance (ANOVA) were performed to test significance of the data. Tukey's multiple comparison test was used to compare the data at a family confidence coefficient of 0.95.

RESULTS

Effect of Needle Size on Injection

Examples of injection force versus syringe plunger displacement are shown in Figure 1, with (A) a paste readily injected through a 10-gauge needle; and (B) the same paste uninjectable using a 25-gauge needle. Such a needle size effect was systematically quantified in Figure 2 for CPC_D at a powder/liquid ratio of 2. From 10-gauge to 21-gauge, the paste was fully extruded, although the injection force (mean ± SD; $n = 4$) significantly increased from (8 ± 2) N to (144 ± 17) N (Tukey's multiple comparison test at p of 0.05). The data at 23-gauge size had more scatter, hence $n = 7$ was done instead of $n = 4$, yielding $(59 \pm 37)\%$ of paste extruded, and an injection force of (264 ± 62) N. Little paste was extruded using the 25-gauge needle when the force reached 300 N.

Effect of Powder-to-Liquid Ratio on Injection

The effect of CPC_D powder/liquid ratio is shown in Figure 3, using two different gauge sizes. In (A-B), using the 10-gauge needle, the paste was fully extruded at powder/liquid ratios from 2 to 3 [for example, $(95 \pm 4)\%$ paste was extruded at powder/liquid of 3]. Then, the percent of extruded paste was significantly reduced to $(70 \pm 12)\%$ when the powder/liquid ratio was further increased to 3.5 ($p < 0.05$). The injection force increased from (8 ± 2) N at powder/liquid of 2, to 300 N at powder/liquid of 3.5. No measurable paste was extruded at a powder/liquid ratio of 4.

In contrast, using the 21-gauge needle [Figure 3(C,D)], the injection force reached 300 N at lower powder/liquid ratios of 2.75 and 3. When the powder/liquid ratio was increased from 2 to 2.5, the force increased from (144 ± 17) to (280 ± 25) N ($p < 0.05$). The extruded paste decreased from $(96 \pm 1)\%$ at powder/liquid of 2 to $(75 \pm 11)\%$ at powder/liquid of 2.5 ($p < 0.05$).

Effect of Powder-to-Liquid Ratio on CPC_D Physical Properties

Since the paste at powder/liquid of 4 was not injectable [Figure 3(B)], mechanical properties were measured for CPC_D at powder/liquid ranging from 2 to 3.5. The results are plotted in Figure 4 on: (A,B) Strength and elastic modulus; and (C,D) density and porosity. In (A), the strength was significantly increased from (5.3 ± 0.8) MPa at powder/liquid of 2, to (8.2 ± 0.7) MPa at powder/liquid of 3, and to (11.0 ± 0.8) MPa at powder/liquid of 3.5 ($p < 0.05$). Elastic modulus was also increased with increasing the powder/liquid ratio.

In Figure 4(C,D), the density was increased from (1.18 ± 0.01) g/cm³ at powder/liquid of 2 to (1.64 ± 0.03) g/cm³ at powder/liquid of 3.5 ($p < 0.05$). The pore volume fraction was decreased from (0.624 ± 0.005) at powder/liquid of 2, to (0.479 ± 0.010) at powder/liquid of 3.5 ($p < 0.05$). A porosity of 0.624 and 62.4% are used interchangeably in this article.

Figure 5 shows SEM of fracture surfaces for the injectable CPC_D at (A) powder/liquid ratio of 2, and (B) powder/liquid of 3.5. Platelet and needle-shaped crystals covered the fracture surfaces at powder/liquid of 2 (arrows). The dimensions of the crystals ranged approximately from 50 to 500 nm. At a higher powder/liquid of 3.5, most of the crystals appeared to be smaller in size than those in (A), with a size range from about 10 to 500 nm. Crystals of such shapes and sizes were not present in the starting powder of the cement, and X-ray diffraction analysis in a previous study³⁴ showed that the set cement had converted to hydroxyapatite.

DISCUSSION

Because of their bioactivity and osteoconductivity, injectable CPCs are highly promising for a wide variety of applications ranging from minimally-invasive techniques such as percutaneous vertebroplasty,²⁴⁻²⁹ to filling defects with limited accessibility or narrow cavities such as in periodontal bone repair and root canal fillings. Previous studies on injectability investigated the effects of time after mixing,²⁴ particle shape,²² particle size,²³ incorporation of a polymeric drug²⁶ and citric acid,²⁷ and ion modification.²⁹ Traditional CPC exhibited poor injectability.^{22,23} In our previous study, using a gelling agent HPMC, and with DCPD replacing DCPA, CPC_D was formulated to be highly injectable without compromising the setting and strength properties.^{33,35}

Effect of Injection Needle Size

The present study differs from these previous studies because it systematically investigated the effects of a wide range of needle sizes and cement powder/liquid ratios on the injectability. Different clinical applications would require the use of needles of different sizes. For example,

percutaneous vertebroplasty would use a large bore needle,^{24,25} while tooth root canal filling would require a small needle.³⁰ Most previous reports studied a single needle or cannula size. For example, an 11-gauge spinal needle was used in injecting into osteoporotic vertebrae.²⁵ In several studies a syringe opening of 2-mm diameter (similar to a 12-gauge needle) was used.^{24,26} In another study, an 18-gauge needle was used.³⁰ The needle size effect was discussed in a previous study,²³ but no data were presented on the relationship between injectability and needle size. In the present study, the injectability was systematically measured versus needle size in Figure 2 at a powder/liquid mass ratio of 2. To establish the relationship between injectability and needle size, the following empirical equation is proposed in the present study:

$$F = \alpha + \beta/A^\gamma \quad (1)$$

where F is the injection force (with unit N), A is the needle lumen cross-sectional area (with unit mm²), and α , β , and γ are coefficients to be determined by fitting this equation to experimental data. The physical meaning of this equation is that for a specific paste, the smaller the A , the larger the F needed to extrude the paste. When A approaches 0, the paste cannot be extruded and F should approach infinity. On the other hand, when A becomes very large, β/A^γ approaches 0, hence F approaches the value of α (α has the unit of N). α depends on the paste characteristics; α is small for a readily injectable paste, and α is large for a difficult-to-inject paste. For the present study, A was calculated using the inner diameters for needle sizes from 10-gauge to 23-gauge (the 25-gauge was not included because the paste could not be injected when the force was cut off at 300 N). Figure 6 plots the measured injection force versus A . The solid line is a regression power-law best-fit to the experimental data, yielding:

$$F = 5.0 + 38.7/A^{0.8} \quad (2)$$

with a correlation coefficient $R = 0.99$. One potential usefulness of this equation is that it could predict the force required to inject the paste, when using different needle sizes. It should be noted that while the form of the equation $F = \alpha + \beta/A^\gamma$ is expected to be applicable to different injectable cement systems, the α , β , and γ values depend on the paste characteristics and hence are expected to be different for different pastes.

Effect of CPC_D Powder/Liquid Ratio

The effect of powder/liquid ratio was studied using a 10-gauge needle as an example for orthopedic applications. The paste was readily injected at powder/liquid ratios from 2 to 3. The powder/liquid of 3.5 appeared to be the transition point [Figure 3(A,B)]: The injection force reached 300 N, and 70% of the paste was extruded. If 70% of extruded paste was acceptable clinically, a powder/liquid of 3.5 should be preferred because it resulted in a strength of 11.0 MPa, higher than the 8.2 MPa at powder/liquid of 3 [Figure 4(A)]. Previous studies concluded that due to the low strength, the use of CPC was "limited to the reconstruction of nonstress-bearing bone,"¹⁹ and "clinical usage was limited by...brittleness..."²⁰ Hence a higher strength for the injectable CPC_D would be desirable to help avoid catastrophic fracture in moderate stress-bearing situations.

The effect of powder/liquid ratio was further studied using the 21-gauge needle as an example for dental applications. This could include periodontal repairs involving precision placement of the paste into small and difficult-to-access locations, filling of tooth root canals, and sealing of furcation perforation in endodontics.³⁰ Nearly 80% of the paste was extruded at powder/liquid of 2.5 [Figure 3(D)]; this then decreased to below 50% at powder/liquid of 2.75. Hence a powder/liquid ratio of 2.5 would be preferred because the cement had a higher strength of 7.5 MPa than the 5.9 MPa at powder/liquid of 2.25 [Figure 4(A)]. In dental applications such

as periodontal osseous repair, tooth occlusion/mobility and flexure could result in stress-bearing situations. Indeed, a previous bone cement failed in periodontal repair and a mechanism for the failure was identified as “the lack of sufficient flexural stress resistance.”⁴³ Therefore, high strength is desirable for the injectable CPC_D to be used in dental applications. It should be noted that the aforementioned flexural strengths of the injectable CPC_D compared well with the reported flexural strength of sintered porous hydroxyapatite implants ranging from 2 to 11 MPa,⁴⁴ and the tensile strength for cancellous bone of about 3.5 MPa.⁴⁵ However, further studies are needed to render the injectable CPC_D sufficiently strong and tough for large stress-bearing repairs.

Effect of Pore Volume Fraction

The different powder/liquid ratios yielded injectable CPC_D with different porosities [Figure 4 (D)]. A previous study modeled porous ceramics as an elastic-brittle foam,⁷ resulting in the following equations:

$$S = \varepsilon d^x \quad (3)$$

$$E = \phi d^y \quad (4)$$

where d is the density of the specimen, and ε , ϕ , x , and y are coefficients.

Since porosity $P = (d_{\text{HA}} - d)/d_{\text{HA}}$, hence $d = d_{\text{HA}} (1 - P)$. Inserting this into Eqs. (3) and (4) yields:

$$S = S_0 (1 - P)^x \quad (5)$$

$$E = E_0 (1 - P)^y \quad (6)$$

where S_0 and E_0 are theoretical values at $P = 0$ (fully-dense). They also predict that when $P = 1$, S and E are 0. In Figure 7, the measured strength and modulus [Figure 4(A,B)] are plotted versus the porosity P [Figure 4(D)]. The solid lines are regression power-law best-fits to the measured data, yielding:

$$S = 47.7 (1 - P)^{2.3} \text{ MPa} \quad (7)$$

$$E = 17.1 (1 - P)^{1.7} \text{ GPa} \quad (8)$$

with $R = 0.98$ for both cases. Hence for this injectable CPC_D containing HPMC as a gelling agent and sodium phosphate as a hardening accelerator, the mechanical properties can be predicted once the specimen porosity is measured. However, while Eqs. (5) and (6) are expected to be generally applicable, Eqs. (7) and (8) were obtained using data of a limited porosity range (from porosity $P = 0.48$ - 0.62). Hence further studies are needed to confirm these equations using a wider range of porosities for injectable CPC.

Nano Apatite

The injectable CPC_D contained nano hydroxyapatite crystals (Figure 5). The size and morphology of the crystals depend on the local water content, the extent of Ca and PO₄ ion supersaturation in the solution with respect to hydroxyapatite, and space available for crystal growth. The cement at a powder/liquid ratio of 2 had more water in the paste to facilitate the TTCP-DCPD dissolution and apatite precipitation, with more space for crystal growth than the cement at powder/liquid of 3.5. This was likely why the cement at a powder/liquid ratio of 2 had crystal sizes larger than those at powder/liquid of 3.5.

The nano hydroxyapatite crystals of CPC_D had sizes similar to the biominerals in natural bones and teeth. In the biomimetic fabrication of biomaterials, bone can be viewed as a nanocomposite of nano apatite minerals and proteins.⁴⁶ The apatite crystals in bone and dentin had dimensions of 5 nm × 30 nm × 100 nm. Tooth enamel rods consisted of larger apatite crystals of about 100 nm in diameter. Such nano particles could have significant advantages over their micron-sized counterparts.⁴⁷ Indeed, the nano crystals in CPC supported osteoblast cell attachment and proliferation, with cytoplasmic extensions readily anchoring on the nano apatite crystals.⁴⁸ Further studies should attempt to evaluate the potential clinical applications of the injectable CPC_D.

SUMMARY

1. The effects of injection needle size and powder/liquid ratio on an injectable CPC were systematically investigated for the first time. A relationship was established between the injection force needed to extrude the cement, F , and the needle lumen cross-sectional area, A : $F = 5.0 + 38.7/A^{0.8}$. This would enable the prediction of the required injection force for different needle sizes suitable for specific applications.
2. Relationships were established among flexural strength S , elastic modulus E , and porosity P of the injectable cement: $S = 47.7 \times (1 - P)^{2.3}$ and $E = 17.1 \times (1 - P)^{1.7}$. The flexural strength of the injectable CPC_D matched/exceeded the reported flexural strengths of sintered porous hydroxyapatite implants, while CPC_D requires neither sintering nor machining.
3. A CPC_D powder/liquid ratio of 3.5 yielded a mechanically strong and injectable cement for orthopedic applications using a large needle. A powder/liquid ratio of 2.5 yielded a paste that could be injected through small needles suitable for dental applications. SEM revealed nano-sized rod-like hydroxyapatite crystals and slightly larger platelets in the injectable cements, similar in size to biominerals in bone and teeth.
4. The novel injectable, mechanically-strong tetracalcium phosphate-dicalcium phosphate dihydrate cement, with sodium phosphate as a hardening accelerator and HPMC as a gelling agent, may have wide clinical applications. This may include the filling of defects with limited accessibility or narrow cavities in periodontal bone repair and tooth root canal fillings, and use in minimally-invasive techniques, such as *in situ* fracture fixation and percutaneous vertebroplasty to fill the lesions and strengthen osteoporotic bone.

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Figure 1. Injection force versus syringe plunger displacement: (A) 10-gauge needle; (B) 25-gauge needle. The paste in (A) was easily injected. The force in (B) rapidly reached 300 N and the test was stopped.

Figure 2.

Effect of needle size on injection: (A) Injection force; and (B) percent of paste extruded. The CPC_D powder/liquid mass ratio was 2. Each value is mean $\pm$ SD; $n = 4$. At 23-gauge, $n = 7$. From 10-gauge to 21-gauge, the paste was fully extruded. At 23-gauge, $(59 \pm 37)\%$ of paste was extruded. Little paste was extruded at 25-gauge when the force reached 300 N.

Figure 3.

Effect of powder-to-liquid ratio on injection: (A, B) 10-gauge needle, and (C, D) 21-gauge needle. In (A, B), the paste was fully extruded at powder/liquid ratios from 2 to 3. (95 ± 4)% of the paste was extruded at powder/liquid of 3. At powder/liquid of 3.5, the percent of extruded paste decreased to (70 ± 12)%. No paste was extruded at a powder/liquid ratio of 4. In (C, D), the injection force reached 300 N at a powder/liquid ratio of 3. Each value is mean $\pm$ SD; $n = 4$.

Figure 4.

Effect of powder-to-liquid ratio on: (A, B) Strength and modulus; and (C, D) density and porosity. In (A), the strength was increased from (5.3 ± 0.8) to (8.2 ± 0.7) and (11.0 ± 0.8) MPa, at powder/liquid ratios of 2, 3, and 3.5, respectively. In (D), the pore volume fraction was decreased from (0.624 ± 0.005) at powder/liquid of 2, to (0.479 ± 0.010) at powder/liquid of 3.5. A pore volume fraction of 0.624 and 62.4% are used interchangeably. Each value is mean $\pm$ SD; $n = 5$.

Figure 5.

SEM of fracture surfaces for the injectable CPCD at (A) powder/liquid ratio of 2, and (B) powder/liquid of 3.5. Arrows indicate platelet and needle-shaped crystals. The dimensions of the crystals ranged approximately from 50 to 500 nm. At a higher powder/liquid of 3.5, most of the crystals were smaller than those in (A), with a size ranging from about 10 to 500 nm.

Figure 6.

Relationship between injection force and needle size for injectable calcium phosphate cement. F is the injection force (with unit N), and A is the needle lumen cross-sectional area (with unit mm²). A is calculated using the inner diameters for needle sizes from 10-gauge to 23-gauge. The CPC_D powder/liquid mass ratio was 2. Each value is mean $\pm$ SD; $n = 4$. The solid line is a regression power-law best-fit to the experimental data.

Figure 7.

Relationship between mechanical properties and porosity for injectable calcium phosphate cement. The measured strength S and modulus E are plotted versus the porosity P . Each value is mean $\pm$ SD; $n = 5$. The solid lines are regression power-law best-fits to the measured data.