Effects of Calcium Phosphate Nanoparticles on Ca-PO$_4$ Composite

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Abstract

Nano-particles of dicalcium phosphate anhydrous (DCPA) were synthesized for the first time. The objectives of this study were to incorporate DCPA nano-particles into resin for Ca-PO$_4$ release to combat dental caries, and to investigate the filler level effects. Nano-DCPA and nano-silica-fused silicon nitride whiskers at a 1:1 ratio were used at filler mass fractions of 0–75%. The flexural strengths in MPa (mean ± SD; n = 6) of DCPA-whisker composites ranged from (106 ± 39) at 0% fillers to (114 ± 23) at 75% fillers, similar to (112 ± 22) of a non-releasing composite (TPH) (p > 0.1). The composite with 75% fillers in a NaCl solution (133 mmol/L, pH = 7.4, 37°C) yielded a Ca concentration of (0.65 ± 0.02) mmol/L and PO$_4$ of (2.29 ± 0.07) mmol/L. Relationships were established between ion-release and DCPA volume fraction V$_{DCPA}$: Ca = 4.46 V$_{DCPA}$1.6, and PO$_4$ = 66.9 V$_{DCPA}$2.6. Nano-DCPA-whisker composites had high strength and released high levels of Ca-PO$_4$ requisite for remineralization. These new nano-composites could provide the needed combination of stress-bearing and caries-inhibiting capabilities.

Keywords

dental composite; nano-particles; whisker reinforcement; tooth caries inhibition; Ca and PO$_4$ ion release

INTRODUCTION

Secondary caries at the tooth-restoration margins is the most-frequent reason for replacement of restorations (Sakaguchi, 2005; Sarrett, 2005). Replacement dentistry accounts for 70% of all operative work and costs $5 billion/year in the U.S. (Jokstad *et al.*, 2001; CDC, 2005). Several calcium-phosphate phases are regarded as biological precursors that form initially and then transform to apatites (LeGeros, 1991). Recent studies showed that methacrylate-based composites containing calcium-phosphate fillers released calcium (Ca) and phosphate (PO$_4$) ions to supersaturated levels for apatite precipitation, and effectively remineralized tooth lesions *in vitro* (Skrtic *et al.*, 1996a, 2000; Dickens *et al.*, 2003).

However, the Ca-PO$_4$ fillers did not reinforce the resin as do glass fillers (Söderholm *et al.*, 1984; Goldberg *et al.*, 1994; Bayne *et al.*, 1998; Ferracane *et al.*, 1998; Drummond and Bapna, 2003). Ca-PO$_4$ composites had flexural strengths half that of unfilled resin (Skrtic *et al.*, 1996b). Such low strengths were "inadequate to make these composites acceptable as bulk restoratives" (Skrtic *et al.*, 2000).

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Whiskers were used as fillers to reinforce dental composites (Xu, 1999). Silica nano-particles were fused onto the whiskers to facilitate silanization and enhance retention in the resin. These composites possessed strength and toughness nearly two-fold greater than those of several commercial composites (Xu *et al.*, 2002a).

Calcium phosphate nano-particles were recently developed and incorporated into resins (Chow *et al.*, 2004; Xu *et al.*, 2006). A recent study investigated the effects of different resins/cure conditions with a single filler level (Xu *et al.*, 2006). In the present study, two hypotheses were tested: (1) DCPA-whisker composites with filler levels from 0–75% would possess strengths matching/exceeding those of a commercial non-releasing, stress-bearing composite; and (2) the Ca-PO$_4$ release would be proportional to the DCPA nano-particle filler level in the resin. The first hypothesis was tested because low filler levels could be envisioned for Ca-PO$_4$-releasing sealant applications, medium filler levels for Ca-PO$_4$ flowable composites, and high filler levels for stress-bearing and caries-inhibiting restorations. The purpose of the second hypothesis was to establish a relationship between release and volume fraction, to guide the tailoring/processing of composites.

MATERIALS & METHODS

Materials

Nano-particles of DCPA (CaHPO$_4$) were synthesized *via* a spray-drying technique for the first time (Chow *et al.*, 2004; Xu *et al.*, 2006). X-ray diffraction indicated that the powder was DCPA. Transmission electron microscopy showed particles having diameters around 50 nm. Due to agglomeration, the Brunauer, Emmet, and Teller (BET) surface-area measurement yielded an equivalent particle diameter of 112 nm (Xu *et al.*, 2006).

Silicon-nitride whiskers (β-Si$_3$N$_4$, UBE, New York, NY, USA) with diameters of 0.1–2 μm (mean = 0.4 μm) and lengths of 2–30 μm (mean = 5 μm) were mixed with silica (Aerosil-OX50, Degussa, Ridgefield, NJ, USA; diameter = 40 nm) at a whisker:silica mass ratio of 5:1. The mixture was heated in a furnace at 800°C for 30 min to fuse the silica onto the whiskers. The powder was silanized with 4% 3-methacryloxypropyltrimethoxysilane and 2% n-propylamine (mass fractions) (Xu, 1999).

A monomer consisting of 48.975% Bis-GMA (bisphenol glycidyl methacrylate), 48.975% TEGDMA (triethylene glycol dimethacrylate), 0.050% 2,6-di-*tert*-butyl-4-methylphenol, and 2.000% benzoyl peroxide formed part I, the initiator, of a two-part chemically activated resin. Part II, the accelerator resin, consisted of 49.5% Bis-GMA, 49.5% TEGDMA, and 1.0% *N,N*-dihydroxyethyl-*p*-toluidine.

The fillers consisted of nano-silica-fused whiskers and nano-DCPA at a DCPA:whisker mass ratio of 1:1 (Xu *et al.*, 2006). The (DCPA+whiskers)/(DCPA+whiskers+resin) mass fractions were: 0%, 30%, 40%, 50%, 60%, 65%, 70%, and 75%. Filler levels ≥80% resulted in a dry paste. Equal masses of parts I and II were mixed and filled into 2×2×25 mm^3 molds. The specimens were incubated at 37°C and 50% humidity for 24 hrs prior to being tested.

A hybrid composite (TPH, Caulk/Dentsply, Milford, DE, USA) was used as a non-releasing control. It consisted of 0.8-μm silicate fillers at 78% level in a urethane-modified Bis-GMA-TEGDMA resin. The specimens were photo-cured (Triad-2000, Dentsply, York, PA, USA).

Flexural Strength and Nano-indentation

Flexural strength was measured by a three-point test with a 10-mm span at a crosshead speed of 1 mm/min on a Universal Testing Machine (5500R, MTS, Cary, NC, USA) at approximately

25°C and 50% relative humidity. Nano-indentation (Nano-Instruments, Knoxville, TN, USA) was used to measure elastic modulus and hardness at a peak-load of 1 N (Xu *et al.*, 2002a).

Ca and PO$_4$ Release

A NaCl solution (133 mmol/L) buffered with 50 mmol/L HEPES (pH = 7.4; 37 C) was used. Following a previous study (Xu *et al.*, 2006), we immersed 3 specimens of approximately $2 \times 2 \times 12$ mm^3 in 50 mL of solution, yielding specimen volume/solution = 2.9 mm^3/mL. This was similar to the specimen volume/solution of approximately 3.0 mm^3/mL in a previous study (Skrtic *et al.*, 1996b). The concentrations of Ca and PO$_4$ released from the specimens were measured *vs*. immersion time (in days): 1, 2, 4, 7, 14, 21, 28, 35, 42, 49, and 56. At each time period, aliquots of 0.5 mL were removed and replaced by fresh solution. The aliquots were analyzed with a spectrophotometer (DMS-80 UV-visible, Varian, Palo Alto, CA, USA) according to established standards and calibration methods (Skrtic *et al.*, 1996b; Dickens *et al.*, 2003).

Potential Diagram

The remineralization potential of a Ca- and PO$_4$-releasing composite can be described *via* a potential diagram (Dickens *et al.*, 2003). For a solution saturated with respect to hydroxyapatite [Ca$_{10}$(PO$_4$)$_6$(OH)$_2$], the solubility constant relationship, $K_{SP} = (Ca^{2+})^{10}(PO_4^{3-})6(OH^-)^2$, applies (Chow and Brown, 1984). Rearranging the equation leads to:

$$K_{SP} = \{[(Ca^{2+})(OH^-)^2]^{10} \times [(H^+)^3(PO_4)^{3-})]^6\}/K_W^9 \tag{1}$$

where $K_W = (H^+)(OH^-)$ is the dissociation constant of water. Taking log of both sides and rearranging the equation lead to:

$$\log[(H^+)^3(PO_4^{3-})] = -1.67 \times \log[Ca^{2+}(OH^-)^2] + K \tag{2}$$

where $K = (1/6)(\log K_{SP} + 9\log K_W)$ is a constant. Eq. (2) shows that, for a solution saturated with respect to hydroxyapatite, the logarithms of the activities of H$_3$PO$_4$ and Ca(OH)$_2$ are linearly related. The activities $(H^+)^3(PO_4^{3-})$ and $(Ca^{2+})(OH^-)^2$ for a solution can be calculated from the pH, the measured Ca-PO$_4$ concentrations, and the ionic strength. Hence, a solution can be represented as a point in the potential diagram. Solutions located to the left of the hydroxyapatite line (*e.g.,* Fig. 8, Dickens *et al.*, 2003) are undersaturated, and those to the right are supersaturated, with respect to hydroxyapatite.

The extent of this supersaturation can be quantified *via* the saturation ratio. The saturation index is (Margolis *et al.*, 1999):

$$I = (\log[IAP] - \log[K_{SP}])/q \tag{3}$$

where q is the number of ions in the ion activity product expression (for hydroxyapatite, q = 10+6+2 = 18). IAP = $(Ca^{2+})^{10}(PO_4^{3-})^6(OH^-)^2$ is the ion activity product, which can be calculated from the measured concentrations with specific software (Chemist, Micromath Research, St. Louis, MO, USA). The saturation ratio

$$SR = 10^{(\text{saturation index})} = 10^I \tag{4}$$

where SR < 1 means that the solution is undersaturated, and SR > 1 means that the solution is supersaturated, with respect to hydroxyapatite (Margolis *et al.*, 1999).

Furthermore, the Gibbs free energy can be used to quantify the thermodynamic driving force for remineralization (Dickens *et al.*, 2003):

$$\Delta G^0 = -2.303(RT/q)\log(IAP/K_{SP}) \tag{5}$$

where R is the ideal gas constant, and T is absolute temperature.

We performed one- and two-way ANOVA to detect the significant effects of the variables. We used Tukey's multiple-comparison test to compare the measured data at a p value of 0.05.

RESULTS

Mechanical Properties

Increasing the filler level did not significantly change the strength (p > 0.1) (Fig. 1A). Flexural strength in MPa (mean ± SD; n = 6) at 60% and 75% fillers were (117 ± 17) and (114 ± 23), respectively, not significantly different from (106 ± 39) of the unfilled resin and (112 ± 22) of the hybrid control (p > 0.1).

Elastic modulus (Fig. 1B) and hardness (Fig. 1C) increased with filler level. Modulus in GPa (mean ± SD; n = 10) at 75% fillers was (14.9 ± 0.7), higher than (11.7 ± 0.4) for the hybrid control and (3.9 ± 0.1) for the unfilled resin (p < 0.05).

Ca and PO$_4$ Release

The release increased with time and then started to plateau (Figs. 2A, 2B). At 56 days, the Ca concentration in mmol/L (mean ± SD; n = 3) was (0.65 ± 0.02) with 75% fillers, significantly higher than (0.59 ± 0.02) with 70% fillers, and (0.39 ± 0.03) with 65% fillers (p < 0.05). The corresponding PO$_4$ concentrations were (2.29 ± 0.07), (1.92 ± 0.14), and (1.26 ± 0.09), significantly different from each other (p < 0.05).

Potential Diagram

In the chemical potential diagram (Fig. 3A), the solution of the composite with 30% fillers was undersaturated, that with 40–50% fillers was supersaturated after 2 days, and those of all other composites were supersaturated from 1 day, with respect to hydroxyapatite. The saturation ratio increased with increasing filler levels (Fig. 3B). The larger the negative value of ΔG^0 (Fig. 3C), the lower the energy state for hydroxyapatite precipitation, and the higher the remineralization potential (Dickens *et al.*, 2003).

DISCUSSION

Synergistic Effects of Nano-particles/Whiskers

Previous studies have measured fluoride release from dental materials (Geurtsen *et al.*, 1999; Anusavice *et al.*, 2005). Other studies developed Ca-PO$_4$ composites with flexural strengths of about 55 MPa (Skrtic *et al.*, 1996b). This led to the observation that "all the amorphous calcium phosphate fillers yielded polymerized materials weaker than unfilled polymers" (Skrtic *et al.*, 1996b). Another composite, with micron-sized DCPA, had a flexural strength of 40–50 MPa (Dickens *et al.*, 2004). In the present study, the nano-DCPA-whisker composites had flexural strengths of about 110 MPa. The DCPA-whisker composite at 75%

fillers had an elastic modulus of 14.9 GPa. It was lower than the 18 GPa of dentin, but higher than the 11.7 GPa of the commercial stress-bearing, non-releasing composite control.

Previous Ca-PO$_4$ composites released to PO$_4$ concentrations of 0.1–0.7 mmol/L, and Ca to 0.3–1.0 mmol/L, measured with a similar method (Skrtic *et al.*, 1996b; Dickens *et al.*, 2003). These composites remineralized tooth lesions *in vitro* (Skrtic *et al.*, 1996a; Dickens *et al.*, 2003). The nano-DCPA-whisker composites released PO$_4$ with concentrations up to 2.2 mmol/ L, and Ca up to 0.65 mmol/L (at 75% total fillers), even when half of the fillers were non-releasing whiskers. This was likely because the DCPA nano-particles had a high surface area, A = 18.6 m^2/g (Xu *et al.*, 2006).

In a previous study (Dickens *et al.*, 2003), the DCPA particle size, d, was 1.1 μm and the TTCP (tetracalcium phosphate) particle size was 16 μm. The density, ρ, is 2.89 g/cm^3 for DCPA and 3.07 g/cm^3 for TTCP. Hence, A = 6/(ρd) = 1.9 m^2/g for DCPA, and A = 0.12 m^2/g for TTCP. These traditional particles had surface areas 1–2 orders of magnitude less than the new DCPA nano-particles. As a result, these traditional composites needed to be fully filled with Ca-PO$_4$ fillers to have significant release. Replacing part of these Ca-PO$_4$ fillers with reinforcing fillers would substantially reduce the release. Even if only 10% of the ACP fillers had been replaced by reinforcing fillers, the Ca-PO$_4$ release would have been decreased from about 0.75 to only 0.1 mmol/L (Skrtic *et al.*, 1996b). Therefore, there was little room left in traditional Ca-PO$_4$ composites for reinforcement fillers without diminishing the ion release capability.

In contrast, with nano-DCPA, high release could be achieved with less filler, thus making room available in the resin for reinforcement fillers. This synergistic releasing-filler/reinforcing-filler approach helped achieve a flexural strength of 110 MPa for the Ca-PO$_4$-releasing composites, matching that of a commercial stress-bearing, non-releasing composite.

Effect of Nano-DCPA Volume Fraction

The masses used in making the composites and the density were used to calculate the volume fraction of DCPA in the composite. The density of DCPA, d_{DCPA}, is 2.89 g/cm^3. The density of the unfilled resin was measured to be d_{resin} = (1.19 ± 0.04) g/cm^3. The density of silicon nitride whiskers is 3.34 g/cm^3 (manufacturer's data), and $d_{fumed-silica}$ = 2 g/cm^3. Hence, $d_{silica-fused-whisker}$ = 2.97 g/cm^3 at a whisker:silica ratio of 5:1. At total filler mass fractions of 30%, 40%, 50%, 60%, 65%, 70%, and 75%, the volume fraction V_{DCPA} was calculated to be 0.075, 0.108, 0.147, 0.192, 0.218, 0.247, and 0.279, respectively.

There appear to be two main factors influencing Ca-PO$_4$ release: (1) the amount of the source of release, V_{DCPA}, with the amount of release expected to increase with increasing V_{DCPA}; and (2) the resin polymerization conversion. Increasing the filler level usually decreases the polymerization conversion (Xu, 1999), because a higher concentration of air in the heavily filled composite may adversely affect the conversion. In addition, the fillers may partially absorb the heat of polymerization, thereby moderating the exotherm of polymerization. Therefore, with higher V_{DCPA} in the composite, there is not only more DCPA for release, but also the diffusion of water and ions through the resin may be somewhat enhanced, due to the decreased polymerization conversion. If only factor (1) had been operative, the relationship between V_{DCPA} and Ca-PO$_4$ release might have been simply linear. However, these two factors may both be operative. Hence, the release may increase with increasing V_{DCPA} at a rate faster than linear. Based on these reasons, the following empirical relationships are proposed:

$$Ca = k_1 V_{DCPA}^{\alpha}$$

(6)

$$PO_4 = k_2 V_{DCPA}{}^{\beta} \qquad (7)$$

$$SR = k_3 V_{DCPA}{}^{\gamma} \qquad (8)$$

where Ca and PO_4 (mmol/L) are concentrations, and k and α-γ are coefficients. Fitting the above equations to the measured data (at 56 days) yielded the equations in Fig. 4.

Regarding potential applications, nano-DCPA-whisker composites with 30–50% fillers may be suitable for use as Ca-PO_4-releasing tooth cavity liners, adhesives, and pit-and-fissure sealants. Flowable DCPA-whisker composites with 50–60% fillers may be used as crown cements and orthodontic bracket cements, and to repair defective margins. Composites with 70–75% fillers may be useful in stress-bearing and caries-inhibiting restorations. The Ca-PO_4 release from the DCPA-whisker composites matched/exceeded those of previous composites known to remineralize tooth lesions (Skrtic *et al.*, 1996a; Dickens *et al.*, 2003). Further research is needed to investigate their potential applications.

The dimensional change of the composite with time is another issue that needs to be investigated. Previous studies on a Ca- and F-releasing composite (Ariston pHc) for buffering the local pH in plaque retention areas showed considerable enamel cracks after 2 yrs, which were related to the water-expansion of the restorations (Braun *et al.*, 2001; van Dijken, 2002; Krämer *et al.*, 2005). Ariston was completely covered with cracks after 24 mos (Frankenberger *et al.*, 2005). It exhibited the highest dimensional expansion among the materials immersed for 2 mos (Martin *et al.*, 2003), and a high wear-rate (Manhart *et al.*, 2000). These failure phenomena may be related to its hydrophilic monomer (Table I, Manhart *et al.*, 2000) and the formation of calcium carbonates with an expanding effect (van Dijken, 2002). One advantage of the new nano-composite was that it released high levels of Ca-PO_4 without the use of a hydrophilic monomer. The Bis-GMA/TEGDMA resin for the nano-composite was similar to the resin in previous composites, showing no significant degradation in thermal-cycling and water-aging for 2 yrs (Xu *et al.*, 2002b; Xu, 2003). However, studies are needed to evaluate the long-term performance of the new nano-composites *in vitro* and *in vivo*.

In summary, we developed novel nano-composites using DCPA nano-particles with Ca-PO_4 release to combat dental caries. The effects of nano-DCPA filler level were systematically investigated and correlated with Ca-PO_4 release for the first time. The Ca-PO_4 release from DCPA-whisker composites matched/exceeded those of previous composites known to remineralize tooth lesions, while the strengths of the DCPA-whisker composites were two-fold those of previous Ca-PO_4 composites. Relationships between Ca-PO_4 release and nano-DCPA volume fraction, V_{DCPA}, were established: $Ca = 4.46 V_{DCPA}{}^{1.6}$, and $PO_4 = 66.9 V_{DCPA}{}^{2.6}$. This suggests that the filler volume fraction is a key factor, and the release increases with V_{DCPA} at a rate greater than linear. The new nano-composites, with substantial Ca and PO_4 release, possessed mechanical properties matching those of a commercial stress-bearing, non-releasing composite. Hence, the nano-DCPA-whisker composites may have both stress-bearing and caries-inhibiting capabilities, a combination not yet available in current dental materials.

Acknowledgements

Certain commercial materials and equipment are identified to specify the experimental procedure. This does not imply recommendation or endorsement by NIST or ADAF, or that the material or equipment identified is necessarily the best available for the purpose. The standard uncertainty of the flexural strength measurement was estimated to be 1%. The standard uncertainty for the Ca and PO_4 release measurements was estimated to be 3%. Unless otherwise specified in the paper, one standard deviation was used as the estimated standard uncertainty of the measurements.

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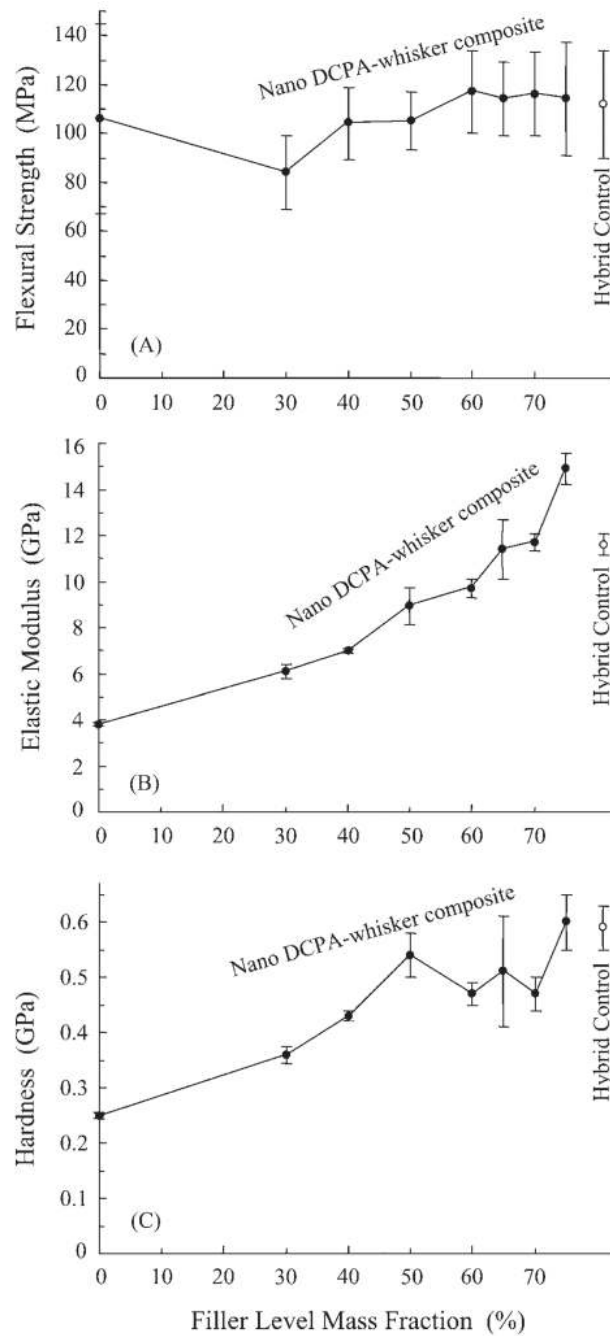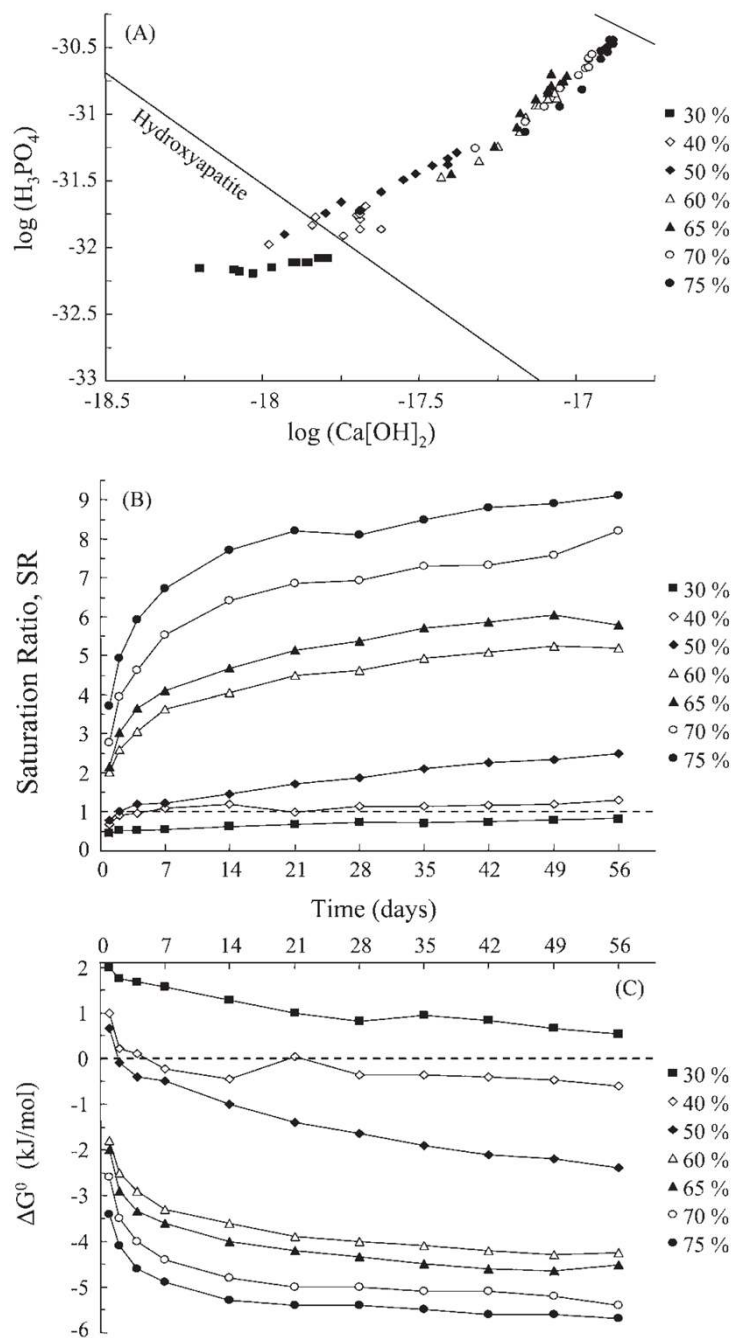
Figure 1.
Mechanical properties. **(A)** Flexural strength, **(B)** elastic modulus, and **(C)** hardness, *vs.* filler level for the nano-DCPA-whisker composites. Values for the stress-bearing, non-releasing hybrid control (TPH, Caulk/Dentsply) are also included. Each value is the mean of 6 measurements for strength (mean ± SD; n = 6), and 10 measurements for elastic modulus and hardness (mean ± SD; n = 10), with each error bar showing the standard deviation (SD). Line connects the datapoints for visual clarity.
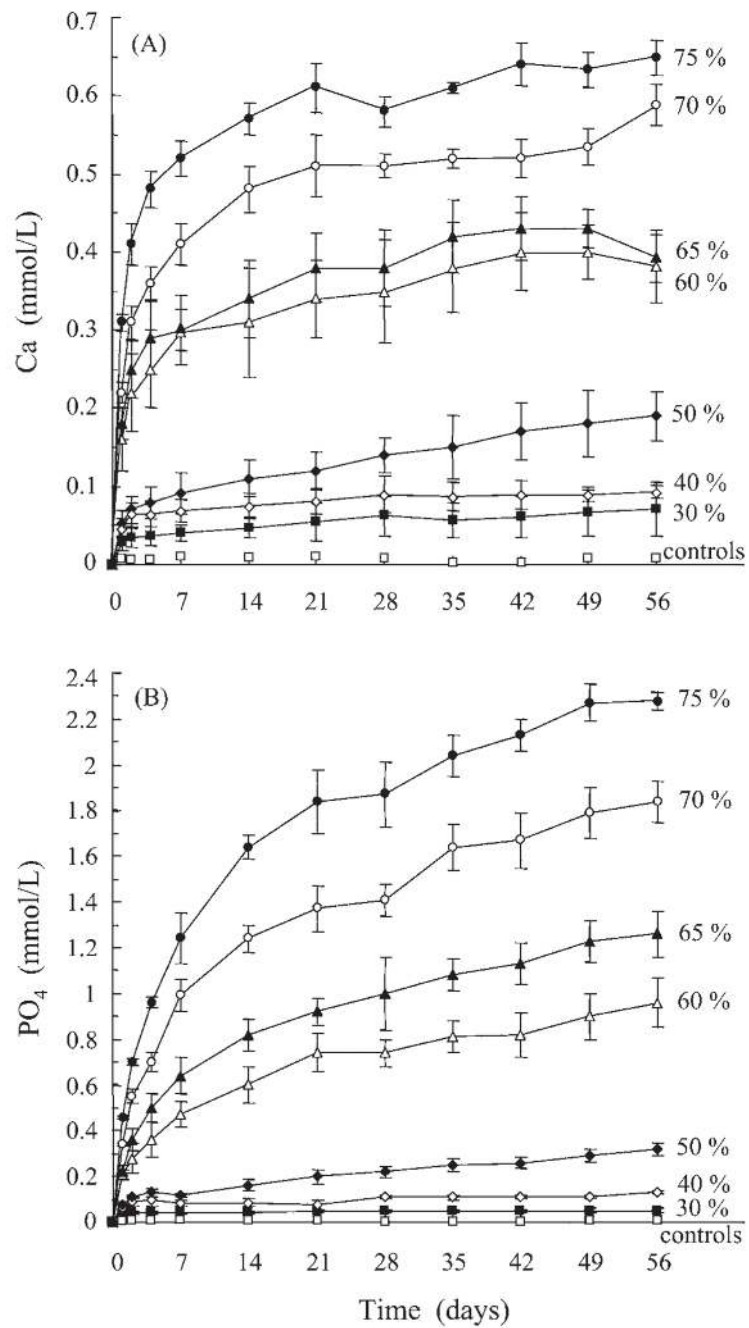
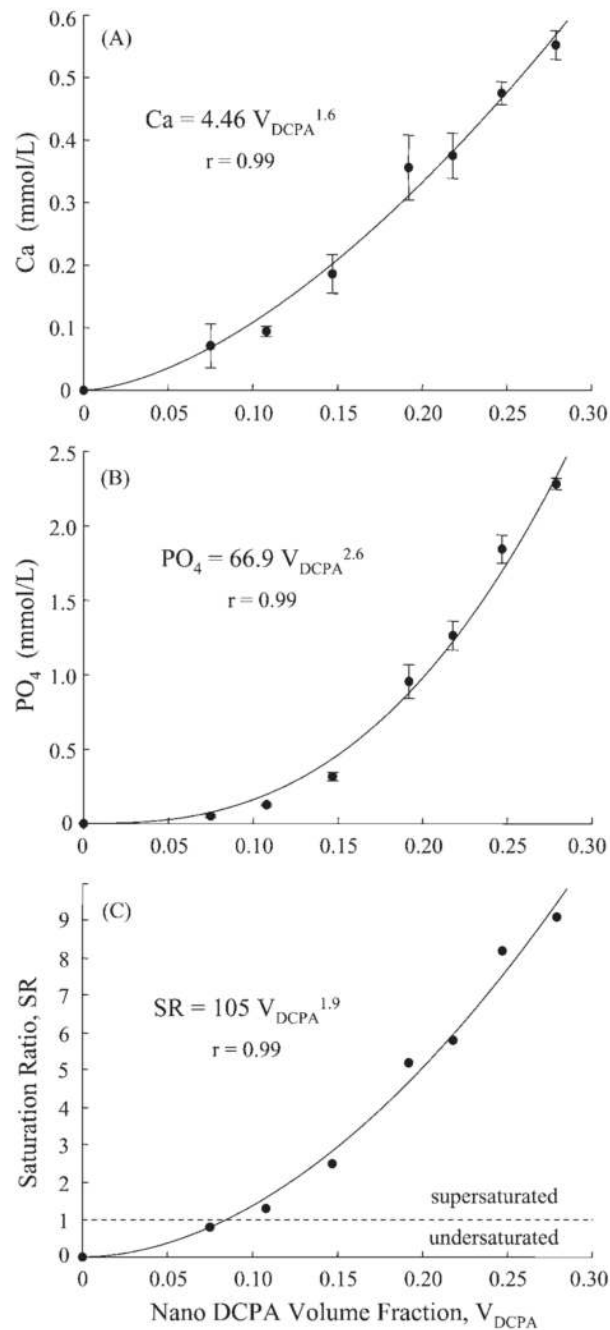**Figure 2.**
Ca and PO$_4$ release. **(A)** Ca ion release and **(B)** total ionic PO$_4$ release, from the nano-DCPA-whisker composites *vs.* filler level and immersion time. The symbols on the x-axis represent the hybrid control (TPH, Caulk/Dentsply) and the unfilled resin that had no Ca or PO$_4$ release. Each value is the mean ± SD; n = 3. Lines connect the datapoints for visual clarity.

Figure 3.
Remineralization potential. **(A)** Diagram demonstrating the potential of DCPA-whisker composites to form hydroxyapatite. The straight line in the middle represents the hydroxyapatite solubility isotherm line. The line at the upper right corner represents the solubility isotherm for DCPD (dicalcium phosphate dihydrate, $CaHPO_4 \cdot 2H_2O$). The dots represent $\log([Ca^{2+}][OH^-]^2)$ *vs.* $\log([H^+]^3[PO_4]^{3-})$ from the measured Ca and PO_4 concentrations. **(B)** Degree of saturation SR < 1 means that the solution is undersaturated, and SR > 1 means supersaturated, with respect to hydroxyapatite. **(C)** Thermodynamic driving force for remineralization. The larger the negative value of the Gibbs free energy ΔG^0, the

lower the energy state for hydroxyapatite precipitation, and the higher the remineralization potential. Values near the right axis are filler level mass fractions.

Figure 4.
Relationships between **(A)** Ca and **(B)** PO$_4$ release and nano-DCPA volume fraction V_{DCPA}. The curves are best fits to the measured data by Eqs. 6–8, yielding Ca = 4.46 $V_{DCPA}1.6$, PO$_4$ = 66.9 $V_{DCPA}2.6$, and SR = 105 $V_{DCPA}1.9$. The correlation coefficient r = 0.99 for all three equations. Ca and PO$_4$ in these equations are ion concentrations and have the units of mmol/L. V_{DCPA} is unitless; *e.g.,* V_{DCPA} = 0.25 means a volume fraction (volume of DCPA/ volume of composite) of 25% (0.25 is equivalent to 25%).