SELF-SETTING ORTHOPEDIC CEMENT COMPOSITIONS BASED ON $CaHPO_4$ ADDITIONS TO CALCIUM SULPHATE

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ABSTRACT

Calcium sulphate-based cements depend on the setting reaction between water and calcium sulphate hemihydrate (CSH, $CaSO_4 \cdot 1/2H_2O$) to form calcium sulphate dihydrate (CSD, Gypsum, $CaSO_4 \cdot 2H_2O$) as the reaction product. Rapid formation of gypsum needles provides the resultant material its initial, dry cohesive strength. Such weak cements, in the form of granules, pellets or cement pastes, are commercially available as bone defect fillers in clinical orthopedic applications. However, pure calcium sulphate cements rapidly deteriorate in aqueous solutions and crumble into a powder. Calcium sulphate cements are also not able to maintain their dry strength when soaked in human blood plasma or synthetic body fluids at 37°C. Additions of calcium phosphate powders (5 to 33 wt%), such as $CaHPO_4$ (DCPA, dicalcium phosphate anhydrous, monetite) to CSH were found to significantly increase the wet mechanical integrity of these new cements. *In vitro* apatite-inducing ability of pure gypsum cements and the DCPA-doped calcium sulphate cements were compared by soaking those in a tris-buffered, 27 mM HCO_3^- containing synthetic body fluid (SBF) solution for 1 week. While the gypsum cement samples were not able to form any carbonated apatitic calcium phosphates on their surfaces, DCPA-doped cement samples were covered with a thick layer of carbonated, apatitic calcium phosphate. Moreover, the DCPA-doped gypsum cements kept their initial mechanical strength after 1 week of soaking in the SBF solution. Samples of pure gypsum cements, on the other hand, simply disintegrated into loose powders during the same SBF soaking.

INTRODUCTION

Since the 19th century, calcium sulphates have been in use as non-load-bearing bone grafts or dental implants, and Dreessmann [1] even noted that some of the ancient Egyptian mummies were found to have dental fillings made out of calcium sulphate. Calcium sulphate has shown excellent biocompatibility [2] and in 1980 Coetzee [3] concluded that it should be regarded as a good bone graft substitute, comparable to autograft, in defects in the skull and facial bone [4]. With the addition of water, calcium sulphate hemihydrate (CSH, $CaSO_4 \cdot 1/2\ H_2O$) converts into calcium sulphate dihydrate (CSD, Gypsum, $CaSO_4 \cdot 2H_2O$) as the end product. This material, after its FDA approval, is widely used as a bone defect-filling material [5-8].

However, calcium sulphate cements have few points of concerns: (*i*) its rapid passive dissolution and *in vivo* resorption even before the host bone has had the time to grow into the defect area [4], (*ii*) its known cytotoxic effect: its dissolution leads to acidic microenvironment responsible for local inflammatory processes at the site of implantation in human bone [3] (Inflammatory tissue was found to disappear after 60

days in bone, but to remain in soft tissue implantation sites of white New Zealand rabbits [9].), (*iii*) pure calcium sulphate is not able to maintain its initial dry strength when soaked in water or synthetic body fluids; it disintegrates, and (iv) pure calcium sulphate does not have the property of osteoconductivity. To address these concerns and to improve the properties of calcium sulphate cements, calcium phosphate additions (β-TCP, α-TCP, HA and $Ca(H_2PO_4)_2{\cdot}H_2O$) have been investigated [4, 10-12].

Compressive strength of pure calcium sulphate dihydrate cements shows a significant variation over the range of 1 to 15 MPa depending on the liquid-to-powder (L/P) ratio employed in preparing the pastes [13, 14]. With an increase in the L/P ratio, strength rapidly deteriorates due to the creation of remnant porosity in the final cement bodies. Fernandez *et al.* [15] reported that α-TCP (which is by itself a self-setting cement powder) additions to CSD can be used to increase the compressive strength values to above 20 MPa. Sato *et al.* [16] showed that osteoconductivity in calcium sulphate cements and new bone formation could be improved when at least 50% of calcium sulphate was substituted by HA powders.

To the best of our knowledge, addition of $CaHPO_4$ to CSH powders has not been studied before. The present paper reports the mixing of $CaHPO_4$ (from 5 to 33 wt%) with CSH powders. The resultant cements were biphasic mixtures of CSD and $CaHPO_4$, with a significant carbonated, biomimetic apatite-inducing ability upon soaking in SBF solutions [17] for 1 week at 37°C.

EXPERIMENTAL PROCEDURE

Pure calcium sulphate pellets were prepared as follows: 12.0 g of CSH powder *(99.8%, Aldrich, Milwaukee, WI)* was kneaded, by using an agate pestle, with 4.8 mL of deionized water (i.e., L/P=0.4) in an agate mortar for 3 minutes. The formed paste was then transferred into a stainless steel die of a diameter of 2.54 cm. The paste in the die was then uniaxially pressed at a pressure of 1.78 kg/mm^2 for 8 minutes. The recovered pellets were dried overnight at 37°C in air.

$CaHPO_4$ (*>99%, J. T. Baker, Phillipsburg, NJ*)-containing calcium sulphate cement pellets were prepared and studied at three compositions: 5, 10 and 33 wt% $CaHPO_4$. For the preparation of, for instance, 33 wt% $CaHPO_4$ samples, 4.0 g of $CaHPO_4$ and 8.0 g of CSH powders were first mixed, under 6 mL of high purity ethyl alcohol, in an agate mortar. These ethanol-mixed powders were then dried in a glass Petri-dish at 37°C, overnight. Dried powders were then mixed with water in an agate mortar at the L/P ratio of 0.4. The remainder of the processing and pellet formation was exactly the same as with those described above for pure calcium sulphate. The obtained pellets were of 2.54 cm diameter and about 4 mm height.

Samples were characterized by using an X-ray diffractometer, XRD, (XDS 2000, Scintag, Sunnyvale, CA) operated at 40 kV and 30 mA with mono-chromated Cu K_α radiation, by using FTIR, Fourier Transformed Infrared Spectroscopy, (Nicolet 550, Thermo-Nicolet, Woburn, MA), and by FESEM, field-emission scanning electron microscopy (S-4700, Hitachi, Tokyo, Japan). Mechanical testing (i.e., the load versus displacement curves) was performed using an Universal Testing Machine (Instron, Phoenix 20K, MTI. Roswell, GA). The pellets were placed between self-levelling plates and compressed at 1 mm/min.

Pellets of pure CSD and $CaHPO_4$-doped CSD cements were both soaked in 100 mL of synthetic body fluid (SBF) solutions for 1 week at 37°C to examine and compare their apatite-inducing ability. SBF solutions were prepared as described in Table I below [17]. SBF solutions were replenished with fresh solutions at every 48 hours during 1 week of soaking.

Table I. Preparation of SBF solution (1 L)

Order	*Reagent*	*Weight (g)*	*Ion*	*Human Plasma(mM)*	*SBF (mM)*
1	NaCl	6.547	Na^+	142	142
2	$NaHCO_3$	2.268	Cl^-	103	125
3	KCl	0.373	HCO_3^-	27	27
4	$Na_2HPO_4{\cdot}2H_2O$	0.178	K^+	5	5
5	$MgCl_2{\cdot}6H_2O$	0.305	Mg^{2+}	1.5	1.5
6	$CaCl_2{\cdot}2H_2O$	0.368	Ca^{2+}	2.5	2.5
7	Na_2SO_4	0.071	HPO_4^{2-}	1	1
8	$(CH_2OH)_3CNH_2$	6.057	SO_4^{2-}	0.5	0.5

RESULTS AND DISCUSSION

Figure 1 depicts the XRD data of the starting powders of $CaSO_4{\cdot}1/2H_2O$ (CSH). The XRD data for the $CaSO_4{\cdot}2H_2O$ (CSD) powders formed after mixing CSH powders with water is also given in Figure 1 (top trace). CSH reacts with water according to the following reaction

$$CaSO_4{\cdot}1/2\ H_2O + 3/2\ H_2O \rightarrow CaSO_4{\cdot}2\ H_2O \qquad (1).$$

The XRD data reported in the top trace of Fig. 1 was gathered from the ground powders of formed CSD pellets described above. In a similar fashion, Figure 2 shows the FTIR traces of pure CSH and pure CSD powders. These XRD and FTIR served as controls prior to the start of $CaHPO_4$-doping in CSH powders.

The XRD data for 5, 10, and 33% $CaHPO_4$-doped calcium sulphate samples (Figure 3) showed that all three samples readily allowed the conversion of CSH into CSD. In other words, even the increasing presence of monetite did not inhibit the CSH to CSD transformation. Figure 4 depicted the FTIR traces of 5, 10, and 33% $CaHPO_4$-doped calcium sulphate samples. The FTIR traces were all quite similar to that of CSD. The shoulder-like bands over the range of 1400 to 1300 cm^{-1}, appeared in the top FTIR trace (i.e., 33wt% $CaHPO_4$) of Fig. 4, was due to the HPO_4^{2-} groups. Characteristic IR bands of pure $CaHPO_4$ were observed at 2803, 2326, 2110, 1630, 1399, 1345, 1124, 1060, 986, 884, 555, 535 cm^{-1} (data not shown here).

SEM morphology of pure CSH powders was shown in Figure 5(a). CSH powders consisted of particles in the range of 5 to 40 μm. On the other hand, the CSH to CSD transformation totally consumed these large particles, and resulted in the formation of CSD whiskers, as shown in Figure 5(b). These interlocking, intermingling whiskers or needles provide the dry strength to the CSD samples.

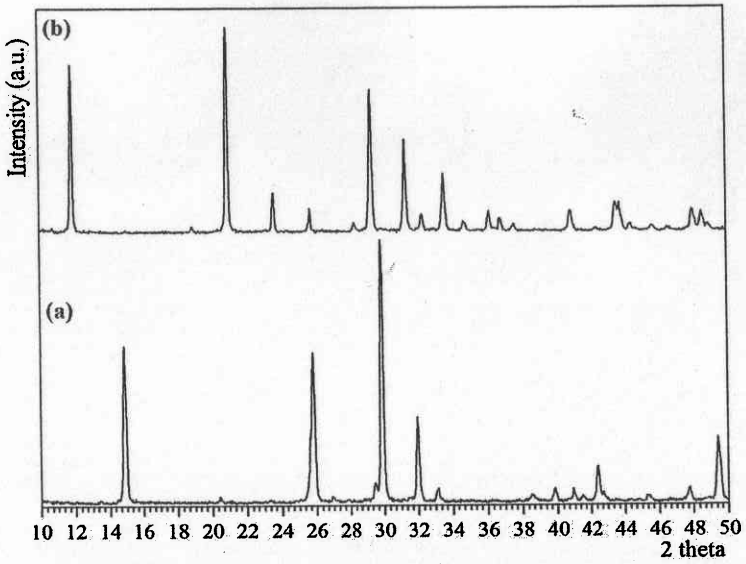

Fig. 1 XRD traces of (*a*) pure CSH and (*b*) pure CSD

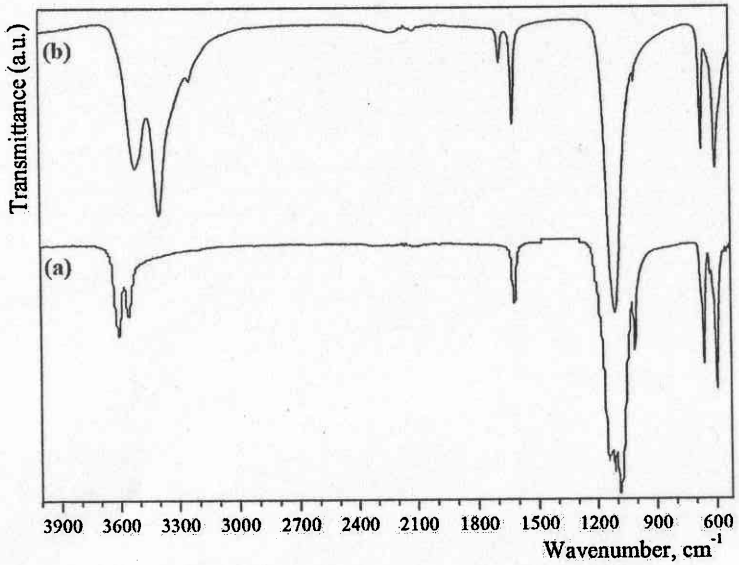

Fig. 2 FTIR traces of (*a*) pure CSH and (*b*) pure CSD

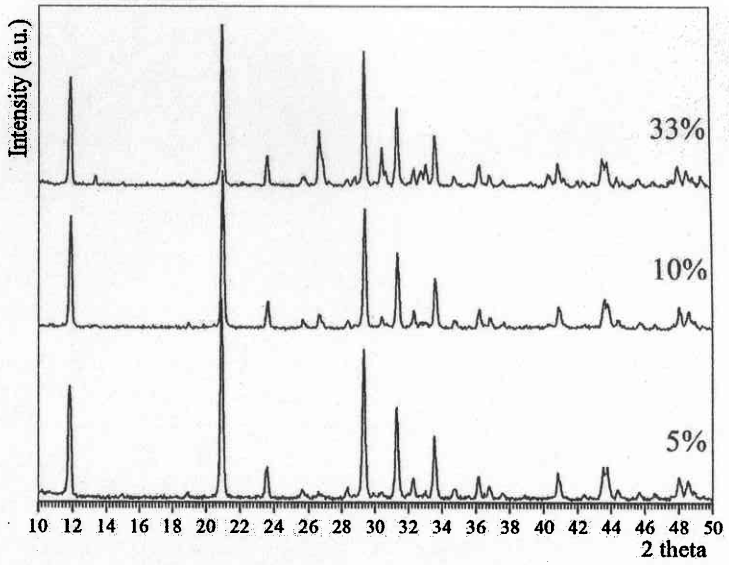

Fig. 3 XRD traces of 5, 10, and 33% $CaHPO_4$ in CSD cement

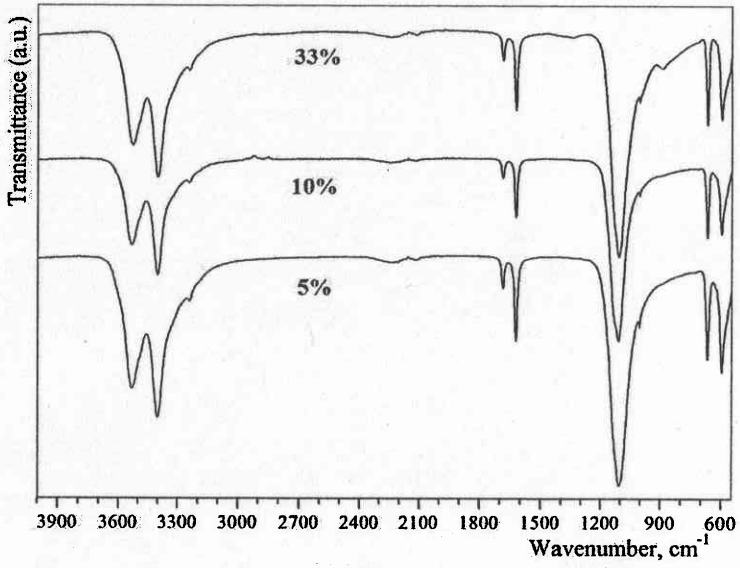

Fig. 4 FTIR traces of 5, 10, and 33% $CaHPO_4$ in CSD cement

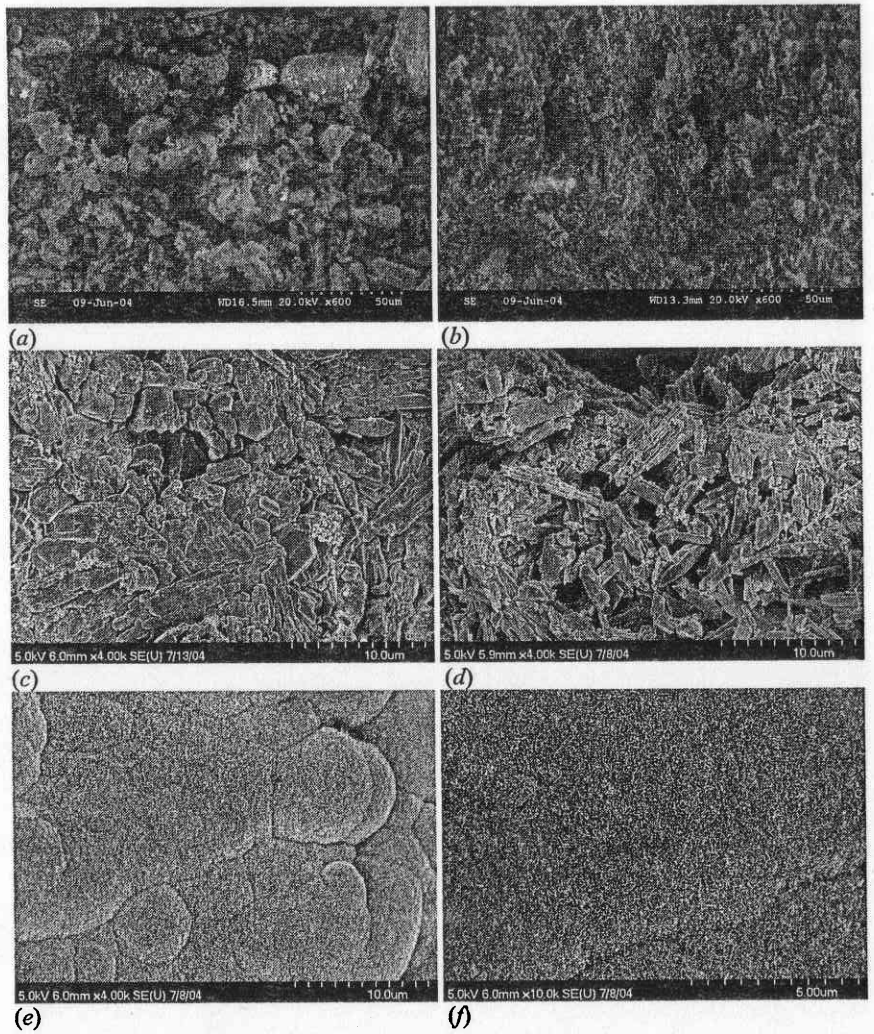

Fig. 5 FESEM micrographs of (*a*) initial CSH powders, (*b*) pure CSD cement, (*c*) 10% $CaHPO_4$ in CSD cement, (*d*) 33% $CaHPO_4$ in CSD cement, (*e*) 33% $CaHPO_4$ in CSD sample after SBF-soaking (*low mag*), (*f*) close up view of the sample in (*e*).

The FESEM micrograph of Figure 5 (c) showed the surface of 10% $CaHPO_4$-containing CSD sample, which was soaked in SBF for 1 week. It was apparent that these samples (like the pure CSD and 5% $CaHPO_4$-containing samples) did not have any apatite-inducing ability. This was the also same morphology of the 10% $CaHPO_4$-

containing samples prior to the SBF soaking. Figure 5(d) depicted the FESEM morphology of a 33% $CaHPO_4$-containing sample prior to the SBF soaking. Figures 5(e) and 5(f) showed the 33% $CaHPO_4$ sample after 1 week of SBF soaking at low and high magnifications. This was the typical morphology of biomimetically (i.e., in SBF, at 37°C and pH 7.4) coated, carbonated, nanoapatites. When one went to higher magnifications, the nanotexture of this material became visible, which comprised interlocking nanocrystals of carbonated, calcium- and OH ion-deficient, apatitic calcium phosphate [18]. Therefore, such 33% $CaHPO_4$-doped gypsum cements revealed, for the first time, a significant apatite-inducing ability, which was not present in pure gypsum.

Moreover, with the addition of $CaHPO_4$ into calcium sulphate, the load-displacement curves (under compression, on cylindrical samples having a surface area of 507 mm^2) improved considerably with respect to those of pure calcium sulphate cements, as shown in Figure 6. 33% $CaHPO_4$-containing samples had a higher load-bearing ability in comparison to pure CSD.

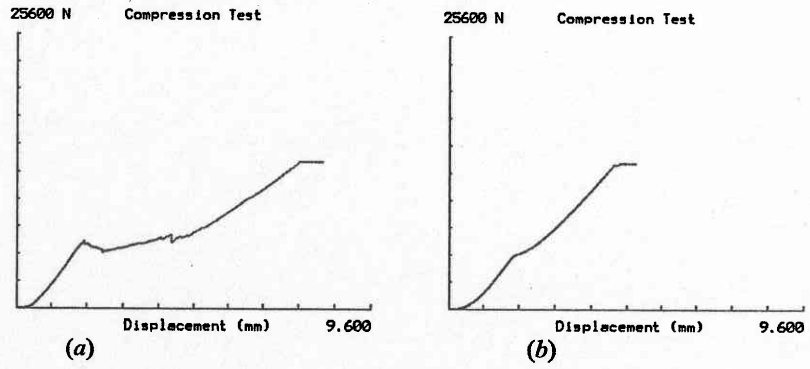

Fig. 6. Load-displacement curves of (*a*) pure CSD, and (*b*) 33% $CaHPO_4$-CSD sample

CONCLUSIONS

$CaHPO_4$ powder additions (5, 10, and 33wt%) were performed in initially CSH powder matrices to test (1) self-setting cement behavior, (2) apatite-inducing ability in SBF solutions, and (3) mechanical integrity of the resultant bodies. While 5 and 10wt% doped CSD bodies did not show any apatite-inducing ability, 33wt% $CaHPO_4$-containing samples displayed a remarkable degree of apatite formation on the sample surfaces after 1 week of SBF soaking at 37°C. 33% $CaHPO_4$ doped samples (prior to SBF soaking) also showed an improved load-bearing ability in comparison to pure CSD cements. These $CaHPO_4$ doped calcium sulphate cements are, thus, expected to show *in vivo* osteoconductivity.

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ADHESIVE STI
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ABSTRACT

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INTRODUCTION

Since the c