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Mendeleev Commun., 2004, 14(4), 179–180

Mendeleev Communications

Cements for biomedical applications

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DOI: 10.1070/MC2004v014n04ABEH001976

New cements of acidic $Ca(H_2PO_4)_2 \cdot H_2O$ and basic Ca_3SiO_5 were developed for biomedical applications.

Calcium phosphate materials are widely used to treat damaged bones and teeth, although they are difficult to deliver to a proper place in a desired shape.[1,2] The application of calcium phosphate cement (CPC) biomaterials in the form of *in situ* hardening pastes could solve this problem.[2–5]

The aim of this study was to develop composite cements based on monocalcium phosphate $Ca(H_2PO_4)_2 \cdot H_2O$ (MCPM) and tricalcium silicate Ca_3SiO_5 mixtures. Tricalcium silicate was chosen as a component to improve the bioactivity of the material: the presence of silicon is known to provide a better bone bonding. The hydrolysis of Ca_3SiO_5 leads to a sharp increase in pH as a result of calcium hydroxide formation.[6] The alkalinity is known to suppress the activity of pathogenic bacteria and makes the cements to be prospective for dentistry, but it also could provoke surrounding tissue necrosis. The acidic monocalcium phosphate monohydrate was selected as a

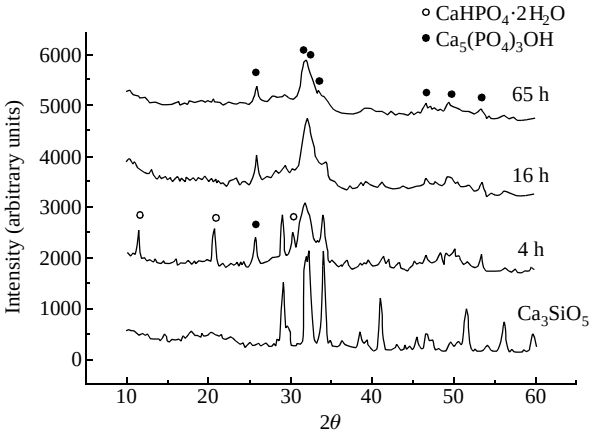

Figure 1 XRD patterns of a cement of Ca_3SiO_5 and $Ca(H_2PO_4)_2·H_2O$.

second constituent of the mixture to correct the pH value of the cement mass.

All the starting chemicals were of analytical grade (MCPM, $CaCO_3$ and SiO_2). The powder of Ca_3SiO_5 was synthesised by a direct solid-state reaction. The starting powders of cement mixtures were intensely crushed in a ball grinder for 30 min. The particle size of as-prepared powders was around 5–10 μm. Cements were fabricated by weighing appropriate amounts of two components to obtain a desired Ca:P:Si ratio. The liquid-to-powder ratio was varied in the range 0.5–0.75 ml g^{-1} with a 0.25 M Na_2HPO_4 solution. The paste was packed into a cylindrical Teflon mould (i.d. 6×12 mm). Compacted specimens were removed from the mould after 10 min and placed in a simulated body fluid (SBF) solution for three days at 37 °C.

The following reactions should be considered to describe the chemical evolution of hardening specimens:

$$Ca_3SiO_5 + (3 - x + y)H_2O \rightarrow (3 - x)Ca(OH)_2 + xCaO·SiO_2·yH_2O, \quad 1.6 < x < 2.0, 1.3 < y < 4 \quad (1)$$

$$Ca(H_2PO_4)_2·H_2O + Ca(OH)_2 + H_2O \rightarrow 2CaHPO_4·2H_2O \quad (2)$$

$$CaHPO_4·2H_2O + Ca(OH)_2 \rightarrow Ca_{10}(PO_4)_6(OH)_2 \quad (3)$$

In case of the two-component cement Ca_3SiO_5–MCPM, the setting reaction proceeded in two steps. The first step was the fast formation of dicalcium phosphate dihydrate $CaHPO_4·2H_2O$ (DCPD) as a result of reactions (1) and (2). The soluble acidic $Ca(H_2PO_4)·H_2O$ temporary decreased the pH value at the beginning of a hardening reaction and promoted the precipitation of DCPD. The following reaction (step 2) was slower and resulted in the formation of the desired hydroxylapatite phase (Figure 1). Hydroxylapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA), a chemical analogue of natural bone minerals, is the main product of the setting reactions.

Significant broadening of apatite XRD peaks evidenced the nanocrystalline nature of the material. The results of electron microscopy proved the suggestion of a high dispersion of the powder. The micrographs demonstrated the aggregates of spherical nanoparticles with a size smaller than 100 nm (Figure 2).

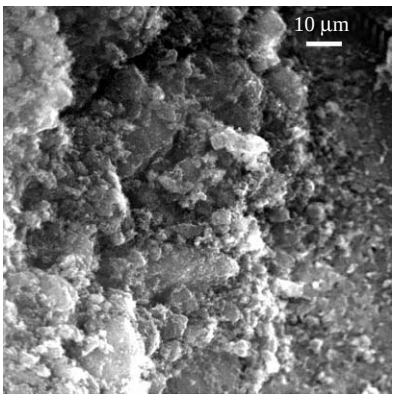

Figure 2 Micrographs of the $Ca(H_2PO_4)_2·H_2O$–Ca_3SiO_5 cement.

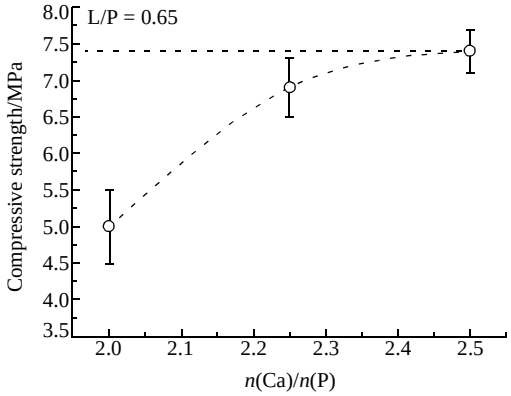

Figure 3 Variations in the compressive strength of cement samples prepared with different Ca/(P + Si) ratios.

The chemical evolution of the cement systems was consistent with their mechanical properties: lower HA content resulted in a poor compressive strength (Figure 3).

To increase the strength of the cements, the Ca/P ratio should be increased (Figure 3). The same results were reported by Serraj *et al.*,[7] who tested a mixture of MCPM and CaO. Tricalcium silicate used in this work can be considered as an analogue of calcium oxide [reaction (1)].

The compressive strength increased up to 7.5 MPa with increasing Ca/P from 2 to 2.5. The increasing ratio was related to a higher fraction of Ca_3SiO_5 (or 'CaO'), which is prone to hydrolysis. High micro- and macroporosity (pore diameter ≤ 10 μm) of the final cement was the main reason for the relatively low mechanical strength of cements.

Cements are often used as drug delivery systems in medicine. Prolonged local treatment of diseased tissue with antibiotics *etc*., favours healing. The macroporosity of the material is also undesirable in this case, taking into account fast drug release at the very beginning of the cement administration. To control the pharmacokinetics of drug release from the cement into the environment, polymer additives are usually applied. The Ca_3SiO_5–MCPM cement was loaded with the sodium gentamycini sulfate antibiotic in combination with gelatin (5 wt.% gelatin in a sodium phosphate solution was used as a liquid component of the cements). Gelatin, which is a very common inexpensive biopolymer, is a denatured form of polypeptide collagen, which is an organic component of bones.

It was found that the cements combined with gelatin could be used as an effective drug delivery system since the average drug release rate from the cement with the biopolymer decreased from 65 to 25% after an hour.

This study was supported by the Russian Foundation for Basic Research (grant no. 02-03-33271-a) and by the programme 'Universities of Russia' (grant no. UR.06.03.006). We are grateful to Professor S. M. Barinov for his assistance in the mechanical testing of samples and for valuable discussions.

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Received: 4th June 2004; Com. 04/2301