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Optimization of a calcium orthophosphate cement formulation occurring in the combination of monocalcium phosphate monohydrate with calcium oxide

O. BERMÚDEZ, M.G. BOLTONG, F.C.M. DRIESSENS, J.A. PLANELL
Dept. de Ciència dels Materials i Enginyeria Metal. lúrgica, E.T.S.E.I.B., UPC, Avda. Diagonal 647, 08028 Barcelona, Spain

In a previous study it has been found that mixtures of monocalcium phosphate monohydrate MCPM and calcium oxide CaO set upon mixing with water. In this study it was found that the optimum composition for such a mixture is a Ca/P molar ratio of 1.35 ± 0.02. The milling procedure for preparation of the powder of this cement was also optimized. The optimum water/powder ratio appeared to be 0.53 ± 0.01. Amounts of precipitated hydroxyapatite up to 7% by weight increased the compressive strength and the diametral tensile strength of the cement. The maximum values found for these properties were 6 and 1.6 MPa, respectively. Finally, it was found that the cement obtained its maximum strength within 5 h but this diminished upon further soaking in Ringer's solution at 37 °C until after 10 weeks of soaking the strength was decreased to 62% of the maximum value.

1. Introduction

The technology of calcium orthophosphate cements can be optimized in various ways. Brown and Chow [1] have prepared a cement powder by mixing tetracalcium phosphate (TTCP) with dicalcium phosphate dihydrate (DCDP). They ground these basic constituents to a particle size of 40 μm and mixed them with a diluted solution of phosphoric acid into a slurry. Such a slurry sets too slowly. By grinding to a particle size of less than 5 μm the setting time comes in the range 20–25 min. By adding various amounts of hydroxyapatite these authors were able to decrease the setting time to 8 min. However, such additions did not increase the compressive strength. A further refinement of this cement formulation has been reported by Fukase *et al.* [2]. They found that an even higher compressive strength was obtained when one used a TTCP with particles between 1 and 10 μm size and a dicalcium phosphate DCP with a median particle size between 0.3 and 4 μm.

Monma *et al.* [3] optimized a calcium orthophosphate cement obtained in the combination of DCPD and α-tertiary calcium phosphate (α-TCP) by determination of the minimum setting time for various Ca/P molar ratios of the mixture of reactants. They found a minimum of about 10 min at a Ca/P molar ratio of 1.33. They also proved that the reaction product was octocalcium phosphate, which has the observed Ca/P ratio.

Mirtchi *et al.* [4] studied a calcium orthophosphate cement which is formed from a combination of β-tertiary calcium phosphate (β-TCP) with monocalcium phosphate monohydrate. They found that the tensile strength increased with increasing amounts of MCPM, and also with increasing particle size of β-TCP from 2 to 6 μm. By adding either calcium sulphate dihydrate or calcium phosphate hemihydrate or calcium pyrophosphate to the cement powder Mirtchi *et al.* [5] were able to increase the setting time of the cement from about 1 min to about 8 min, whereas such additions also had the advantage that the diametral tensile strength rose from 1.1 to 3.2 MPa.

From similar studies on plaster and dental stone (different forms of gypsum) [6] it is known that the water/powder ratio is also a factor which is of importance in cement-like materials in which the setting is caused by the entanglement of newly formed crystals which precipitate after mixing the powder with water.

The purpose of the present study was to optimize a calcium orthophosphate cement, which we know from previous studies [7, 8] is formed in the combination of MCPM with calcium oxide.

2. Materials and methods

The brand of monocalcium phosphate monohydrate (MCPM) used here was obtained from Panreac, Montplet and Esteban SA, Barcelona, Spain, code number 141225. The calcium oxide CaO was made from marble and bought from E. Merck, Darmstadt, Germany, catalogue number 2109. In addition to these reactants, as a filler or seed material a precipitated hydroxyapatite was chosen, sold also by

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Merck, catalogue number 2143 under the name of tricalcium phosphate. First, CaO was crushed in a mortar and then milled to a particle size of less than 10 µm using an agate ball mill (Pulverisette, Fritsch, Idar Oberstein, Germany). The particle size of MCPM was too large to work with, but attempts to mill it on its own failed due to the fact that the material smeared out against the inside wall of the milling agate pot. However, when it was premixed with the desired amount of CaO it could be milled without such problems.

Twenty-three mixtures of MCPM and CaO were made with a Ca/P molar ratio varying from 1.00 to 1.80. Their mortaring and milling were not yet standardized in this phase, but milling was carried out until, by subjective feeling between the finger tips, the powder was considered to be fine enough. At certain Ca/P ratios duplications were made. The initial setting time *I* and the final setting time *F* were determined with a pair of Gilmore needles as described elsewhere [7] at a water/powder ratio of 0.6 $g g^{-1}$. Cylindrical samples with a diameter of 6 mm and a length of 12 mm were prepared at the same water/powder ratio and soaked for 1 day in Ringer's solution at 37 °C. These samples were then removed from the moulds and the compressive strength *C* as well as the diametral tensile strength *T* (both $n = 6$–8) were determined at a crosshead speed of 1 $mm\,min^{-1}$. From these values the optimum Ca/P ratio was derived. Some samples were analysed by X-ray diffraction (XRD) to determine the reaction products.

Sixteen samples at the optimum Ca/P ratio were made and were subjected to 4 min of mortaring, but milling was carried out at different speeds and different durations, first with four heavy agate balls (30 mm diameter) and then with eight light balls (10 mm diameter). From these 16 samples determinations of *I*, *F*, *C* and *T* were carried out at a water/powder ratio of 0.6 $g g^{-1}$. From a plot of *C* versus *F* or *T* versus *F* the optimum milling conditions were derived.

Some of these samples were subjected to determinations of particle size.

At the optimum Ca/P ratio and using the optimum milling conditions and applying the optimum water/powder ratio seven samples were prepared containing amounts of precipitated hydroxyapatite varying from 0 to 35% by weight. Again determinations of *I*, *F*, *C* and *T* were carried out ($n = 6$–8) in order to determine whether the incorporation of the apatite had a reinforcing effect on the cement.

Finally, at the optimum Ca/P ratio, using the optimum milling conditions, applying the optimum water/powder ratio and choosing the optimum hydroxyapatite content a time series was carried out in order to find eventual changes of *C* and *T* as a function of the time of soaking in Ringer's solution, which was varied from 5 h to 10 weeks.

The pH of the setting cement at the optimum Ca/P ratio and HA content was determined at room temperature as a function of time up to a period of 4 h.

3. Results

Fig. 1 shows the values of *F* for the 23 samples which did not have standardized milling. The values of *F* are located between an upper and a lower envelope which has yet to be explained as a variation due to differences in the milling procedure. Interesting is the plateau for *F* between Ca/P = 1.4 and 1.67 and the lower plateau beyond Ca/P = 1.67.

Fig. 2 and Fig. 3 show the values of *C* and *T*, respectively, as a function of the Ca/P ratio. At certain Ca/P ratios the duplicate specimens differed significantly, presumably also due to differences in milling. It is observed that the optimum value is for the Ca/P ratio of 1.35 ± 0.02 which is equal to the value of octocalcium phosphate. In order to investigate whether octocalcium phosphate was the reaction product in this range of compositions three products were investigated with X-ray diffraction. These showed indeed that octocalcium phosphate was the main reaction product. Some monetite was also formed and the excess of CaO reacted to $Ca(OH)_2$. Beyond Ca/P = 1.67 it was found that hydroxyapatite was formed. However, as the products at that composition were extremely weak, it is suspected that the crystals of hydroxyapatite formed during the reaction of MCPM with CaO in that composition range did not entangle. This is corroborated by the fact that the peaks of the X-ray diffraction pattern were broadened, indicating a small particle size of the apatite formed.

In the second series of samples at the optimum Ca/P ratio of 1.35 the milling conditions were varied. Table I gives the range of variation for the Ca/P ratio expected to occur, at least for *F*, *C* and *T* at a

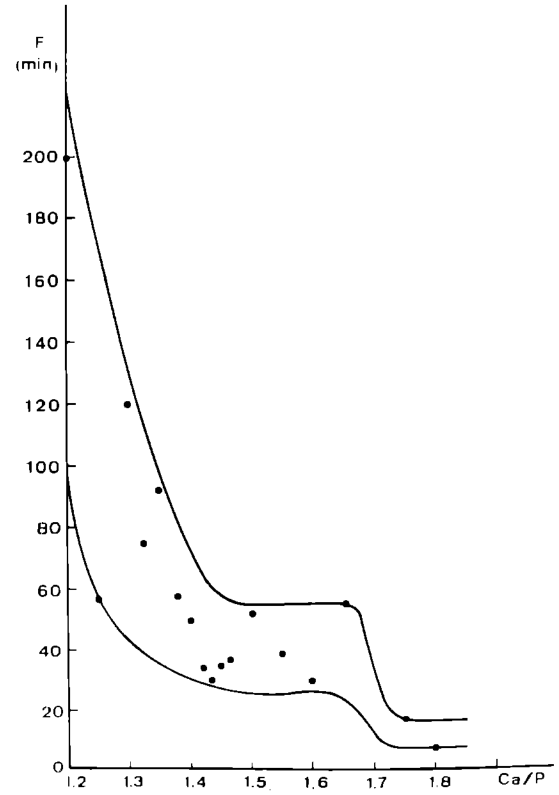

Figure 1 Final setting time *F* (min) of mixtures of MCPM and CaO with different Ca/P molar ratios after milling (not yet standardized) and mixing into a paste with water at a water/powder ratio of 0.6 $g g^{-1}$. The data are circumscribed by an upper and a lower envelope.

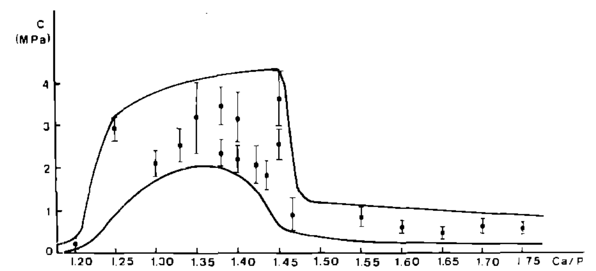

Figure 2 Compressive strength C (MPa) of cements made out of MCPM and CaO mixtures having various Ca/P molar ratios after milling (not yet standardized) and mixing into a paste with water at a water/powder ratio of 0.6 g g^{-1}. The samples were soaked for 1 day in Ringer's solution at 37 °C. The data are circumscribed by an upper and a lower envelope.

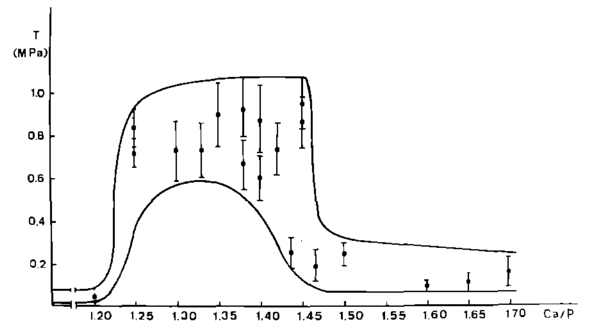

Figure 3 Diametral tensile strength T (MPa) of cements made out of MCPM and CaO mixtures having various Ca/P molar ratios after milling (not yet standardized) and mixing into a paste with water at a water/powder ratio of 0.6 g g^{-1}. The samples were soaked for 1 day in Ringer's solution at 37°C. The data are circumscribed by an upper and lower envelope.

TABLE I Variations of the final setting time F, the compressive strength C and the diametral tensile strength T as expected on the basis of Figs. 1–3, and as actually found among the 16 samples prepared at a Ca/P ratio of 1.35 with different milling times and speeds

	Expected range	Range found
F (min)	35–100	13 ± 2–80 ± 10
C (MPa)	2.0–4.0	1.9 ± 0.5–4.0 ± 0.5
T (MPa)	0.50–1.08	0.42 ± 0.15–1.11 ± 0.10

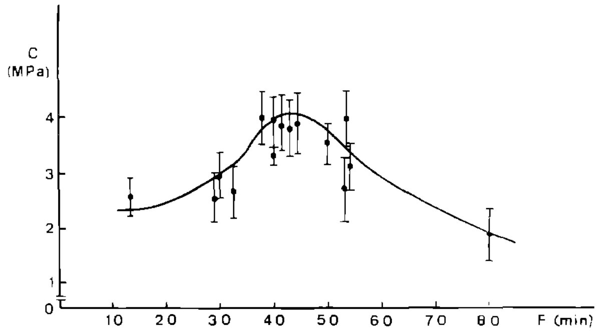

Figure 4 Final setting time F (min) versus compressive strength C (MPa) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 after different milling procedures.

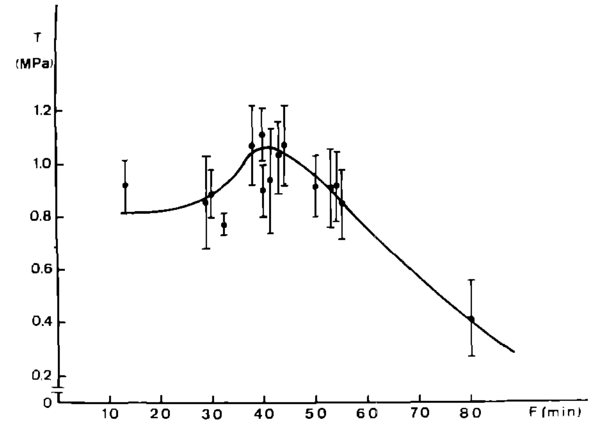

Figure 5 Final setting time F (min) versus diametral tensile strength T (MPa) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 after different milling procedures.

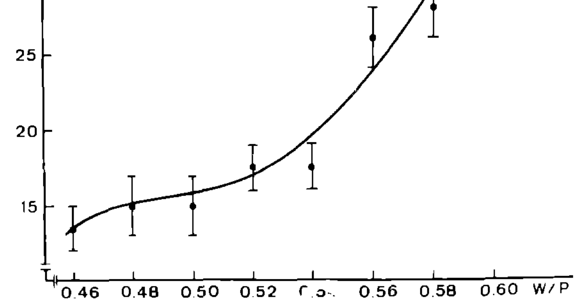

Figure 6 Final setting time F (min) versus water/powder ratio (g g^{-1}) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 and using the optimum milling procedure.

water/powder ratio of 0.6, on the basis of the upper and lower envelopes of Figs. 1–3 in comparison with the data found. From the table it can be concluded that the variations underlying the results of Figs 1–3 were mainly due to variations in the milling procedure. In order to find the optimum milling procedure, a plot of C versus F as given in Fig. 4 or a plot of T versus F as given in Fig. 5, were made. These figures show that a maximum in C and T is reached for $F = 40 \pm 2$ min. As there were about six out of 16 samples which represent this situation, we chose the procedure which was the least time consuming of these six milling procedures.

Investigation with laser diffraction showed that with this milling procedure the particle size ranged from about 1–30 µm and resulted in a medium value of 12 µm.

In the third series of samples a Ca/P ratio of 1.35 was applied and the optimum milling procedure was used, but the water/powder ratio was varied. The results for *F*, *C* and *T* are given in Figs. 6, 7 and 8, respectively. It is observed that there is a plateau in the setting time running from a water/powder ratio of about 0.48 to 0.54. Further there is a maximum in both *C* and *T* at a water/powder ratio of 0.53 ± 0.01.

In the fourth series of experiments a Ca/P ratio of 1.35 was applied using the optimum milling procedure and a water/powder ratio held at 0.52, but now several amounts of precipitated hydroxyapatite (PHA) were added to the mixture of reactants. In Figs. 9 and 10 the variations of *C* and *T* show a maximum around 7 ± 1% of PHA. The setting time did not change much upon addition of PHA.

In the last series the Ca/P ratio of the mixture of reactants was kept at 1.35 but now 7% of PHA was added to that mixture. The optimum milling procedure was applied and the water/powder ratio was maintained at 0.52. Samples were soaked in Ringer's solution at 37 °C for times varying from 5 h to 10 weeks before being tested for compressive strength and diametral tensile strength. The results are given in Fig. 11. It is observed that the maximum strength is reached within 5 h and that this strength diminishes upon further storage in Ringer's solution at 37 °C over 10 weeks to 62% of its maximum value.

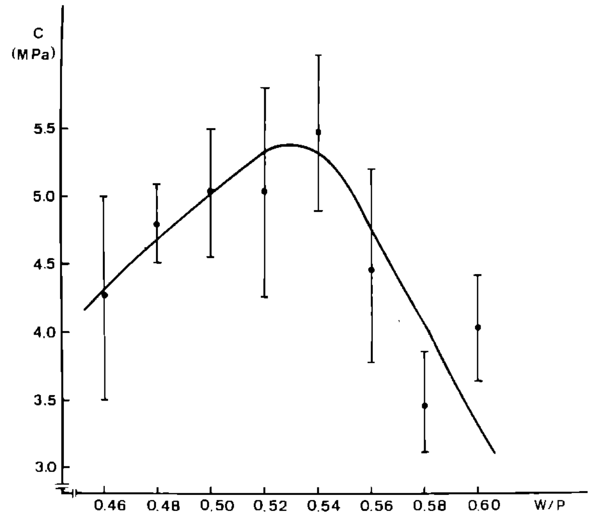

Figure 7 Compressive strength *C* (MPa) versus water/powder ratio ($g\,g^{-1}$) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 and using the optimum milling procedure.

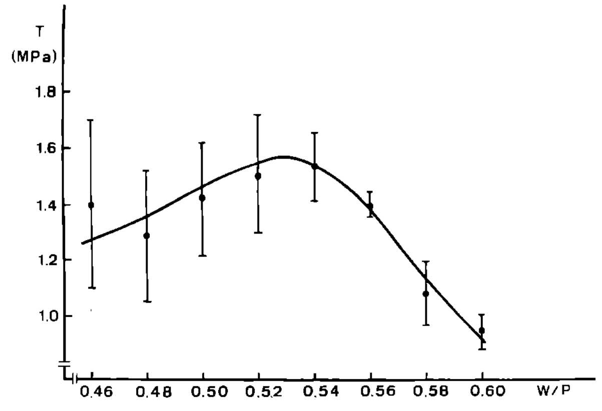

Figure 8 Diametral tensile strength *T* (MPa) versus water/powder ratio ($g\,g^{-1}$) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 and using the optimum milling procedure.

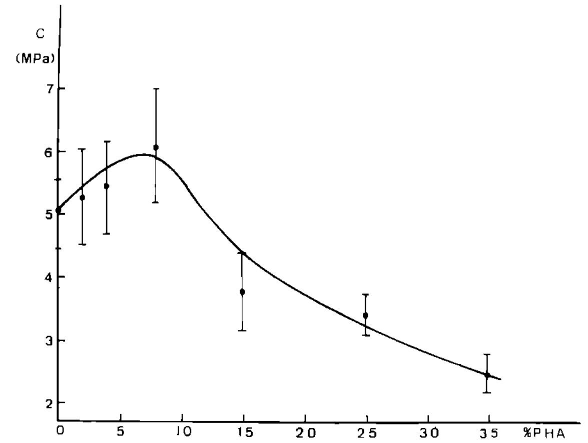

Figure 9 Compressive strength *C* (MPa) versus content of precipitated hydroxyapatite PHA (% by weight) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 under application of the optimum milling procedure and after mixing into a paste with a water/powder ratio of 0.52 $g\,g^{-1}$.

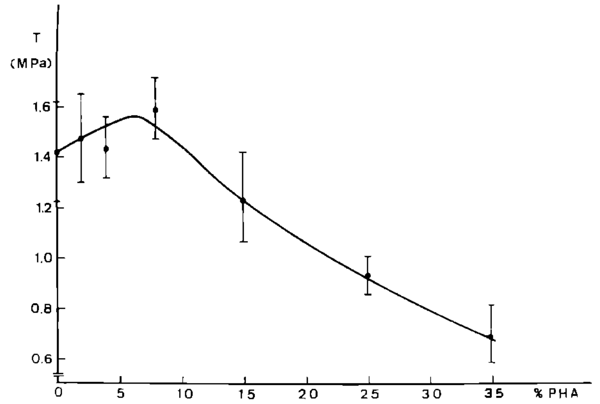

Figure 10 Diametral tensile strength *T* (MPa) versus content of precipitated hydroxyapatite PHA (% by weight) of cements prepared from a mixture of MCPM and CaO having a Ca/P molar ratio of 1.35 under application of the optimum milling procedure and after mixing into a paste with a water/powder ratio of 0.52 $g\,g^{-1}$.

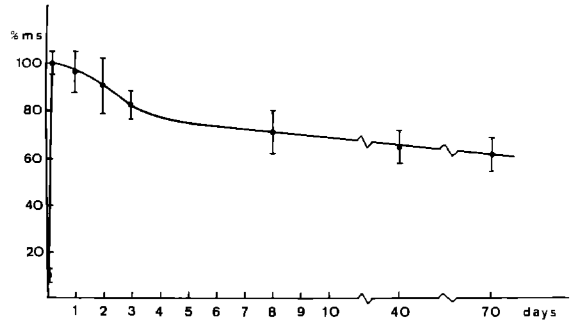

Figure 11 Percentage of maximum strength (% ms) as a function of time of soaking at 37 °C in Ringer's solution for the cement optimized for a Ca/P ratio, milling conditions, water/powder ratio and apatite seed content.

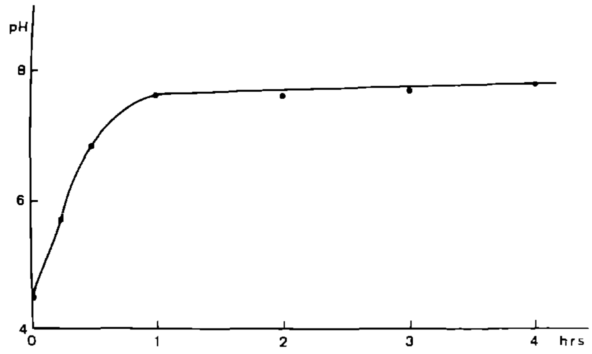

Figure 12 pH of the cement paste at the optimum Ca/P ratio, the optimum HA content and the optimum W/P ratio as a function of time at room temperature.

In Fig. 12 the pH of the setting cement is given as a function of the time from the start of mixing.

4. Discussion

The cement optimized in this study is the second example of a calcium orthophosphate cement which sets due to the entanglement of OCP crystals. Like the cement developed by Mirtchi *et al.* [4, 5] in which the reaction product is DCPD, the present cement deteriorates *in vitro* upon further soaking in aqueous solutions, contrary to the results found by Monma *et al.* [3] for other OCP-like cement formed upon reaction of DCPD with α-TCP.

The calcium phosphate glass cement developed by Nishimura *et al.* [9] sets by entanglement of crystals of calcium ammonium phosphate. These authors implanted their cement in the muscles of rats and found that the crystals were transformed into apatite crystals within 1 week of implantation. Thereby their strength increased considerably compared to the *in vitro* strength.

It is known that during the formation of bone and also during the turnover of bone the precursor crystals are those of OCP [10]. In a previous study we found that this OCP is transformed within about 1 month into a mixture of other calcium phosphates which make up the bulk of bone mineral [11]. Similarly, implantation of calcium orthophosphate cements like the one developed in this study may, upon implantation, be subjected to a transformation of their OCP crystals. Thereby, an important question is whether their mechanical properties will improve or deteriorate during such a transformation under *in vivo* conditions. This will ultimately determine the suitability of such cements for replacement or augmentation of bone structures in orthopaedics and dentistry. In general, the biocompatibility of calcium orthophosphate cements has proven to be as good as that of calcium orthophosphate ceramics [9, 12, 13] so that this property does not give any problem. Only during the first 20 min from the start of mixing does this cement deviate by more than 1 pH unit from neutrality. Therefore, it is expected that no acute inflammatory response will result when this cement is implanted.

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