JOURNAL OF MATERIALS SCIENCE **40** (2005) 3677 – 3682

Effect of iron on the setting properties of α-TCP bone cements

E. FERNÁNDEZ*, M. D. VLAD, M. HAMCERENCU, A. DARIE, R. TORRES, J. LÓPEZ
Interdepartmental Research Group for the Applied Scientific Collaboration (IRGASC), Division of Bioengineering & Biomaterials, Technical University of Catalonia (UPC), Avda. Diagonal 647, E-08028-Barcelona, Spain
E-mail: enrique.fernandez@upc.edu

New ceramic materials with the ability to set like cement, after mixing a powder phase made of one and/or several of these new reactants and a liquid phase, have been obtained within the ternary system "CaO-P_2O_5-FeO". These new reactants have magnetic properties, i.e. cement made from them maintains its magnetic property during the whole setting and hardening. These new materials can be of use, for example, in dental applications, in the treatment of certain types of bone cancer and, in general, in the fields of Biomaterials and Bone Tissue Engineering. In this article, we report on the effect of iron-modified α-tricalcium phosphate, which is the main reactant of commercial calcium phosphate bone cements, on their new setting and hardening properties.

1. Introduction

Nowadays, it is well known that the number of patents and scientific publications related to calcium phosphate bone cements (CPBCs) has been growing exponentially since Brown and Chow presented his first patent application in 1985 [1].

The main idea behind CPBCs consists in making use of the different acidity of calcium phosphates to precipitate, after mixing a powder of at least two different calcium phosphates with a liquid phase, an apatitic mineral phase similar to that in bone tissues [2–9]. In such situation, the precipitated apatitic crystals evolve, due to the chemical reactions controlling the setting, into a mechanically stable microstructure of entangled crystals of hydroxyapatite [10, 11]. This apatitic structure could be then reabsorbed *in vivo* by osteoclastic and osteoblastic activity [12–14]. In fact, due to the apatitic nature of the products of the setting reactions, these CPBCs have osteoconductive property [15]. Moreover, depending on the degree of crystallinity and porosity, CPBCs can be made to be more or less stable after implantation [15–19].

Due to all these advantages and versatility, CPBCs are nowadays being applied through minimally invasive surgery techniques, for example, in spinal surgery applications (*kypho-* and *vertebro-plasties*) [20].

However, further research on CPBCs should be done to extent their use to the treatment of certain types of bone cancer and, in this sense, new thermally active bone cements need to be developed.

A possible approach is to develop magnetically active bone cements. In this way, an applied magnetic field during the first steps of the setting could be modulating the initial strength of the cement (*magnetorheology*), while the true setting and hardening chemical reactions continue until the expected maximum strength is attained at saturation. Moreover, this kind of magnetic cements will have a characteristic magnetic hysteresis that could be of use to thermally activate their whole setting, and so accelerating it, with the added value of being useful for the treatment of certain bone cancers (*hyperthermia therapies*).

The main objective of this study was to obtain new ceramic materials in the ternary system "CaO-P_2O_5-FeO" with the ability to set as cement-like material when mixing a powder phase, made of one and/or several of these new reactants, and an aqueous liquid phase. In this study, we report on the setting and hardening properties of solid solutions like $(3.CaO\text{-}1.P_2O_5)_{1-x}(FeO)_x$, which is the first approach to the magnetic modification of α-tricalcium phosphate (α-TCP; $3.CaO\text{-}1.P_2O_5$) based cements. The setting of the new iron-modified α-TCP cements is the result of their hardening properties due to the hydration reactions of the new reactants.

2. Materials and methods

2.1. Preparation of α-TCP

In this study we followed two different protocols to sinter the iron-modified α-TCP ceramic phase, i.e. α-$(3.CaO\text{-}1.P_2O_5)_{1-x}(FeO)_x$. This approach was important in order to assure the stability of the properties of the end product. The manufacture protocols were as follow:

*Author to whom all correspondence should be addressed.

(a) *Protocol "A"*: Calcium hydrogen phosphate $CaHPO_4$ (DCP; Sigma-Ref. C-7263) and calcium carbonate $CaCO_3$ (CC; Sigma-Ref. C-4830) were mixed in a 2:1 molar ratio. Then, iron citrate $Fe(C_6H_5O_7)$ (IC; Sigma-Ref. 22897-4) was added at different weight proportions (1, 4, 8, 16 and 24 wt%) in respect of the theoretic weight of α-TCP produced. The whole mixture was homogenised by mixing in a planetary rotary mill (Pulverisette 6, by Fritsch GmbH) at low speed. Then, it was sintered at 1400°C for 2 h and quenched in air to room temperature ("($T_0 = 20°C \rightarrow T_1 = 300°C$); $r = 2°C$/min; $d = 1$ h", "($T_1 = 300°C \rightarrow T_2 = 1100°C$); $r = 2°C$/min; $d = 2h$", "($T_2 = 1100°C \rightarrow T_3 = 1400°C$); $r = 2°C$/min; $d = 2$ h". The resulting ceramic material was powdered to an appropriate particle size ($d_{50} = 10\ \mu$m) for cement production.

(b) *Protocol "B"*: In this case, α-TCP was first sintered by a 2:1 molar ratio of a mixture of DCP and CC, following the same sintering program as that in "A". The resulting ceramic material was powdered following the same milling protocol as that in "A" and then, different amounts of IC (1, 4, 8, 16 and 24 wt%) were added to the α-TCP phase. The resulting mixture was homogenised and sintered again to 1400°C during 2 h and then, quenched in air to room temperature ("($T_0 = 20°C \rightarrow T_3 = 1400°C$); $r = 20°C$/min; $d = 2$ h"). The final ceramic was powdered as in "A" to obtain an identical particle size distribution to avoid the influence of this factor on the reactivity of the α-TCP powders, so as to highlight the main influence on the setting properties due to iron modification.

2.2. Preparation of cement

In this study, it was decided to produce *Biocement-H* [21], which is made of 98 wt% of α-TCP and 2 wt% of precipitated hydroxyapatite (PHA; Merck-2143), added as a seed in the powder phase. The liquid phase is an aqueous solution of 2.5 wt% of disodium hydrogen phosphate Na_2HPO_4 (DHP; Merck-6586). The liquid to powder (L/P) ratio was initially selected as 0.32 mL/g, which is the minimum ratio that assures suitable workability and cohesive properties, for *Biocement-H* [21]. However, for the new iron-modified cements the minimum L/P ratio was 0.30 mL/g. This L/P ratio's difference was maintained throughout the study. *Biocement-H* was selected mainly because it is ≈100 wt% α-TCP. In this sense, magnetic modification of *Biocement-H* should be of interest to other commercial α-TCP cements [20].

2.3. Preparation of controls

A positive and a negative control (+/−Control) of *Biocement-H* were produced. "+Control" behaved as expected from the point of view of the setting and hardening data reported in the literature [22]. However, "−Control" did not show hardening properties with time. The main difference between the controls was the lot number of the DCP ("+Control" = Sigma-Lot.11k0303; "−Control" = Sigma-Lot.122k0127) used to manufacture the α-TCP. This was studied to highlight the problem of scaling up production of α-TCP, which affects commercial and experimental α-TCP based cements, and especially reproducibility of data between different scientists. However, in this study it is shown (see 3. Results) that the modification of the α-TCP phase with small amounts of iron is a good solution to recover the standard setting and hardening properties.

2.4. Compressive strength measurements

Cylindrical (5 mm of diameter and 10 mm of height) cement samples ($n = 10$ for statistics) were moulded in a stainless steel mould and immersed in Ringer's solution at 37°C for different hardening times. After completion they were removed from the mould and tested for compressive strength at a crosshead speed of 1 mm/min in a Universal Electromechanical Testing Machine.

2.5. Setting times measurements

Initial (I) and Final (F) setting times were measured, as many times reported [22], with the *Gillmore* needles [23]. Each measurement was repeated three times for statistic analysis.

2.6. Magnetic evaluation

The new iron-modified α-TCP based cements were evaluated for magnetic properties with a standard Cobalt-Nickel magnet by visual inspection of the effect of movement of compressive strength samples at different reaction times. Iron-modified α-TCP in both powder and granule form was also tested in the same way before cement sample preparation. This general magnetic behaviour has been highlighted in section "4 Discussion" in the absence of a proper magnetic characterisation, which is under way.

3. Results

3.1. Effects on the compressive strength

Figs 1 and 2 show the results of the evolution of the compressive strength, C(MPa), *versus* the amount of

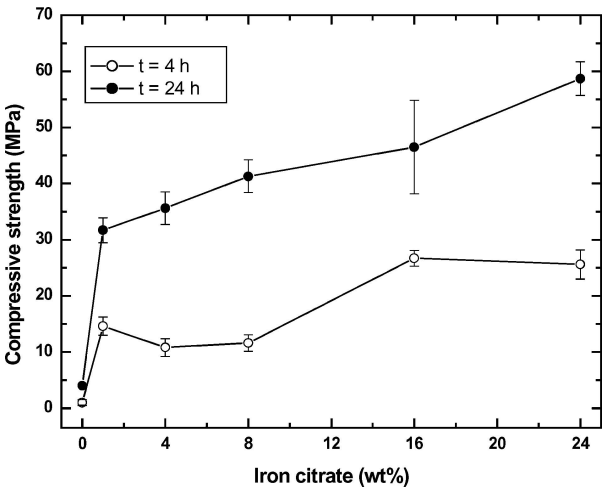

Figure 1 Evolution of the compressive strength, C(MPa), as a function of the iron citrate, IC(wt%), for the "−Control" ($L/P = 0.30$ mL/g) and the protocol "A".

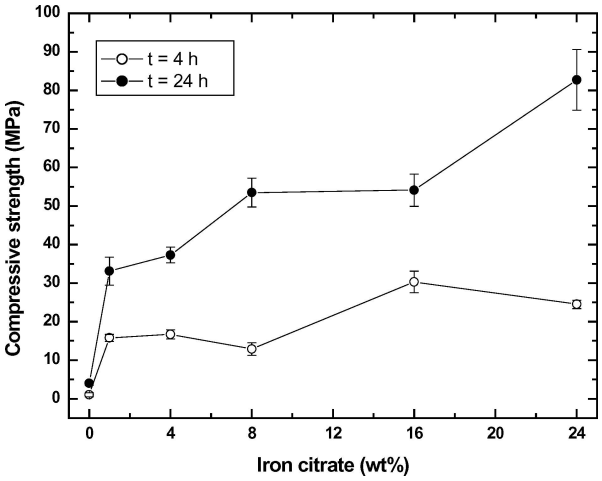

Figure 2 Evolution of the compressive strength, C(MPa), as a function of the iron citrate, IC(wt%), for the "−Control" ($L/P = 0.30$ mL/g) and the protocol "B".

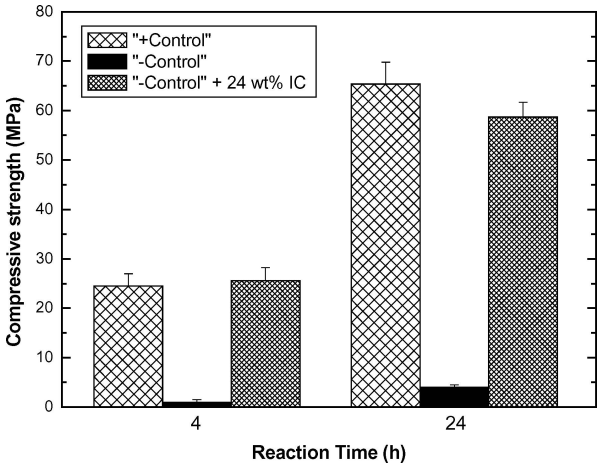

Figure 3 Compressive strength, C(MPa), at 4 and 24 h of reaction time, for "+Control" ($L/P = 0.32$ mL/g), "−Control" ($L/P = 0.30$ mL/g) and the recovered "−Control + 24 wt%IC" ($L/P = 0.30$ mL/g), all of them made with the protocol "A".

the iron citrate, IC(wt%), for the "Control" ($L/P = 0.30$ mL/g) and for the manufacturing protocols "A" and "B", respectively. The figures contain data at two different hardening times, 4 and 24 h.

Fig. 3 shows the evolution of the compressive strength, at two different hardening times, 4 and 24 h, for the positive ("+Control"; $L/P = 0.32$ mL/g), the negative ("−Control"; $L/P = 0.30$ mL/g) and the recovered ("−Control + 24 wt%IC"; $L/P = 0.30$ mL/g) control. In this figure the data correspond to cement made with the "A" protocol.

Figs 4 and 5 show the effect of the manufacture protocols, "A" and "B", for a 4 wt% IC-modified "+Control" ($L/P = 0.30$ mL/g), on the compressive strength, after 4 and 24 h of hardening, and on the setting times, respectively.

Figs 6 and 7 show the evolution of the compressive strength *versus* the reaction time (hardening curves) as a function of the iron citrate, IC(wt%), for "−Control" ($L/P = 0.30$ mL/g) made with the protocols "A" and "B", respectively.

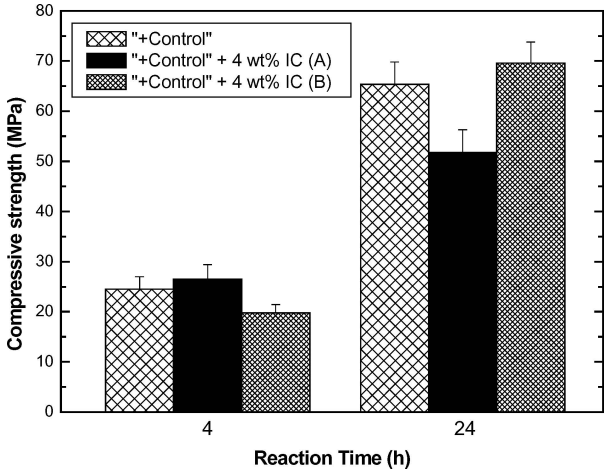

Figure 4 Compressive strength, C(MPa), at 4 and 24 h of reaction time, for a 4 wt% IC-modified "+Control" ($L/P = 0.30$ mL/g): Effect of protocols "A" and "B".

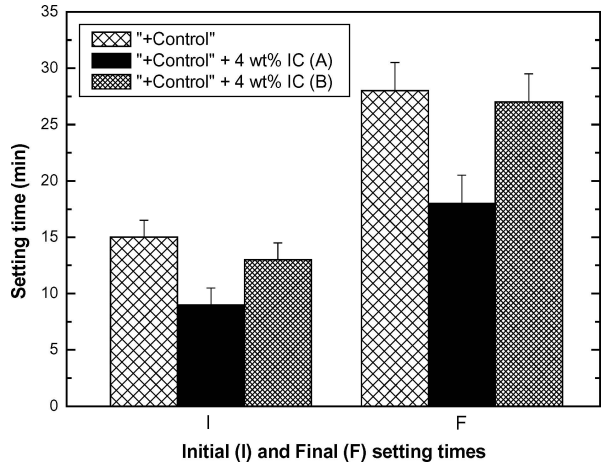

Figure 5 Setting times, I(min) and F(min), for a 4 wt% IC-modified "+Control" ($L/P = 0.30$ mL/g): Effect of protocols "A" and "B".

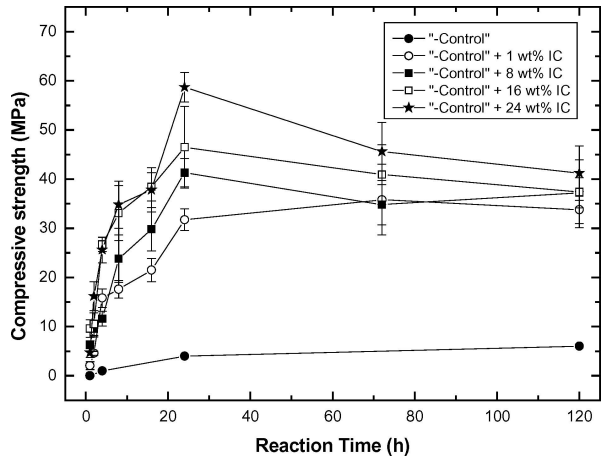

Figure 6 Hardening curves as a function of the iron citrate, IC(wt%), for "−Control" ($L/P = 0.30$ mL/g) made with the protocol "A".

3.2. Effects on the setting times

Finally, Fig. 8 shows the evolution of the setting times, I(min) and F(min), *versus* the amount of the iron citrate, IC(wt%), for "−Control" ($L/P = 0.30$ mL/g), as a function of the protocols "A" and "B".

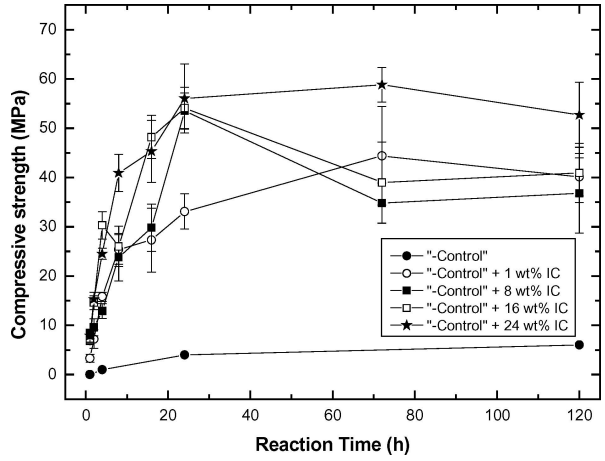

Figure 7 Hardening curves as a function of the iron citrate, IC(wt%), for "−Control" ($L/P = 0.30$ mL/g) made with the protocol "B".

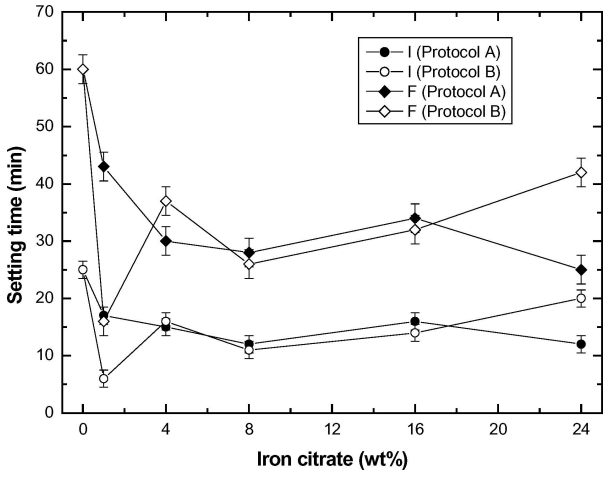

Figure 8 Setting times, I(min) and F(min), for "−Control" ($L/P = 0.30$ mL/g) as a function of the iron citrate, IC(wt%): Effect of protocols "A" and "B".

4. Discussion

One of the most practical and important results of this study is found in Figs 1 and 2. No matter the protocol used to manufacture the α-TCP, i.e. "A" and "B", those figures show that to recover the normal setting and hardening properties of a "−Control" of *Biocement-H*, it is just enough to modify the standard α-TCP production with less than 0.3 wt% of iron (i.e. 1.57 mol%-Fe over 99.43 mol%-α-TCP). In this case, the XRD of these powders were identical. Obviously, no one working in bone cements makes negative controls of his experimental and commercial formulations; this is something that simply occurs, and scientists working on this field know the headache produced every time this happens. At the moment there is not in the literature any study focussing on the deleterious or the beneficial effect of very small amounts of certain ionic elements on the hydration properties of the α-TCP. Sometimes, it has been reported that magnesium contamination of the reactants used during the fabrication of the α-TCP, and especially that of the monetite ($CaHPO_4$), is the cause for not having setting and hardening properties on α-TCP based cements. This has sense because, as it is known, the hardening of α-TCP cements is due to nucleation, precipitation and growth of calcium deficient hydroxyapatite crystals (CDHA; $Ca_9(HPO_4)(PO_4)_5OH$), [24, 25] and nucleation of apatite crystals is blocked by magnesium ions [26]. Unfortunately, chemical analysis of the positive and the negative α-TCP batches did not show any significant difference in the minor ionic contaminants. For this reason, α-TCP production tailored in advance with small amounts of "iron-contaminants" seems a novel and useful method to assure standard properties even in the case the main reactants could come negatively contaminated.

Moreover, Figs 1 and 2 show the same increasing tendency for "−Control" (no matter the protocol used to fabricate the α-TCP, i.e. "A" in Fig. 1 or "B" in Fig. 2) of the compressive strength, attained at 4 and/or 24 h of hardening, as the amount of iron citrate was increased during the α-TCP manufacturing protocols.

In fact, Fig. 3 shows how relevant iron-modification could be to recover the standard properties of a "+Control" of *Biocement-H*. In this case, the compressive strength, after 4 and 24 h of hardening, was around 25($\pm$3) and 65($\pm$4) MPa, respectively. In comparison, "−Control" showed 1($\pm$0.5) and 4($\pm$0.5) MPa for the same conditions. If we consider that the static strength supported by the cement at its final setting time, F, as measured by the *Gillmore* needles, is the equivalent to 5 MPa [23] then, "−Control" simply did not set and so it was easily deformed under the pressure of two fingers. However, when "−Control" was modified with 24 wt%-IC, under the protocol "A", the values encountered for the compressive strength were statistically the same ($p > 0.05$) as those reported for the "+Control". In this case, the XRD showed that the α-TCP was not a pure phase but a mixture of α-TCP, β-TCP and iron-phases.

Whether or not the different protocols "A" and "B" had significant effects on the hardening and the initial setting of a "+Control" of *Biocement-H* is analysed from Figs 4 and 5. Fig. 4 shows no significant differences ($p > 0.05$) after 4 h of hardening between the "+Control" and the same control modified with 4 wt%-IC, no matter the protocol. However, after 24 h of hardening, the protocol "B" showed better compressive strength ($p < 0.05$), as compared to the protocol "A" and in agreement with the values of the "+Control". If we consider, at the same time, what happened with the initial setting properties (see Fig. 5 for the setting times) then, the protocol "B" also agreed to the data of "+Control" but the protocol "A" showed statistically better results (i.e. lower I and F setting times). This means that with protocol "A" the chemical reactions controlling the initial setting of *Biocement-H* (i.e. dissolution of α-TCP particles, nucleation and precipitation of apatite-like crystals) are faster than with protocol "B". This is in agreement with the results in Fig. 4 where in fact it is known, experimentally, that higher setting times (i.e. slow chemical reactions) are directly correlated to also higher values of compressive strength (i.e. finer and compact crystalline microstructure). A possible explanation could be related to a more significant presence of iron (both, in the form of α-TCP iron solid solutions and/or stable iron phases) on

and/or around the surface of the α-TCP particles in protocol "B" rather than a more favoured volume diffusion and/or precipitation of phases of iron in protocol "A". This has been corroborated by monitoring continuously the pH, where α-TCP manufactured with protocol "B" showed less basic values (pH $\approx$ 8.7) than both the one with "A" (pH $\approx$ 9.2) and the "+Control" (pH $\approx$ 9.7). This is in agreement to a higher iron protonation in the solution. This chemical reaction should be lowering the supersaturation of the solution and so retarding the precipitation of apatite-like crystals. A further study is on its way to understand exactly what is happening.

If we look at the hardening curves, Figs 6 and 7 also show interesting results. For example, when the "−Control" of *Biocement-H* was modified with IC, from 1 wt%-IC to 24 wt%-IC, the hardening curves of modified *Biocement-H*'s cements graduated in average to higher values as the amount of IC increased. This is a noticeable result because thanks to the iron-modification of the α-TCP, which is also applicable to tetracalcium phosphate and β-TCP, we have a way to increase at the same time the mechanical and the magnetic strength of both experimental and commercial new bone cements.

Moreover, this synergetic effect had also its influence on the setting times. The I and the F setting time for the "−Control" were 25($\pm$1) min and $\geq$24 h, respectively (note that in Fig. 8 the F-time has been represented for clarity as $F \equiv 60$ min). However, with just 1 wt%-IC the I-time was reduced to $\approx$ 6($\pm$1) min and the F-time to $\approx$ 16($\pm$2) min when the protocol "B" was used. In this case, i.e. 1 wt%-IC, protocol "A" showed higher values for the setting times, $I \approx 17(\pm 1)$ min and $F \approx 44(\pm 2)$, but for the rest of the IC values the differences between protocols were not significant ($p > 0.05$) until 24 wt%-IC, where protocol "B" did show higher values than protocol "A". Despite the individual differences between values, which are difficult to explain, the most important result is the fact that the setting times of *Biocement-H* are not drastically affected by the IC modification. On the other hand, they are controlled into an appropriate range of values that could be even further optimised to the present medical applications, for example, by using increasing amounts of accelerators such as DHP.

These results in conjunction with the results obtained for the hardening curves in Figs 6 and 7 and the fact that IC modification gives *Biocement-H* magnetic properties, as an added value, are the most relevant results both from the scientific and the commercial point of view.

5. Conclusion

In this study, it is reported that a new family of iron modified calcium phosphates, whose chemical compositions can be written [27], in general, as α/β-$(3.CaO\text{-}1.P_2O_5)_{1-x}(FeO)_x$, $(4.CaO\text{-}1.P_2O_5)_{1-x}(FeO)_x$, $(10.CaO\text{-}3.P_2O_5)_{1-x}(FeO)_x$, show magnetic properties and, at the same time, they present intrinsic different acidities. Thus, these new reactants show cement-like properties when mixed together into a cement powder phase while being magnetic throughout the whole setting. These new magnetic cements could be of use: (a) to stabilise bone fractures and/or to fill bone cavities; (b) to treat osteosarcoma; (c) as new thermal and magnetic activated drug delivery systems; and (d) as new scaffolds to bone tissue engineering, among others [28].

Acknowledgements

The authors thank the European Commission for funding through project HPMT-CT-2000-00003.

References

1. W. E. BROWN and L. C. CHOW, Dental Restorative Cement Pastes, US Patent No.: 4,518,430. Priority Data, May 21, (1985).
2. *Idem*., in A New Calcium Phosphate Water-Setting Cement, edited by P. W. Brown, "Cements Research Progress" (American Ceramic Society, Westerville, Ohio, 1986), p. 351.
3. J. LEMAITRE, A. MIRTCHI and A. MORTIER, *Sil. Ind. Ceram. Sci. Tech*. **52** (1987) 141.
4. L. C. CHOW, S. TAKAGI, P. D. CONSTANTINO and C. D. FRIEDMAN, *Mat. Res. Soc. Symp. Proc*. **179** (1991) 3.
5. L. C. CHOW, *J. Ceram. Soc. Japan (International Edition)* **99** (1992) 927.
6. T. SUGAMA and M. ALLAN, *J. Am. Ceram. Soc*. **75**(8) (1992) 2076.
7. J. LEMAITRE, *Innov. Tech. Biol. Med*. **16**(1) (1995) 109.
8. E. FERNÁNDEZ, F. J. GIL, S. M. BEST, M. P. GINEBRA, F. C. M. DRIESSENS and J. A. PLANELL, *J. Mater. Sci. Mater. Med*. **10** (1999) 169.
9. *Idem*, *ibid.* **10** (1999) 177.
10. M. NILSSON, E. FERNÁNDEZ, S. SARDA, L. LIDGREN and J. A. PLANELL, *J. Biomed. Mater. Res*. **61**(4) (2002) 600.
11. E. FERNÁNDEZ, F. J. GIL, S. M. BEST, M. P. GINEBRA, F. C. M. DRIESSENS and J. A. PLANELL, *ibid*. **41** (1998) 560.
12. C. KNABE, F. C. M. DRIESSENS, J. A. PLANELL, R. GILDENHAAR, G. BERGER, D. REIF, R. FITZNER, R. J. RADLANSKI and U. GROSS, *ibid.* **52** (2000) 498.
13. K. OHURA, M. BOHNER, P. HARDOUIN, J. LEMAITRE, G. PASQUIER, B. FLAUTRE and M. C. BLARY, *ibid.* **30** (1996) 193.
14. R. O. C. OREFFO, F. C. M. DRIESSENS, J. A. PLANELL and J. T. TRIFFITT, *Biomaterials* **19** (1998) 1845.
15. F. C. M. DRIESSENS, J. A. PLANELL, M. G. BOLTONG, I. KHAIROUN and M. P. GINEBRA, *Proc. Instn. Mech. Engrs.* **212H** (1998) 427.
16. E. CHARRIÈRE, J. LEMAITRE and P. H. ZYSSET, *Biomaterials* **24** (2003) 809.
17. S. SARDA, M. NILSSON, M. BALCELLS and E. FERNÁNDEZ, *J. Biomed. Mater. Res.* **65A** (2003) 215.
18. J. E. BARRALET, L. GROVER, T. GAUNT, A. J. WRIGHT and I. R. GIBSON, *Biomaterials* **23** (2002) 3063.
19. M. BOHNER, *Key. Eng. Mater.* **192–195** (2001) 765.
20. *Idem*., *Eur. Spine. J.* **10** (2001) S114.
21. I. KHAIROUN, F. C. M. DRIESSENS, M. G. BOLTONG, J. A. PLANELL and R. WENZ, *Biomaterials* **20** (1999) 393.
22. M. P. GINEBRA, F. C. M. DRIESSENS and J. A. PLANELL, *ibid.* **25** (2004) 3453.
23. Standard Test Method: ASTM C266-89. Time of Setting of Hydraulic Cement Paste by Gillmore Needles, in "Annual Book of ASTM Standards," Cement, lime, Gypsum (Philadelphia, ASTM, PA, 1993) Vol. 04.01, p. 444.
24. M. P. GINEBRA, E. FERNÁNDEZ, E. A. P. DE MAEYER, R. M. H. VERBEECK, M. G. BOLTONG, J.

GINEBRA, F. C. M. DRIESSENS and J. A. PLANELL, *J. Dent. Res.* **76**(4) (1997) 905.
25. E. FERNÁNDEZ, M. P. GINEBRA, M. G. BOLTONG, F. C. M.DRIESSENS, J. GINEBRA, E. A. P. DE MAEYER, R. M. H. VERBEECK and J. A. PLANELL *J. Biomed. Mater. Res.* **32** (1996) 367.
26. F. C. M. DRIESSENS, in "Bioceramics of Calcium Phosphate," edited by K. De Groot (CRC Press, Inc., Boca Raton, Florida, 1993) p. 1.
27. H. HOSHINO and M. IWASE, *Metall. Mater. Trans. B* **27B** (1996) 595.
28. E. FERNÁNDEZ Fosfatos de calcio modificados con hierro. Spanish Patent No. P200302342. Universidad Politécnica de Cataluña. Priority Date: 01/10/2003.

Received 6 October 2004
and accepted 18 February 2005