COBEM 99
XV Congresso Brasileiro de Engenharia Mecânica
15th Brazilian Congress of Mechanical Engineering
22 - 26 de Novembro de 1999 / November 22 - 26, 1999 Águas de Lindóia, São Paulo,

INFLUENCE OF POLYMERIC ADDITIVES ON CALCIUM PHOSPHATE CEMENT

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Código: AACBJC

Abstract. *Recently, great attention has been paid to calcium phosphate cements, because of their advantages compared to conventional calcium phosphate bioceramics employed for bone repairing, regarding "in situ" handling and shaping abilities. Nevertheless the calcium phosphate cements exhibit relatively low mechanical strength. The aim of this work was the improvement of the compressive strength of α-tricalcium phosphate-based cement. The hydraulic setting reaction of this system produces a calcium deficient hydroxyapatite phase suitable for bone repairing:*

$$\alpha\text{-}\ Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5OH$$

Mechanical strength can be improved using technological solutions developed for other applications, such as Portland cement and dual-setting glass-ionomers, by using polymeric additives. The additives used in this work were sodium alginate, sodium polyacrylate and an "in situ" polymerization system resulting in a polyacrylamide crosslinked hydrogel.Parameters evaluated were setting time, compressive strength before and after immersion in Simulated Body Fluid, density, porosity, crystalline phases and microstructure.Sodium alginate and sodium polyacrylate were deleterious to both setting time and mechanical strength.When the "in situ" polymerization system was added two setting reactions progressed in parallel: the conventional hydraulic reaction and the copolymerization of acrylamide and crosslinking water-soluble monomers. The initial and

final setting times of the "dual-setting" cement were 9 and 35 min, respectively and they can be regulated varying the initiator, catalyst and monomers concentrations. The initial compressive strength of the "dual-setting" cement (6,8 MPa at 0 h, and 15,2 MPa at 24 h) is higher than that of unmodified cement. Mayor crystalline phase after setting is hydroxyapatite. The "dual setting" cement seems to be suitable for clinical applications in bone repairing and remodeling.

Key Words: α-Tricalcium Phosphate, Calcium Phosphate Cement, Hydroxyapatite, Bioceramic, Biomaterial.

1. INTRODUCTION

Calcium phosphate cements (CPC's) have attracted considerable attention in Medicine and Dentistry fields because of their excellent biocompatibility and bone-replacing behavior over long period (Driessens *et al.,* 1997). The term "calcium phosphate cement" was introduced by Gruninger *et al.,* 1984. According to them, this type of cement can be prepared by mixing a calcium phosphate salt with water or with an aqueous solution so that is formed a paste that can react at room or body temperature to give a precipitate that it contains one or more calcium phosphates, setting by the precipitated crystals intercrossing. They are constituted by one basic component and one acid component which when they are mixed with water they react to form one or several products with an intermediary acidity.

These cements have a series of advantages that permit use as graft and substitute of bone system damaged parts:

- Moldability
- Minimum bone cavity
- Complete adaptation to the bone cavity
- Preparation at surgical act
- Direct in vivo placing
- Setting in situ
- Optimal bone-implant contact
- Biocompatibility and bioativity

Moreover the calcium phosphate cements can be used as drug delivery system in which can be added, with easiness, several medications or drugs, such as, antibiotics, antitumors, anti-inflammatory (Yu *et al*., 1982), etc.. The main disadvantage of the calcium phosphate cements is the low mechanical resistance, that in the better case it's equal to the trabecular bone, or 20% of cortical bone. In the literature there are no deep studies to elevate the mechanical resistance of these cements. The readiness of calcium phosphate cements with close mechanical resistance to the human bones would grow considerably the potential applications field, now limited to the dentistry and maxillofacial surgeries. These compositions would be applicable in orthopaedics and neurosurgery, as an alternative for the knitting of multiple fractures of long bones, fixing of cemented articulation prostheses, iliac crest prostheses, intervertebral spacers and substitution of vertebral bodies. A promising solution to this problem could be the addition of polymers to the CPC (Miyazaki *et al.,* 1993).

Among the several CPC systems studied, that based on α-tricalcium phosphate (α-TCP) is specially interesting because it yields when setting a calcium deficient hydroxyapatite phase, similar to bone mineral, and with excellent biocompatibility, bioactivity and osseointegrability:

$$\alpha\text{-}\ Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5OH \quad (1)$$

Dual-setting glass ionomer cements (GIC), recently introduced in Dentistry, set as the result of two parallel reactions; the typical acid-base reaction between the glass and the alkenoic acid, and the polymerization reaction of acrylic monomers such as HEMA, HDMA and Bis-GMA. The resulting structure is a cement matrix reinforced by the interpenetrating chains of the acrylic polymer. Dual-setting GIC have shorter setting time, lower solubility, and higher mechanical strength than conventional GIC (McLean *et al.*, 1994).

A water-soluble "in situ" polymerizing system based in acrylamide, N,N'-methylenebisacrylamide, N,N,N',N'-tetramethylethylendiamine (accelerator) and ammonium persulfate (initiator) has been employed in gel-casting technology. When polymerization is conducted in aqueous slurry of ceramic powder the resulting crosslinked polyacrylamide hydrogel is able to bind the ceramic particles and to provide strength to the resulting system (Young *et al.*, 1991).

Sodium alginate (SA) and sodium polyacrylate (SPA) are macromolecules with carboxylic groups on their chains. SA reacts with calcium ions forming an insoluble 3-dimensional network. SPA could react in a similar way. So SA and SPA could exhibit a reinforcing effect when added to α-TCP-based cement. Both are biocompatible and have been used as components of implant devices. In this work the effects of the addition of SA, SPA and an "in situ" acrylamide-based polymerization system to α-TCP cement were studied.

2. MATERIALS AND METHODS

Compositions of unmodified and modified cements are shown in Table 1. The α-tricalcium phosphate (α-TCP) was prepared as described in literature (Driessens *et al.*, 1997), by the reaction:

$$CaCO_3 + \gamma\text{-}Ca_2P_2O_7 \rightarrow \alpha\text{-}Ca_3(PO_4)_2 \quad (2)$$

The reagents were mixed in a mill with zirconia balls, being calcined at 1300°C for 15 hours, and quenched in an inox steel plate(Monma *et al.*, 1984). The reaction product was grounded in polyethylene jar with zirconia balls in alcoholic medium (anidrous etanol). The resulting material was reduced to the particle size range of 1 to 9 μm (Sedigraph-Micromeritics 5100 equipment using isopropanol as dispersing agent) and contained 2 wt-% HA and 5 wt-% β-TCP as impurities. The presence of β-TCP as impurity in the α-TCP is reported for several authors(Bermúdez *et al.*, 1994; Tampieri *et al.*, 1997; Famery *et al.*, 1994; Fernández *et al.*, 1996), not being known works that register the obtaining of pure α-TCP, and usually the α-TCP obtained contains about 15% of β-TCP(Ginebra *et al.*, 1997). Moreover the β-TCP it was detected HA as impurity. The presence of the HA can be explained by the balance reaction: HA⇔β-TCP⇔α-TCP, in which the speed of the first reversion reaction is smaller than the direct reaction (Tampieri *et al.*, 1997).

Precipitated hydroxyapatite was prepared by neutralization of an aqueous slurry of $Ca(OH)_2$ (1 dm^3; 0,5 $mol.dm^{-3}$) at 90 °C with a solution of H_3PO_4 (1 dm^3; 0,3 $mol.dm^{-3}$), then filtered and dried at 110 °C. SPA solutions were prepared by neutralization of polyacrylic acid 2000 M.W. with NaOH. Other chemicals were used as supplied. Simulated Body Fluid (SBF) was prepared as described elsewhere (Kokubo *et al.*, 1992).

The cement compositions were characterized by X-ray diffraction, model D 5000 x-ray diffratometer (Siemens, Karlshüre) with CuK_α radiation and Ni filter, generated at 40 kV and 40 mA, angular interval (2θ) analysed was from 20 to 40°, with goniometer speed at 2°/min,

for qualitative phase analysis and Scanning Electron Microscopy (SEM - Carl-Zeiss I model DSM 940A) for microstructural analysis. Initial and final setting times were determined by the Gillmore method (ASTM: C 266-89). Cylinders (12-mm height and 6 mm diameter) were prepared in a silicone mould and conditioned 1 h at 100 % relative humidity at room temperature. Conditioned cylinders were immersed in SBF at 36,5 °C during 24, 48 and 192 h. At least five cylinders from each period of time were tested for compressive strength (σ_c) at a loading rate of 1 $mm.min^{-1}$. Density and porosity were determined by the Arquimedes method.

3. RESULTS AND DISCUSSION

The mixing liquids prepared according to the compositions II, III and IV shown in Table 1 presented a high viscosity. Wetting of powder by liquid during mixing was poor for the three formulations and it was necessary to use a higher L/P ratio compared to non-added composition (I). The cements II, III and IV did not set 1 hour after mixing. Cylinders prepared with these compositions and conditioned 1 h at 100% R.H. completely decayed when immersed in SBF.

Table 1.Composition of unmodified and modified cements.

No	POWDER	LIQUID	L/P
I	98 % α-TCP; 2 % PHA	2,5% Na_2HPO_4	0,35 ml/g
II	98 % α-TCP; 2 % PHA	31,2 % SPA; 2,5 % Na_2HPO_4	0,64 ml/g
III	98 % α-TCP; 2 % PHA	15,6 % SPA; 2,5 % Na_2HPO_4	0,64 ml/g
IV	98 % α-TCP; 2 % PHA	3,12 % SA; 2,5 % Na_2HPO_4	0,72 ml/g
V	97,9 % α-TCP; 2% PHA; 0,1% AP	5% AA; 0,5% MBAM; 0,25% TEMED; 2,5% Na_2HPO_4	0,35 ml/g

PHA: precipitated hydroxyapatite; AA: acrylamide; MBAM: N,N'-methylenbisacrylamide; TEMED: N,N,N',N'-tetramethylethylendiamine; AP: ammonium persulfate.

A less marked effect was previously reported for α-TCP cement added with 0,5 wt-% alginic acid in the powder (Ginebra *et al.*, 1995). However, in a previous work the authors of this report got increments of up to 50% in the compression strength for cements of the system β-$Ca_3(PO_4)_2$ – H_3PO_4 with 5 wt-% of SA added to the cement powder. The same amount of polyacrylic acid in the powder evoked negative effects on the setting time and the compression strength (Carrodeguas *et al.*, in press).

Another modifier studied in this work was the system of water-soluble monomers composed by monofunctional acrylamide (AA) and bifunctional N,N'-methylenebisacrylamide (MBAM). Polymerization "in situ" was achieved using N,N,N',N'-tetramethylethylendiamine (TEMED) (accelerator) and ammonium persulfate (AP) as initiator, as showed in Tables 1 and 2.

The viscosity of the liquid did not increase significantly by the monomers and catalyst addition. Thus it was possible to maintain the same L/P ratio for the modified cement that for the unmodified one (0,35 $cm^{-3}.g^{-1}$).

Varying the concentrations of initiator, catalyst and monomers was possible to adjust the initial and final setting times to values appropriate for a potential clinical application. At the same time the heat evolved during the polymerization setting reaction could be regulated at a level safe for the living tissues (see Table 2).

The density of the modified cement increased in the first 24 h of immersion in SBF, due to the transformation of the α-TCP (d = 2,86 $g.cm^{-3}$) into CDHA (d ≅3,16 $g.cm^{-3}$) caused by the setting reaction (Eq. 1). However, the porosity of the cement remains approximately constant at around 30% (see Table 3).

Table 2. Influence of the contents of AA, MBAM, TEDMA, and AP on the setting time and the evolved heat during setting.

No.	**POLYMERIZATION SYSTEM COMPOSITION (*)**	**t_i (min)**	**t_f (min)**	**ΔH**
I	0 % AP; 0 % AA; 0 % MBAM; 0 % TEDMA	22	> 60	≅ 0
V-1	1,0 % AP; 20 % AA; 2 % MBAM; 1 % TEDMA	< 1	-	+++
V-2	1,0 % AP; 10 % AA; 1 % MBAM; 0,5 % TEDMA	< 1	-	+++
V-3	0,5 % AP; 10 % AA; 1 % MBAM; 0,5 % TEDMA	2	-	++
V-4	0,5 % AP; 5 % AA; 0,5 % MBAM; 0,25 % TEDMA	3	-	+
V-5	0,1 % AP; 10 % AA; 1 % MBAM; 0,5 % TEDMA	5	-	+
V	0,1 % AP; 5 % AA; 0,5 % MBAM; 0,25 % TEDMA	9	35	≅ 0

+++: Very exothermic; ++: Exothermic; +: Lightly exothermic; ≅ 0: Insignificantly exothermic. t_i y t_f: initial and final setting times. (*) AP added to powder and AA, MBAM, and TEDMA to liquid like in cement composition V of the Table 1.

Table 3. Mechanical and physical properties of unmodified (I) and modified (V) α-TCP after immersion for different times in SBF at 36,5 °C.

IMMERSION TIME IN SBF AT 36,5 °C	**UNMODIFIED (I)**	**MODIFIED (V)**		
	σ_C (s; n) Mpa	**σ_C (s; n) MPa**	**D_{app} (s; n) $g.cm^{-3}$**	**P (s; n) %**
0 h	N.M.	6,8 (1,7; 5)	1,87 (0,04; 3)	30,0 (1,3; 3)
24 h	11,7 (1,3; 5)	15,2 (1,5; 5)	2,34 (0; 3)	27,5 (2,1; 3)
48 h	20,7 (1,7; 5)	21,0 (2,9; 5)	2,28 (0,02; 3)	29,6 (3,4; 3)
192 h	22,0 (1,8; 5)	22,4 (2,5; 5)	2,36 (0,05;3)	29,0 (1,0; 3)

N.M.: No- measurable; s: Standard deviation; n: replicas number.

A remarkable increase in compressive strength for immersion times in SBF of 0 and 24 h was noticed for the modified cement (V) compared to unmodified (I). For longer times no significant difference in compressive strength was detected. These results suggest that the polymerization reaction is responsible for the increasing of the initial strength. As the hydraulic setting reaction (Eq. 1) progress its contribution to cement strength is higher. Thus, for a sufficiently long immersion time, the compressive strength of modified (V) and unmodified (I) cements converge to a common value (Table 3).

This initial reinforcing effect is advantageous for clinical applications where the material is loaded from the very beginning of the implantation.

The crosslinked polyacrylamide hydrogel coexisting in the bulk of the modified cement should not elicit toxic nor immunologic responses since polyacrylamide-based biomaterials have been successfully in several applications (Silver & Doillon , 1989).

Figure 1 shows the X-RD patterns corresponding to cements I and V at different stages of setting. When the powder and liquid are mixed the hydraulic reaction (Eq. 1) starts for both unmodified and modified cements. The X-RD diffraction peaks corresponding to α-TCP weaken while HA peaks become stronger. The rate of α-TCP $\rightarrow$ HA conversion is slightly slower in presence of the acrylamide hydrogel. The trace amounts of β-TCP and HA in the unreacted cement powders are impurities present in the α-TCP employed.

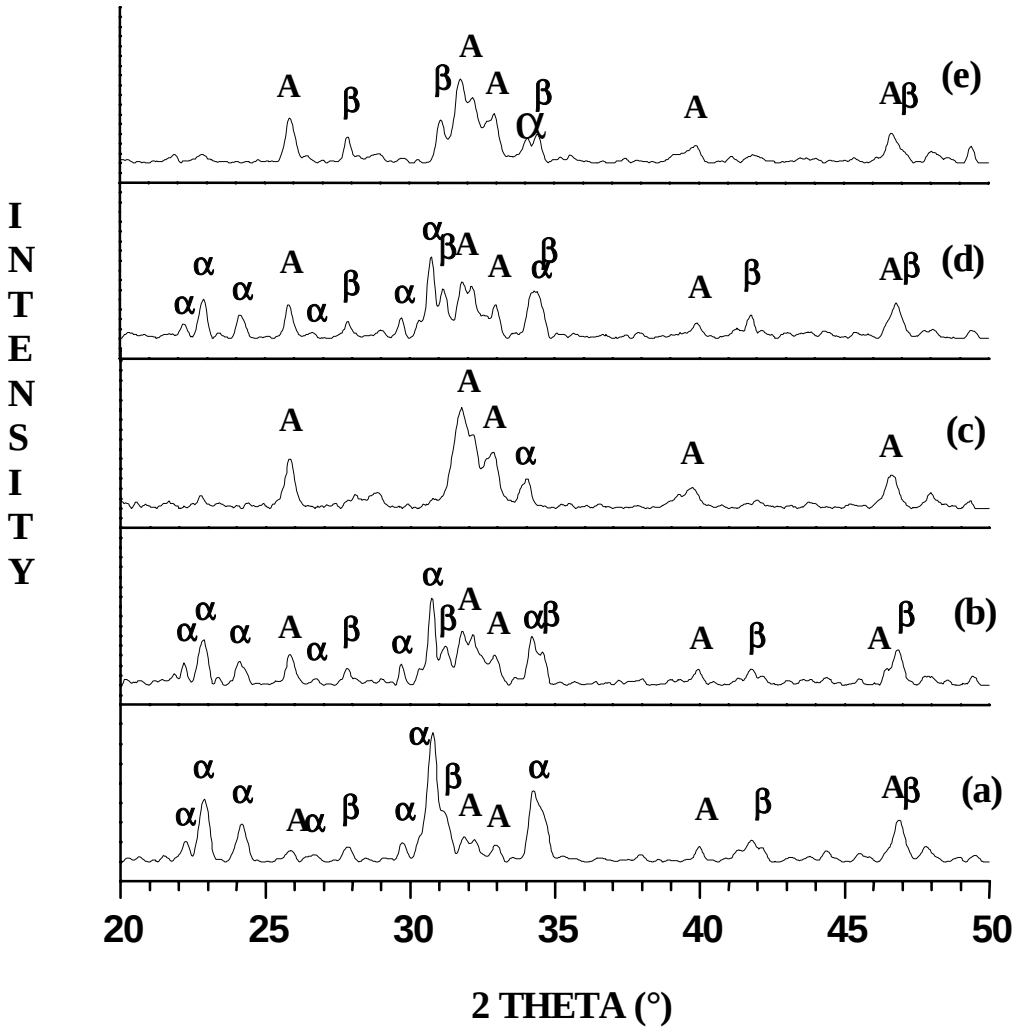

Figure 1. X-RD patterns of cements I and V at different stages of setting.(a): I unreacted powder; (b): I after mixing and conditioning 1 h at 100 % R.H.; (c): (b) after immersion in SBF at 36,5 °C for 192 h; (d): V after mixing and conditioning 1 h at 100 % R.H.; (e): (d) after immersion in SBF at 36,5 °C for 192 h. α: α-TCP; β: β-TCP; A: hydroxyapatite.

Figure 2 displays the SEM microphotographs of the as-prepared and fracture surfaces of unmodified (I) and modified (V) cements after immersion for 192 h in SBF. Spherules composed of thin needles of HA precipitated on the cements surface from the Ca^{2+} and PO_4^{3-} saturated SBF. Fracture surface morphologies differ drastically. Plate crystals with petaloid habit form the crystalline entanglement responsible for the mechanical strength of the cements. Similar microstructures have been previously described for α-TCP cement (Ginebra *et al.*, 1997).

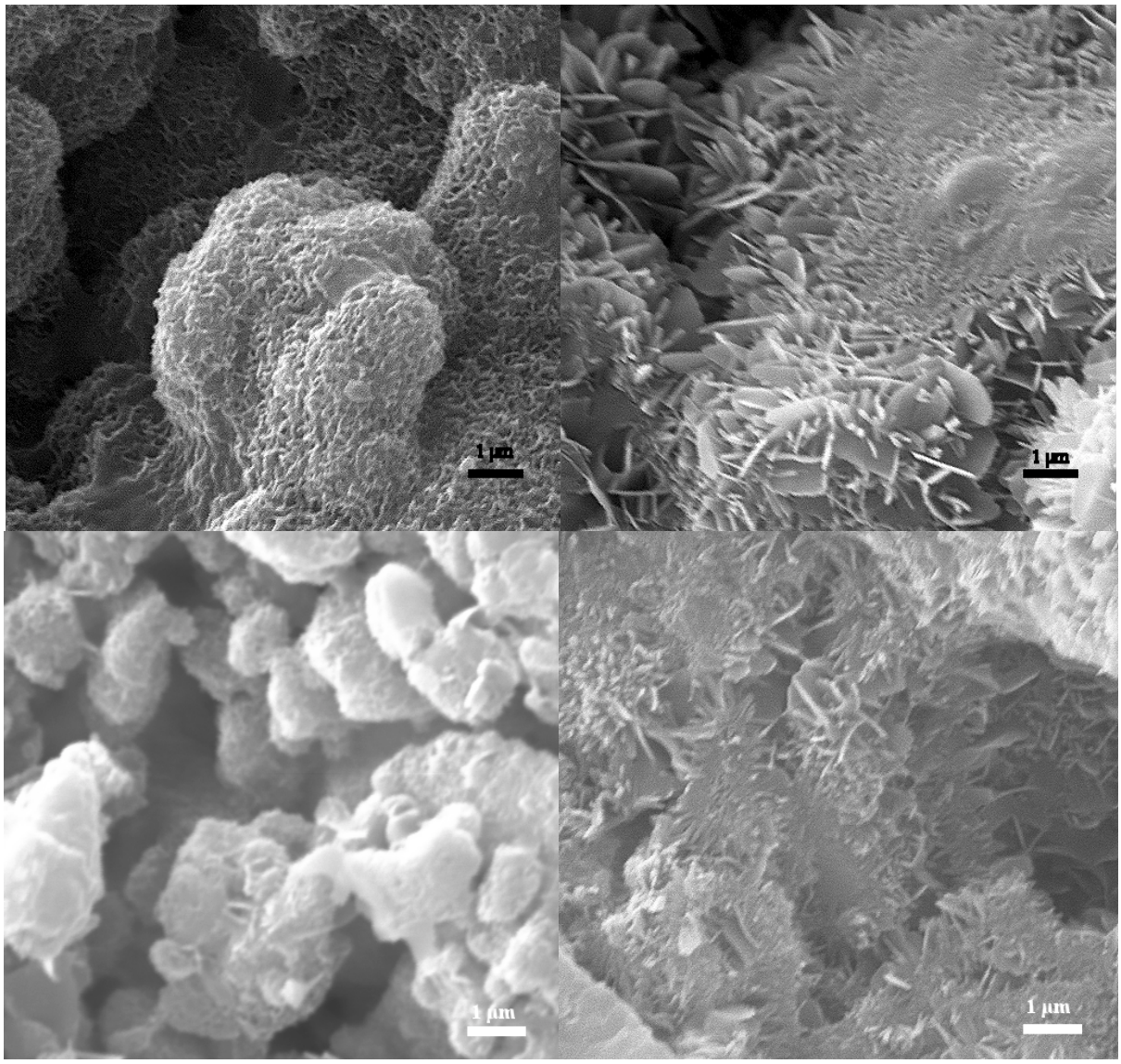

Figure 2. SEM microphotographs of as-prepared and fracture surfaces of unmodified (I) and modified (V) cements after setting and immersion in SBF for 192 h (10000 X). Upper left: I external surface; Upper right: I fracture surface; Lower left: V external surface; Lower right: V fracture surface.

4. CONCLUSIONS

Additions of SA and SPA were deleterious for the setting of α-TCP cement at the levels studied in this work.

The "dual-setting" α-TCP cement containing water soluble acrylic monomers showed initial and final setting times of 9 and of 35 minutes, respectively. The setting time can be modified varying the concentration of initiator, catalyst and monomers.

The initial strength resistance of the "dual-setting" cement (6,8MPa after setting for 1 h at 100 % R.H. and 15,2MPa after setting and immersion in SBF for 24 h) is higher than the corresponding to unmodified cement. The polymerization of the water-soluble acrylic monomers and the formation of a crosslinked hydrogel are the responsible for the initial strength of the "dual-setting" cement. The final strength is the result of the hydraulic reaction of transformation of α-TCP into HA.

The “dual-setting” α-TCP cement seems to be appropriate for clinical applications specially if initial strength is required in the first stages of the implantation.

Acknowledgments

This study was supported by the Grants Nos. 97/11569-0 and 98/00563-3 from FAPESP (Foundation for Research Support of the São Paulo State, Brazil). Fourth author recognizes the financial support received from The Third World Academy of Sciences through the JRP 18/95. The authors also recognize the Project CYTED VIII.6 "Obtención y Caracterización de Materiales Compuestos con Carga de Hidroxiapatito”.

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