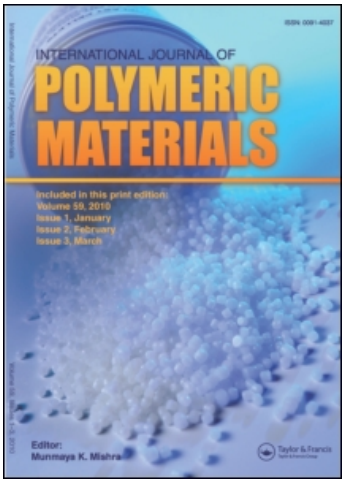

International Journal of Polymeric Materials
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

Kinetic effect of hydroxyapatite types on the polymerization of acrylic bone cements

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Online publication date: 27 October 2010

To cite this Article Morejón, L. , Delgado, J. A. , Davidenko, N. , Mendizábal, E. , Barbosa, E. H. and Jasso, C. F.(2003) 'Kinetic effect of hydroxyapatite types on the polymerization of acrylic bone cements', International Journal of Polymeric Materials, 52: 7, 637 — 654
To link to this Article: DOI: 10.1080/00914030304903
URL: http://dx.doi.org/10.1080/00914030304903

International Journal of Polymeric Materials, 52:637–654, 2003

ISSN: 0091-4037 print/1543-5253 online
DOI: 10.1080/00914030390198599

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KINETIC EFFECT OF HYDROXYAPATITE TYPES ON THE POLYMERIZATION OF ACRYLIC BONE CEMENTS

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The effect of type and amount of hydroxyapatite on the setting kinetics of an experimental bone cement based on poly(methyl methacrylate-co-styrene) was studied. The average molecular weights of the polymeric beads synthesized were determined by SEC and the average particle size was determined by Optical Microscopy. Three types of hydroxyapatites were synthesized in the laboratory and then characterized by ICP, FTIR and X-ray diffraction. To obtain more compatible fillers, the hydroxyapatites were treated with 3-trimethoxysilylpropylmethacrylate. Bone cements formulations filled with 0, 10, 30, and 50 weight % of hydroxyapatite powders were prepared and the kinetics of setting was followed by Differential Scanning Calorimetry. The presence of hydroxyapatite decreased the reaction rate and increased the degree of conversion, which could be beneficial for the long time stability of the implant.

Keywords: hydroxyapatite; bone cement; setting kinetic; acrylics

Received 22 March 2001; in final form 29 March 2001.

We acknowledge the support from the MUTIS Program of the Agencia Española de Cooperación Internacional as scholarships for L. Morejón and J. A. Delgado. We also acknowledge the support of the University of Guadalajara for this project.

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I. INTRODUCTION

Acrylic bone cements are widely used in orthopedic surgery to fix artificial prostheses to the body osseous structure. One of the most important applications in this area is in Total Hip Arthroplasty (THA). The cement has two main functions: to assure the short and long term anchorage of the implant to the bone, and to allow a better distribution of body loads between the prostheses and the bone [1–3].

The following adverse effects are associated with the use of bone cements: the high temperature of the polymerization reaction may cause thermal necrosis to adjacent tissues [4–6] the release of unreacted monomer, methyl methacrylate (MMA) may have possible adverse biological effects [7] and the shrinkage of the cement upon curing may produce gaps in the bone/cement and cement/prostheses interfaces [8]. Another adverse effect is the growth of a fibrous membrane around the cement, which could partially isolate the implant and weaken the cement and bone interconnection [9, 10]. All of these adverse effects lead to a deficient secondary anchorage, causing aseptic loosening of the implant. In order to improve the mechanical performance and the biocompatibility of bone cement formulations, bioactive particles have been used as fillers [11–16]. Among them, inorganic bone particles, tricalciumphosphate (TCP), and hydroxyapatite (HA) which stimulate bone growth and favor tissue ingrowth in the cement mantle have been used [13, 15].

Curing of the acrylic cement is a complex process and plays an important role in determining its performance and durability in the human body. Polymer molecular weight, reaction rate and final conversion depend on the history of viscosity and temperature of the reaction media. Viscosity of the initial mixture should be low enough to allow material insertion in the bone cavities. However, when the curing process starts, monomer is rapidly consumed by the propagation reaction and the viscosity increases, producing an increment in reaction rate and in temperature because of the so-called "gel effect" [17]. There are several studies dealing with the cure behavior of acrylic bone cements, and some models have been proposed to describe their polymerization kinetics [17–20].

It has been reported that the presence of hydroxyapatite in bone cements may be beneficial for the duration of an implant [15]; however, the effect of the presence of HA on the setting kinetics of a cement formulation curing has not been well studied. Borzacchiello *et al*. reported that an experimental bone cement filled with hydroxyapatite presented a lower exothermic reaction and higher degree of conversion than a commercial one [18]. However, they did not make a

systematic study of the effect of the hydroxyapatite on the polymerization kinetics.

In this work, three hydroxyapatite types with different morphology were synthesized and used as fillers. Also, to obtain adequate linkage between the inorganic fillers and the organic matrix, hydroxyapatites were surface modified by silanization. Their influence on the curing kinetics of experimental acrylic bone cement was studied. The kinetic study was carried out by Differential Scanning Calorimetry (DSC). The effect of type and amount of hydroxyapatite on induction time, reaction rate and maximum degree of conversion was determined.

II. MATERIALS AND METHODS

IIa. Materials

IIa.1. Acrylic Beads

Beads of poly(methyl methacrylate-co-styrene) obtained by suspension polymerization with a 90/10 mol per cent composition were used for the solid part of the cement formulations. Their average molecular weights $\bar{M}_n = 99,000$, $\bar{M}_w = 186,000$, $\bar{M}_z = 255,000$ were determined by Size Exclusion Chromatography (SEC) (Perkin Elmer 410). Average particle size was determined by Optical Microscopy (Olympus B $\times$ 40 with video recorder KP-D51). The particles presented spherical shape with an average diameter of 32.1 ± 8.9 μm.

IIa. 2. HA Powders

The three types of hydroxyapatite were prepared as follows: (a) Hydroxyapatite powder (HAP) was obtained by precipitation from reaction between $Ca(OH)_2$ and an aqueous solution of H_3PO_4; (b) Calcinated hydroxyapatite (HAC) was prepared by heating HAP for two hours at 800°C, (HAC); (c) sintered hydroxyapatite (HAS) was obtained by maintaining HAC for four hours in humid oxygen atmosphere at 1250°C.

The hydroxyapatites were characterized by infrared spectroscopy (FTIR), (Nicolet 5ZDX) and X-ray diffraction (Siemens D-500). Net parameters of the unit cell of hydroxyapatite crystals were determined by X-ray diffraction using quartz crystals as internal standard. The content of calcium (Ca) and phosphorus (P) of the samples were determined by Induction Coupled Plasma (ICP) (Spectrometer Polyscan^{TM} 61E, Thermo Jarrel ASH Corp.). Hydroxyapatites micrographs were obtained by Scanning Electron Microscopy (Hitachi S-2300). Surface area was determined by the BET method, using a Micromeritics equipment (ASAP 2000).

The surface of hydroxyapatites was modified by silanization reaction with 3-trimethoxysilylpropylmethacrylate (MSPM) using the Gorski method [21]. FTIR and ICP confirmed the reaction between MSPM and hydroxyapatite.

IIa. 3. Bone Cements Formulations

The solid part of the cement consisted of polymer beads mixed with 2.0% weight of benzoyl peroxide (BP), 10.0 weight % of barium sulfate, and hydroxyapatite particles in different amounts (0, 10, 30 and 50 weight %). Chemical composition of the liquid part was 99.0 weight % of methyl methacrylate (MMA), 1.0% of N,N dimethyl-p-toluidine (DMT), and 80.0 ppm of hydroquinone (HQ). A 2/1 solid/liquid ratio was used for all formulations.

IIb. Methods

IIb.1. DSC Study

The kinetic study was carried out by Differential Scanning Calorimetry (DSC) using a Perkin Elmer DSC7. Isothermal polymerizations were carried out at 10, 15, 20, 25 and 30°C for 20 min. Non-isothermal polymerizations were carried out after isothermal runs using the same samples at a heating rate of 10°C/min from 5 to 150°C. The solid and liquid parts of the cement formulations were hand mixed at room temperature for 30 seconds and then, approximately 15 mg of the mixture, were transferred to a DSC capsule.

A typical DSC thermogram at 25°C for acrylic cement curing is presented in Figure 1. The total heat generated by the reaction (H_{tot}) was calculated as:

$$\mathrm{H_{tot}} = \mathrm{H_{(iso)tot}} + \mathrm{H_{res}} \tag{1}$$

where $H_{(iso)tot}$ is the total heat of reaction determined by DSC in an isothermal experiment and H_{res} is the heat generated in the non-isothermal experiment. Degree of conversion (α) was calculated with the heat generated at a given time in an isothermal experiment, $H_{(iso)}$, divided by the total heat generated by the reaction:

$$\alpha = \frac{\mathrm{H_{(iso)}}}{\mathrm{H_{tot}}} \tag{2}$$

Final degree of conversion ($\alpha_{\max}$) was calculated by:

$$\alpha_{\max} = \frac{\mathrm{H_{(iso)tot}}}{\mathrm{H_{tot}}} \tag{3}$$

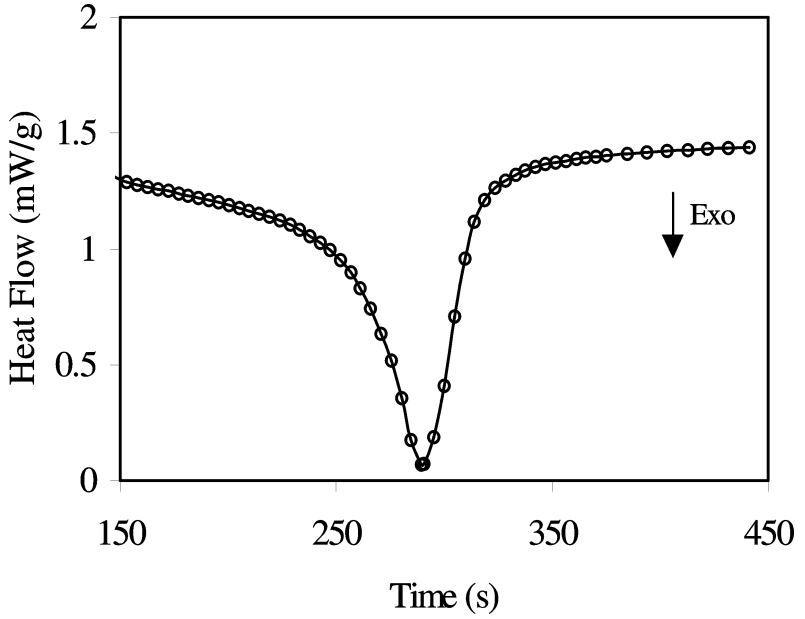

FIGURE 1 DSC Thermogram obtained in isothermal polymerization (25°C) of bone cements.

Reaction rate ($d\alpha/dt$) was obtained from:

$$\frac{d\alpha}{dt} = \frac{1}{H_{tot}} \frac{dH}{dt} \tag{4}$$

where dH/dt is the heat flow obtained from isothermal DSC experiments.

III. RESULTS AND DISCUSSION

It has been reported that hydroxyapatite improves the bioactivity and osteoconductivity of polymer composites [22, 23]. However, its inclusion in a bone cement formulation should modify curing kinetics of the cement. Three types of hydroxyapatite with different morphology were prepared in our laboratory and used as fillers, and their effect on the curing kinetics of the bone cement was studied.

The three types of hydroxyapatite (HAP, HAC and HAS) were characterized by different techniques. Table 1 shows that the Ca/P molar ratio of these hydroxyapatites is similar to the value reported for a stoichiometric hydroxyapatite (1.67) [24].

TABLE 1 Ca/P Ratio of HA Powder and % of HA Bond to Silane in Weight per cent

Type of HA	Ca/P	%HA bond to OSi
HAP	1.679	–
HAC	1.678	–
HAS	1.675	–
HAPS	–	34.6
HACS	–	62.2
HASS	–	30.6

Figure 2 shows infrared spectra of the synthesized hydroxyapatite powders. The band at $\lambda = 3{,}300\ cm^{-1}$ shows that the water content of hydroxyapatite samples decreases in the following order: HAP> HAC>HAS. This is a result of the heating treatment. The higher the processing temperature, the less the water content. Heat treatment also causes an increase on crystallinity [25], which improves the resolution of IR bands.

Infrared spectra of silanized samples are shown in Figure 3. Characteristic bands of CH_2 and CH_3 groups ($\lambda = 2945\ cm^{-1}$, $2841\ cm^{-1}$) and carbonyl group ($\lambda = 1720\ cm^{-1}$), can be observed. The silanizing process consisted of hydrolyzing $Si{-}OCH_3$ groups of the MSPM to produce the corresponding silanols, which were then condensed with OH groups of the hydroxyapatite to form a $Si{-}O{-}P$ bond [26]. The $Si{-}O$ ($\lambda = 1080\ cm^{-1}$) band of the MSPM is present in the infrared spectra, however; this band is superimposed over hydroxyapatite absorption bands, and for this reason it can not be differentiated with clarity. The amount of silanized hydroxyapatite (Table 1) was determined by ICP (Ca weight per cent of HA powder bounded to MSPM). The table confirms the silanization of hydroxyapatite.

The powder X-ray patterns (Figure 4) show that peak resolution increases in the following order: HAS>HAC>HAP, which indicates an increase of crystallinity of the samples and corroborates IR results. Difractograms of heat-treated hydroxyapatites show no traces of thermal decomposition at temperatures up to 1250°C.

Net parameters of the hexagonal unit cell are shown in Table 2. HAP net parameters are similar to the values reported for hydroxyapatite: $a = 9.418\ 0\ A^\circ$, $c = 6.8840\ A^\circ$, $V = 528.80\ A^{\circ 3}$ (PDF No. 9-432, 1998). HAC shows a small decrease in net parameter values, which indicates that because of the heat treatment some oxyhydroxyapatite is formed (due to the loss of OH radicals) [27]. HAS was obtained at a higher temperature treatment than HAC; however, in this case net

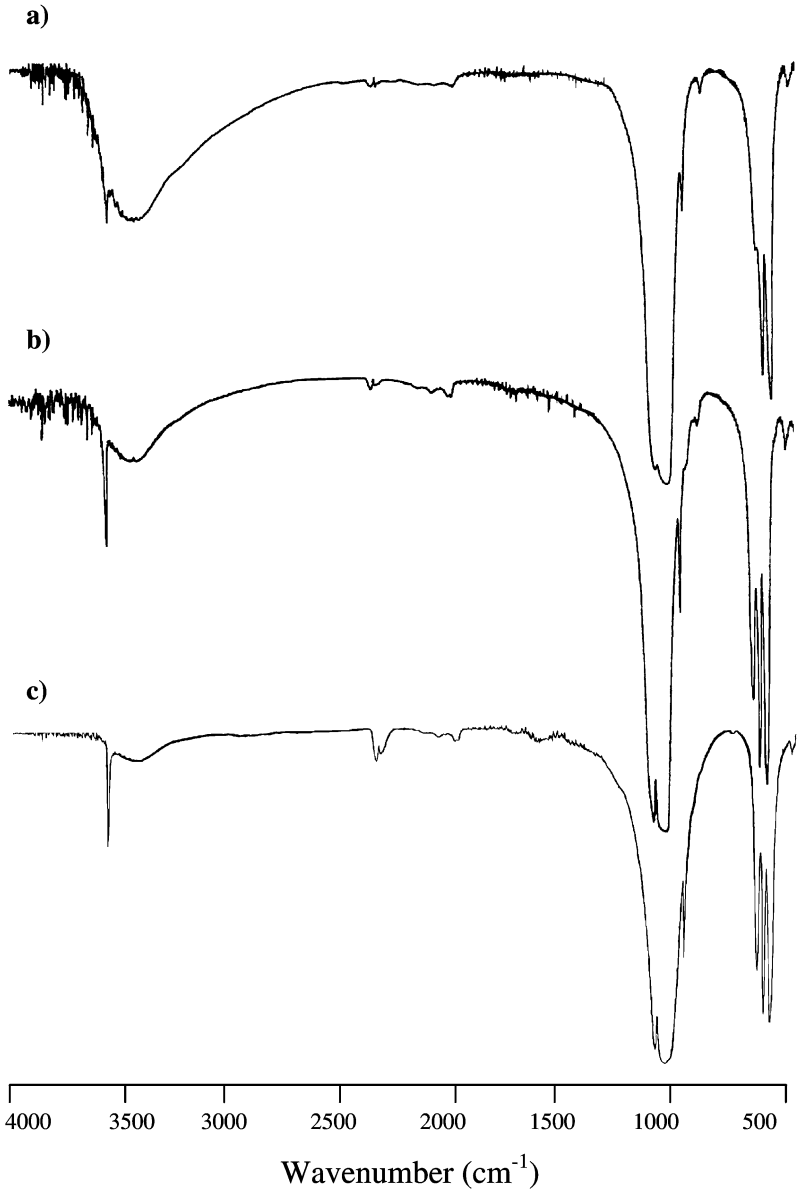

FIGURE 2 Infrared Spectrum of hydroxyapatites, (a) HAP, (b) HAC, (c) HAS.

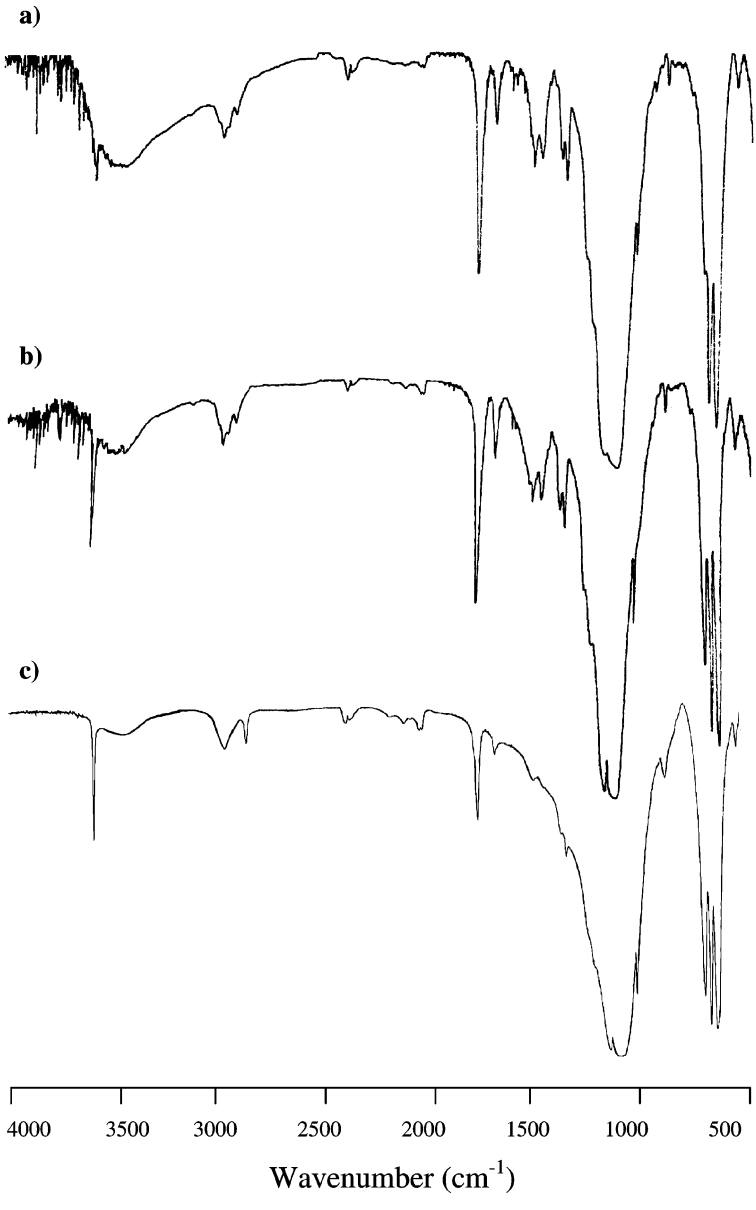

FIGURE 3 Infrared Spectrum of silanized hydroxyapatites, (a) HAPS, (b) HACS, and (c) HASS.

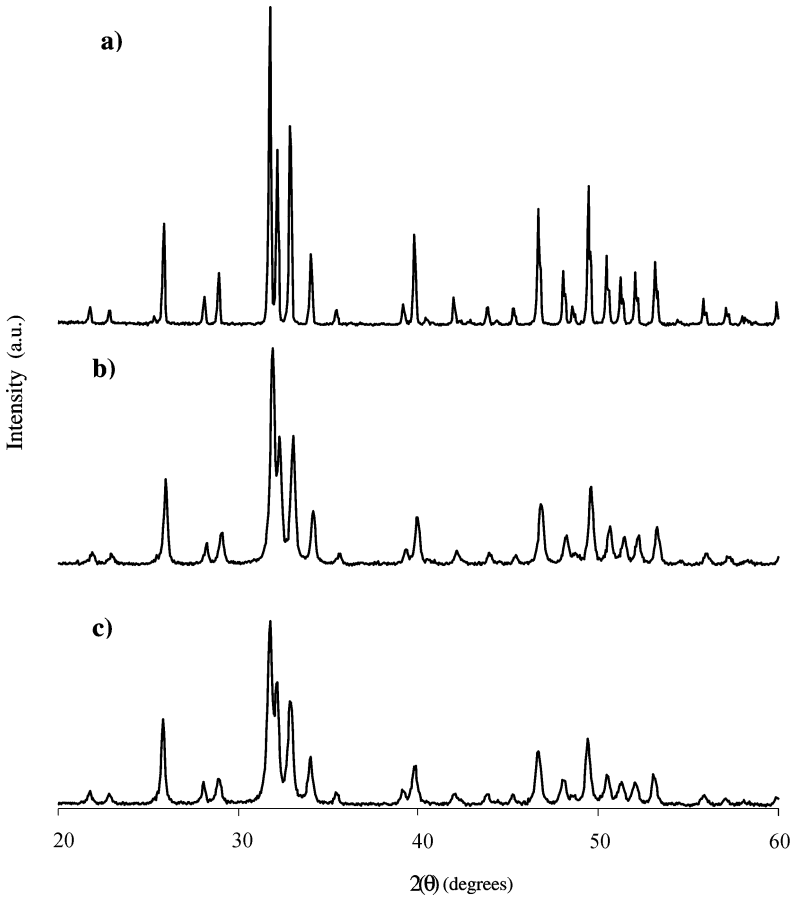

FIGURE 4 XRD patterns of hydroxyapatite powders: (a) HAS, (b) HAC, (c) HAP.

TABLE 2 Net Parameters, BET Surface Area, and Pore Volume of HA Powders

Type of HA	Net parameters			Surface area m^2/g	Pore volume cm^3/g
	a(A°)	c(A°)	V($A^{\circ 3}$)		
HAP	9.416	6.893	529.27	47.7	0.0240
HAC	9.397	6.875	525.83	22.5	0.0110
HAS	9.411	6.892	528.65	1.3	0.0026
HAPS	9.417	6.899	529.84	29.0	0.0150
HACS	9.403	6.874	526.36	10.0	0.0050
HASS	9.418	6.895	529.61	1.3	0.0017

parameter values were not modified because a humid oxygen atmosphere was used to prevent sample dehydroxylation and decomposi tion [28]. Since MSPM incorporation occurs only at the sample surface, the size of the unit cell was not notably modified by the silanization treatment.

Because of crystal growth, surface area and pore volume of the hydroxyapatites decrease with increasing treatment temperature (Table 2). Figure 5 shows micrographs of the three types of hydroxyapatite at similar magnification. HAP and HAC show a rough surface, indicating that they have smaller crystal size and a larger surface area than HAS. Data in Table 2 confirms the micrograph results since a larger surface area and larger volume were obtained for HAP and HAC hydroxyapatite powders. Silanized hydroxyapatites present smaller surface area than non-silanized samples because MSPM reacts with surface OH molecules, causing a decrease in the surface area (Table 2).

Figure 6 shows the results of non-filled cements isothermal polymerizations. Since molecular mobility increases with temperature,

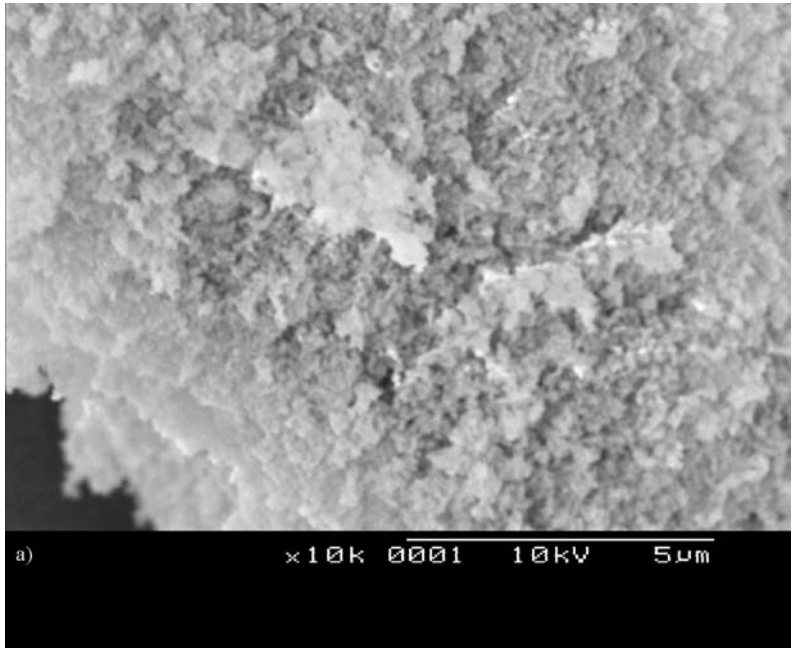

FIGURE 5 Micrographs of the hydroxyapatite powders, (a) HAP, (b) HAC, (c) HAS. (Continued.)

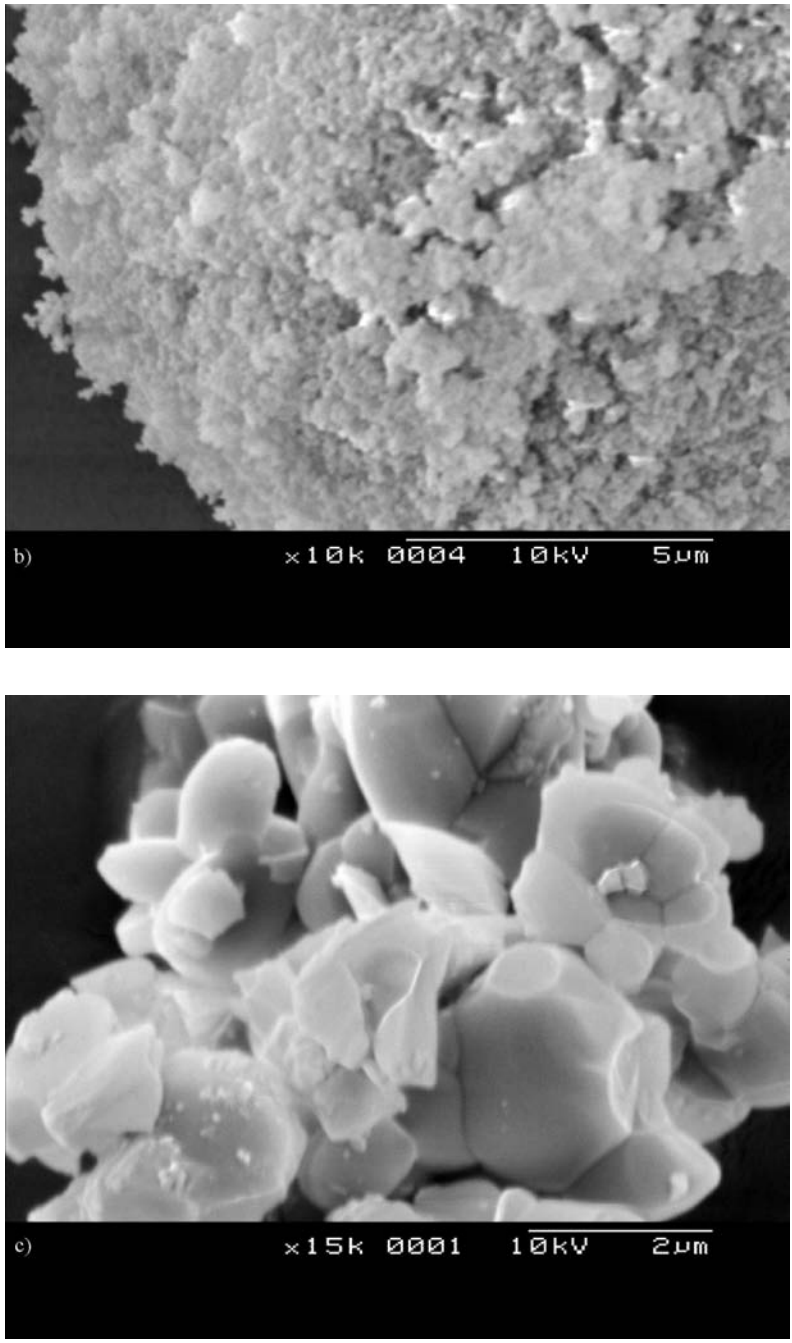

FIGURE 5 (Continued.)

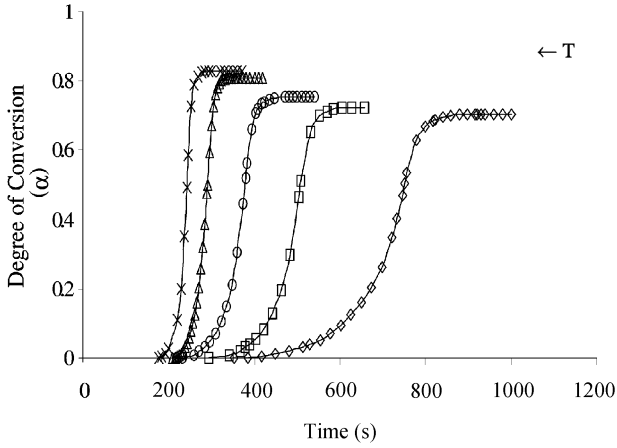

FIGURE 6 Experimental degree of conversion for the isothermal polymerization of non-filled cements: -◇- 10°C; - - 15°C; -○- 20°C; Δ 25°C; × 30°C.

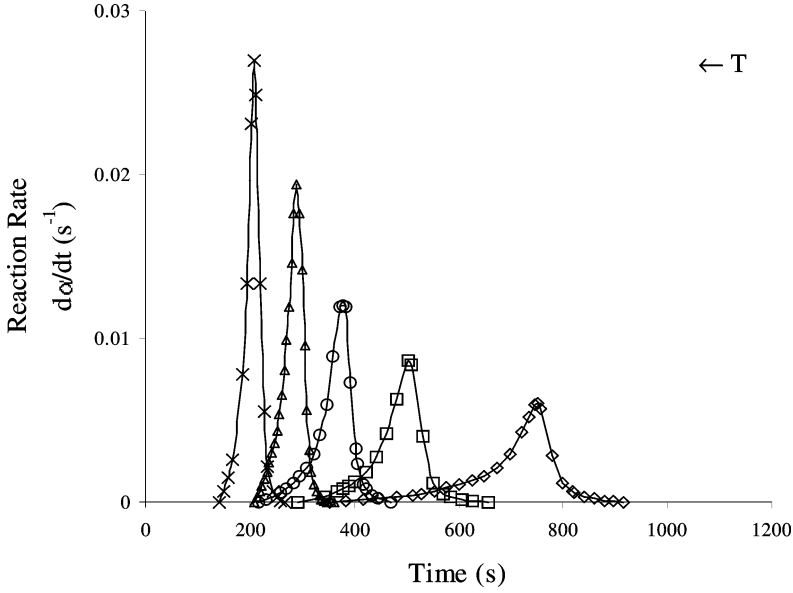

FIGURE 7 Reaction rate for the isothermal polymerization of non-filled cements: -◇- 10°C; - - 15°C; -○- 20°C; Δ 25°C; × 30°C.

higher reaction temperatures will lead to higher degrees of conversion [17]. A high conversion level is desired since residual monomer can migrate to the surrounding tissue and may cause damage to it [7, 29].

Reaction rate increases with temperature (Figure 7) due to the higher rate of radical generation combined with an increase in reaction rate-constant values.

The time running from the beginning of components mixing until the onset of heat generation, represents reaction induction time. Induction time is due to the presence of inhibitors (hydroquinone and

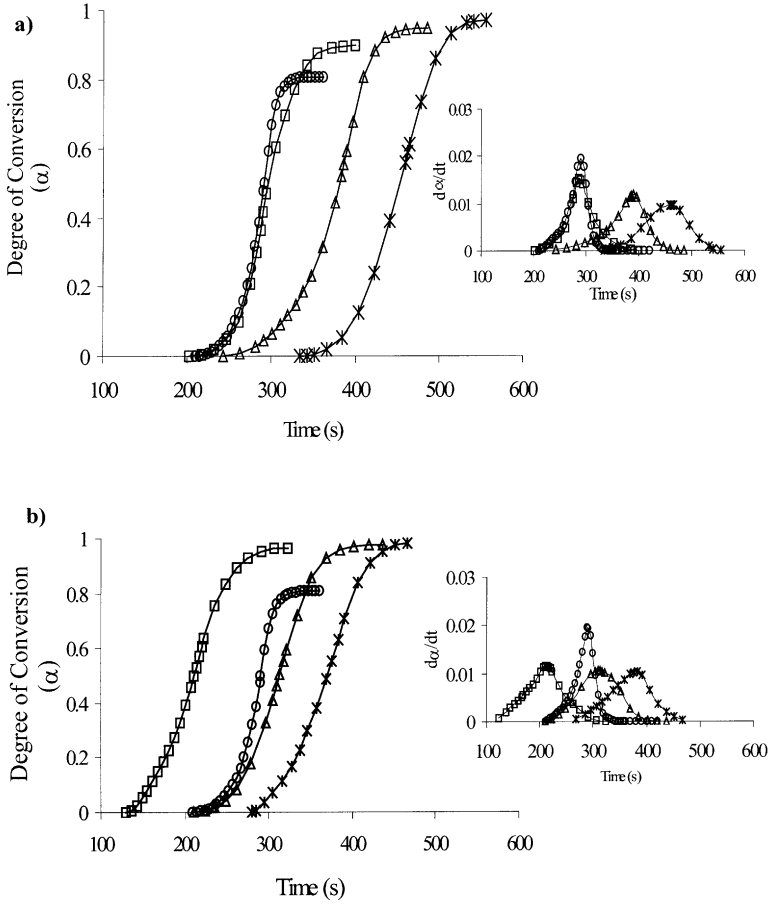

FIGURE 8 Comparison between experimental degree of conversion of composites without HA and with 50 weight % of HA, (a) Non- Silanized, (b) Silanized. ⊖ Cement, -*-HAP, -Δ-HAC, -□- HAS.

oxygen) [30, 31], which capture free radicals and delay the polymerization reaction. The hydroquinone is added to the formulation to prevent prepolimerization and the oxygen appears solubilized by the water present in the fillers and also trapped in the micropores. Curing of an autopolymerizing methyl methacrylate resin reinforced with glass fiber has shown that the presence of oxygen trapped in the fibers caused inhibition [31]. Since the higher generation rate of free radicals leads to faster inhibitor consumption, increasing reaction temperature causes a reduction in induction time (Figure 7).

Figure 8a compares the conversion curve of the bone cement with those of the cements filled with 50 weight per cent of hydroxyapatite. All of the filled cements present a higher maximum degree of conversion and a lower reaction rate than the non filled cement (insert of Figure 8a). Similar results were reported for the polymerization of a hydroxyapatite filled IRC bone cement [18]. Since a lower temperature peak and a smaller amount of residual monomer may cause less damage to surrounding tissues, lower reaction rates and a higher maximum degree of conversion are favorable for the long term fixation of an implant. Cement formulations filled with 50 weight per cent of silanized hydroxyapatites (Figure 8b) have shown a higher maximum degree of conversion and lower reaction rates than the non filled cement (insert of Figure 8b).

Figure 9 shows that as the content of HAP increase, reaction rate decreases. As a consequence, heat would be generated more slowly, giving as a result lower temperature peaks. Similar behavior was obtained for curing of cements filled with the other types of hydroxyapatite, either silanized or not silanized. Alvarez *et al.* reported on the polymerization of bisphenol-A-(glycidylmethacrylate) triethyleneglycol dimethacrylate that the decrease in reaction rate

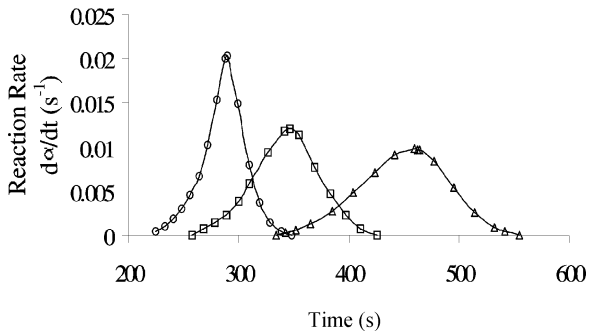

FIGURE 9 Reaction rate of the bone cement setting process with different content of HAP. -O- 10% HAP, -□-30% HAP, -Δ-50% HAP.

could be explained using the three-layer model for particulate composites [32, 33]. In such model, it is assumed that three different and distinguishable phases are present in the composite: the filler, the matrix and the mesophase. The mesophase is an hybrid lying between the two other phases, where transition phenomena between the properties of the two phases occur. The mesophase is characterized by higher viscosity and density than the matrix, which cause lower molecular mobility, giving as a result a decrease in polymerization rate.

Figure 10a shows that induction time is affected by the type and amount of hydroxyapatite used. HAP has the largest amount of water

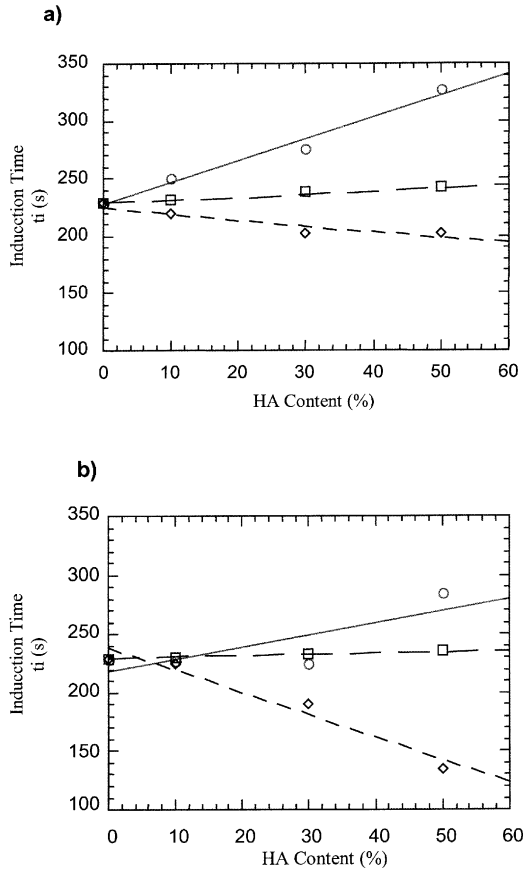

FIGURE 10 Induction Time at 25°C with different HA content. (a) Non-Silanized, (b) Silanized.

(Figure 2a) and the highest surface area and pore volume (Figure 5a and Table 2). For these reasons, it is the filler that causes the longest induction time. Of course, increasing HAP content increases induction time. Because by heating HAP at 800°C some water was lost, and surface area as well as pore volume of the resulting HAC decreased, HAC filled cements show only a slight increase in induction time with increasing filler content (Figure 5b, Table 2).

Due to the high temperature treatment (at 1250°C), HAS filler has the lowest water content (Figure 2c), and the lowest surface area and pore volume (Figure 5c) giving as a result a cement formulation with the shortest induction time. Furthermore, its induction time decreased with increasing filler content. These results suggest that by thermal treatment, probably the hydroxyapatite surface was modified in such way that caused an higher rate of initiator decomposition, which in turn produced a faster consumption of the hydroquinone and oxygen present. Other authors have reported that mineral fillers produced both catalytic and inhibitor effect in the curing of different resins. These behaviors were specific for each type of resins and filler [34].

Figure 10b shows that cements filled with silanized hydroxyapatites exhibited a shorter induction time than cements with non-silanized particles. This can be explained because by the silanization treatment, surface area and pore volume decreased (Table 2). Also, because of the methyl methacrylate groups in the silanized hydroxyapatite, the fillers participated in the polymerization process. For these reasons, induction times were shorter than those obtained when non-silanized hydroxyapatites were used.

IV. CONCLUSIONS

Three types of hydroxyapatite were synthesized with different water content, crystallinity and surface area. Hydroxyapatites thermal treatment did not change their basic chemical structure, but produced a material with larger crystal size and less pore volume. By silanization, hydroxyapatite fillers with less surface area and smaller pore volume were obtained.

The presence of hydroxyapatite fillers, aside from the potential of lowering cement shrinkage and increasing the compatibility between implant and osseous structure, decreased reaction rate (lower temperature peak) and produced cured cements with higher degree of conversion (lower residual monomer).

Induction time increased when using HAP and HAC hydroxyapatite types, and induction time increased with filler content. HAS filled formulations showed shorter induction time than the non filled

cement, but filler content decreased the induction time. By using silanized hydroxyapatite fillers the induction time was decreased.

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