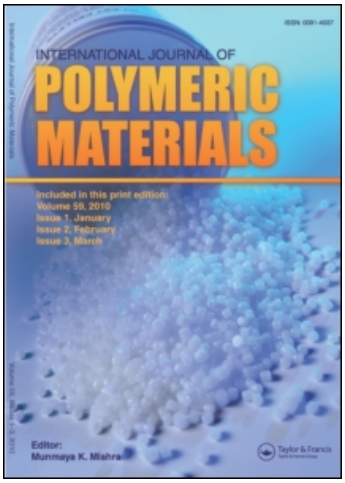

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MODELING OF THE CURING KINETICS OF AN ACRYLIC BONE CEMENT MODIFIED WITH HYDROXYAPATITE

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In this work, setting kinetics of a poly(methylmethacrylate-co-styrene) bone cement with and without hydroxyapatite filler were studied. Three types of hydroxyapatite with different morphologies were used. Polymerization kinetics were followed by Differential Scanning Calorimetry (DSC). A modification to the Maffezoli kinetic model for bone cement curing process is presented. The proposed kinetic model can predict the whole curing kinetics process of the bone cements studied here. It clearly follows the delay in the "autoacceleration effect" caused by the hydroxyapatites and can predict the behavior of k_t, as the system approaches limiting conversion.

Keywords: hydroxyapatitie, bone cement, kinetic model

I. INTRODUCTION

Acrylic bone cements are widely used in orthopedics to fix artificial prosthesis onto the osseous structure of the human body. In Total Hip Arthroplasty (THA), the use of acrylic cements permits a fast

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anchorage of the prosthesis to the bone, as well as an adequate body load distribution. However, this technique presents some drawbacks, which decrease the lifetime of the implant.[1–5]

1. After cement curing, some of the monomer remains unreacted. The monomer may migrate to surrounding tissues causing osseous necrosis by citotoxic action.[6,7]
2. Radical polymerization of conventional acrylic bone cements is highly exothermic. The heat generated can produce thermal damage to the tissues and weaken the bone-cement union.[8] It has been reported that threshold for thermal damage of the bone is 48°C, whereas, at temperatures higher than 60°C, osseous necrosis is clearly shown.[9,10]
3. Shrinkage of the cement upon curing may produce small gaps in the bone/cement and cement/prosthesis interfaces.[11]

In order to minimize the damage to the surrounding tissues of an implant and to increase the lifetime of a prosthesis, it is necessary to lower the amount of residual monomer and the peak temperature of the curing process. To decrease these parameters, it is a common practice to use a mixture of poly(methyl methacrylate) and methyl methacrylate monomer in a ratio of 2:1 by weight.[12–13] To improve the mechanical performance and the biocompatibility of the bone cement formulations, along with a lower peak temperature, bioactive particles have been used as fillers. 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.[14–20] In a previous work we reported that using hydroxyapatite as a filler, lower reaction rates and cured cements with higher degree of conversion (lower residual monomer) were obtained.[21]

Since reaction thermal effects and the amount of unreacted monomer play an important role in implant durability, it is necessary to have a reliable kinetic model for bone cements curing that will permit prediction and optimization of the curing process.

In this work, a hydroxyapatite was synthesized and divided in three parts. Two of them were heat treated at different conditions obtaining, in that way, hydroxyapatites with different morphology. These hydroxyapatites were used as fillers in an acrylic bone cement. To describe polymerization kinetics of the cement formulations (filled and non-filled) studied here, we propose a modification to the Maffezoli[20,22] model for the curing of acrylic bone cements. Our model takes into consideration inhibition and autoacceleration

effects. Curing kinetics were followed by Differential Scanning Calorimetry (DSC)and experimental data were used to evaluate the model parameters.

Model

In radical polymerization, at low degrees of conversion, reaction rate (R_p) is given by:[22]

$$R_p = -\frac{dM}{dt} = k_p\left(\frac{fk_d}{k_t}\right)^{0.5}[M][I]^{0.5} \quad (1)$$

Where M is monomer concentration, k_p and k_t, are the propagation and termination rate constants respectively, k_d is the initiator decomposition constant and f is its efficiency.

However, as conversion increases, the medium viscosity increases until a critical value is reached, where the diffusive processes start to control reaction rates. At this point, termination rate decreases, and because of the large number of growing chains, reaction rate auto-acceleration occurs and equation (1) is no longer valid.[23] At higher conversions the mobility of small molecules (monomer) decreases, causing a lower reaction rate.[24] As the reaction proceeds further, viscosity can be so high that the propagation reaction practically stops and some monomer remains unreacted.[25–27]

Because of the large polymer proportion in the cement formulation, curing of bone cements starts with a high medium viscosity, and equation (1) cannot be used. Furthermore, due to the presence of hydroquinone and oxygen (inhibitors), which capture the free radicals produced by the initiator, an induction time is always present.[28] After the inhibitors are consumed, the polymerization reaction starts, reaction rate increases steadily until it reaches a maximum, and then it decreases.

Some mathematical models have been suggested for modeling the curing of bone cements. Jen-Ming Yang considers that the reaction is first order and can be represented by the following equation:[29]

$$R_p = -\frac{dM}{dt} = k[M] \quad (2)$$

where M is monomer concentration and k is the rate constant. By analyzing the curing kinetics, he proposed two sequential reaction rate constants, k_1 and k_2. In the first period, where reaction rate

increases, polymerization kinetics is governed by k_1 and after the peak temperature, k_2, which has a value greater than k_1, is the constant that governs kinetics. However, his model has some drawbacks: in his model k changes abruptly and it is not a continuous function of conversion, and according to equation (2), since monomer concentration decreases, the reaction rate will also decrease continuously. However, at the start of the reaction, experiments show that the reaction rate increases until it reaches a maximum. For these reasons it is considered that the Yang model cannot describe correctly the curing kinetics of a cement.

Due to the increase in medium viscosity with conversion, Maffezoli *et al.*[22] proposed that propagation and termination rate constants depend on the degree of conversion (α) according to the following expressions:

$$k_p = k'_p(\alpha_{max} - \alpha)^n \tag{3}$$

$$k_t = k'_t\alpha^{-2m} \tag{4}$$

where m and n are fitting parameters non dependent on temperature, k'_p and k'_t are the initial reaction rate constants for propagation and termination, respectively. By substitution of these expressions in equation (1) and considering that $[M]/[M_o] = 1 - \alpha$, the following simple pseudo catalytic expression is obtained:

$$\frac{d\alpha}{dt} = K\alpha^m(\alpha_{max} - \alpha)^n(1 - \alpha) \tag{5}$$

where

$$K = k_p\left(\frac{fk_d}{k_t}\right)^{0.5}[I]^{0.5} \tag{6}$$

by using equation (5) and non-linear regression, Maffezoli *et al.* evaluated the K, m and n kinetic parameters for several acrylic bone cement formulations.

Although their model predicts fairly well the curing kinetics of bone cements, the form of equation (4) predicts that k_t will never approach a zero value, which does not agree with the value experimentally obtained at very high conversions, when the molecules translational movement stops, because the system reaches the glass transition temperature (T_g).[20,30–32]

Since k_t approaches zero as the system approaches T_g, we propose a modification to equation (4), which becomes:

$$k_t = k'_t(\alpha_{max} - \alpha)\alpha^{-2m} \tag{7}$$

And then the expression for the reaction rate will be:

$$\frac{d\alpha}{dt} = K\alpha^{m}(\alpha_{max} - \alpha)^{(n-0.5)}(1 - \alpha) \quad (8)$$

Estimation of the kinetic parameters (m, n and K) can be made by using equation (8), experimental data and non-linear regression analysis (Levenberg Marcquard method[33]).

II. EXPERIMENTAL

Beads of poly(methyl methacrylate-co-styrene) obtained by suspension polymerization with a 90/10 mol percent compostion represented the solid part of the cement formulations. Their average molecular weights $\overline{M}n = 99,000$, $\overline{M}w = 186,000$, $\overline{M}z = 255,000$ were determined by Size Exclusion Chromatography (SEC) (Perkin Elmer 410). Average particle size was determined by Optical Microscopy (Olympus Bx40 with video recorder KP-D51). The particles had a spherical shape with an average diameter of $32.1 \pm 8.9\,\mu m$.

The hydroxyapatites used in the experiments were prepared as follows: a) Hydroxyapatite powder (HAP) was obtained by precipitation from a 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; c) Sintered hydroxyapatite (HAS) was obtained by maintaining HAC for four hours in humid oxygen atmosphere at 1250°C. Surface area was determined by the BET method, using a Micromeritics equipment (ASAP 2000).

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 50% by weight of hydroxyapatite particles (HAP, HAC or HAS). 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.

Reaction kinetics were followed by Differential Scanning Calorimetry (DSC) using Perkin Elmer (DSC7) equipment. The solid and liquid parts of the cement formulations were hand−mixed at room temperature for 30 seconds and then approximately 15 mg of mixture were transferred to a DSC capsule. The DSC runs started between 0.9−1.2 min after mixing the components. Isothermal polymerizations were carried out at 25°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 15 to 150°C.

Degree of conversion (α) was calculated by dividing the heat generated at a given time in an isothermal experiment, H_{iso}, by the total heat generated by the reaction, H_{tol}, which was calculated as the sum of the total heat generated in the isothermal experiment and the total heat generated in the non isothermal experiment.

$$\alpha = \frac{H_{iso}}{H_{tot}} \tag{9}$$

Reaction rate ($\frac{d\alpha}{dt}$) was obtained from:

$$\frac{d\alpha}{dt} = \frac{I}{H_{tot}} \frac{dH}{dt} \tag{10}$$

where $\frac{dH}{dt}$ is the heat flow obtained from isothermal DSC experiments.

III. RESULTS AND DISCUSSION

Polymerization reaction of bone cement formulations (filled and non filled) was carried out at 25°C. Induction time and final degree of conversion are reported in Table I.

In all cases induction time is larger than 200 seconds. This induction time is due to inhibitor and oxygen present in the system; they capture the free radicals generated by the initiator, causing a delay in the polymerization reaction. Because of the larger surface area of the HAP and HAC (Table I) particles, these fillers should have more oxygen trapped in the pores and for that reason they cause a longer induction time than HAS and the nonfilled cement. This behavior is similar to that reported on the curing of poly(methylmethacrylate) (PMMA) composites filled with glass fiber (GF), where, because of the oxygen trapped in the fibers, there is inhibition of the polymerization reaction.[34]

TABLE I Hydroxyapatites BET Surface Area and Average Pore Volume; Induction Time and Fractional Final Conversion Degree for Bone Cements Curing

Filler	Surface area m^2/g	Pore volume cm^3/g	Induction time s	Final degree of Conversion (α_{max})
None			225	0.807
HAP	47.7	0.0240	335	0.967
HAC	22.5	0.0110	240	0.947
HAS	1.3	0.0026	205	0.897

Table I also shows that inclusion of hydroxyapatite produces a cement with higher conversion and therefore less residual monomer. Also, the use of hydroxyapatite as a filler produces a lower reaction rate (Figure 1), which will result in a lower temperature peak. Alvarez *et al.* reported a decrease in reaction rate for hydroxyapatite filled cements, that can be explained in terms of the three-layer model for particulate composites (TLMPC).[34,35]

In order to predict curing kinetics of the bone cements, it is necessary to have an estimate of n, m and K kinetic parameters of the proposed model. The polymerization of acrylic cements initiates in a medium with high viscosity and high content of inhibitor and oxygen. Since k_p decreases only at very high viscosities, the reported literature value for methyl methacrylate can be used to calculate K. However, because k_t, is affected at lower viscosities than those encountered at the beginning of cement curing, and because the presence of oxygen and inhibitor increase greatly the value of k_t, it is not possible to predict from reported literature data the k_t value at the beginning of the reaction. For such reasons we cannot estimate the initial value of K, making it necessary to obtain K from experimental data.

The n, m and K kinetic parameters of equation (8) were calculated by linear regression using the experimental data and are reported in

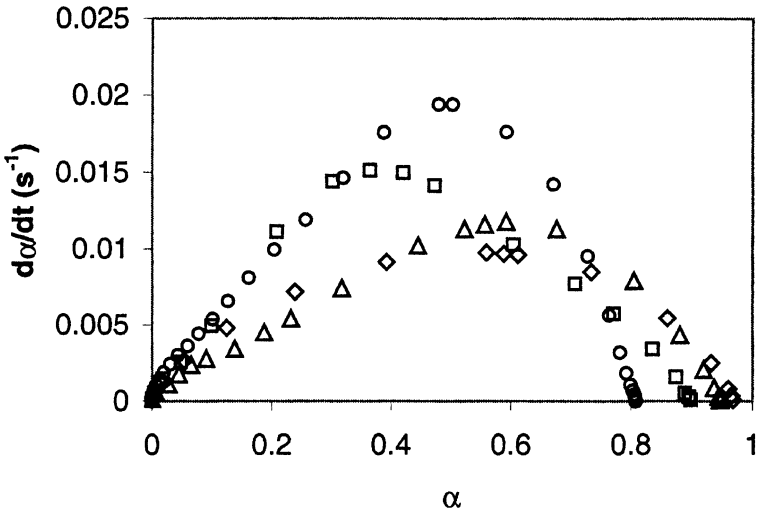

FIGURE 1 Experimental reaction rate $d\alpha/dt$ vs. degree of conversion (α) for bone cement formulations filled with 50 weight % of HA. -○-, non-filled cement; -◇-, HAP; -△-, HAC; -□-, HAS.

TABLE II Calculated Kinetic Constants for Reaction Setting of Bone Cements

Material	*m*	*n*	K
Bone cement	1.86	1.24	0.344
50% HAP	0.986	0.515	0.041
50% HAC	1.627	0.755	0.086
50% HAS	1.162	1.124	0.110

Table II. The pseudo-kinetic constant, K, decreases by the presence of hydroxyapatite, giving as a result slower reaction rates (Figure 1), and as filler surface area increases, the K value decreases.

The m value decreases by the presence of hydroxyapatite filler (Table II). A lower m value indicates that k_t decreases more slowly with conversion and for that reason the "autoacceleration effect" is delayed to higher conversions where, because monomer concentration is smaller, a lower peak temperature is obtained.

Figure 2 shows the variation of k_t/k_t' as a function of conversion degree. At the start of the reaction, because of the presence of inhibitors, which rapidly consume the radicals, k_t/k_t' has a value much greater than one. However, as conversion increases, k_t/k_t' rapidly

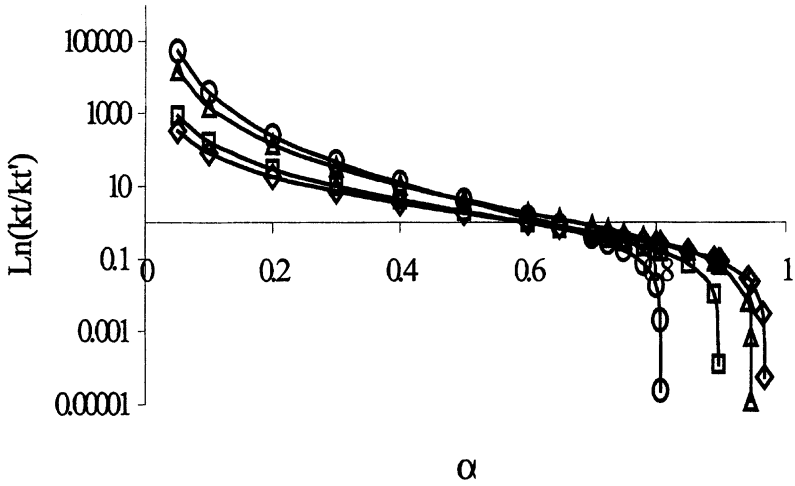

FIGURE 2 $Ln(k_t/k_t')$ vs. degree of conversion (α) for bone cement formulations filled with 50 weight % of HA. -○-, non-filled cement; -◇-, HAP; -△-, HAC; -□-, HAS.

decreases and approaches a zero value at the limiting conversion, which agrees with reports in the literature that as the glassy conditions are reached, molecular mobility ceases and k_t becomes practically zero.[20,30–32]

Upon using hydroxyapatite, lower n values are obtained compared to cement without filler. This indicates that k_p decreases more slowly with conversion (Figure 3), which is beneficial for achieving a higher degree of conversion (lower residual monomer). As expected, the comparison of curves in Figure 2 and Figure 3 shows that k_p/k_p' starts to decrease at much higher conversions than k_t/k_t'.

To test the proposed model, simulations for the different formulations were performed using the kinetic parameters obtained by nonlinear regression, and the results were compared with experimental data.

Figure 4 shows that there is good agreement between experimental and calculated reaction rate vs. conversion curves for the non-filled cement and the 50% HAP–filled cement. Similar results were obtained for the other two hydroxyapatite filled cements.

Figure 5 shows that the proposed model can predict conversion curves versus time for the bone cements (filled or non-filled) studied here, even at limiting conversions.

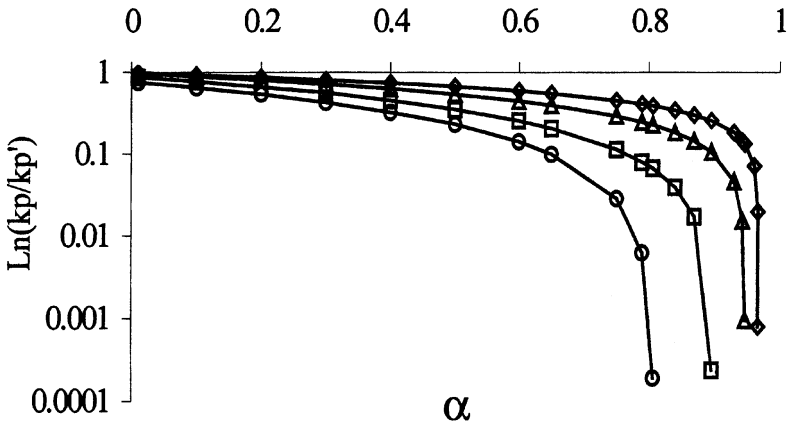

FIGURE 3 $Ln(k_p/k_p')$ vs. degree of conversion (α) for bone cement formulations filled with 50 weight % of HA. -○-, non-filled cement; -◇-, HAP; -△-, HAC; -□-, HAS.

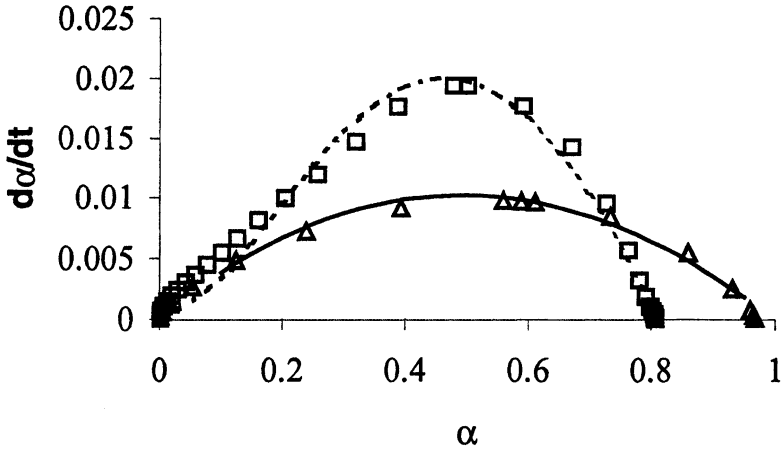

FIGURE 4 Comparison of experimental and simulated reaction rate $d\alpha/dt$ vs. degree of conversion (α) for bone cement formulations. HAP, △ experimental; —, Model; non-filled cement, □, experimental, – – model.

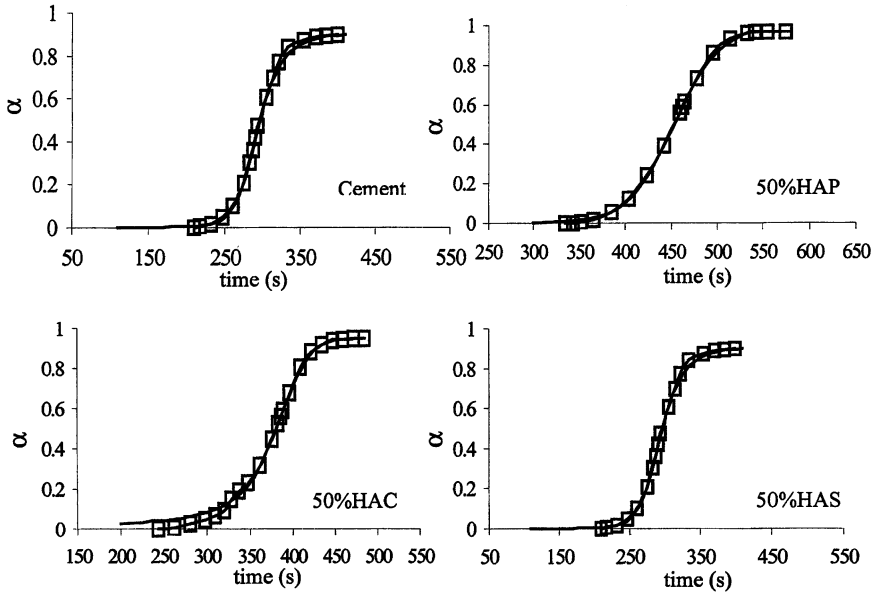

FIGURE 5 Comparison of experimental degree of conversion (α) as a function of time (t) with model predictions. □, experimental; —, model.

CONCLUSIONS

The proposed kinetic model can predict the curing kinetics of the bone cements studied here. It follows the delay in the "autoacceleration effect" caused by the hydroxyapatites and can predict the behavior of k_t as the system approaches limiting conversion.

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