Brazilian Journal
of Chemical
Engineering

ISSN 0104-6632
Printed in Brazil
www.abeq.org.br/bjche

Vol. 30, No. 04, pp. 865 - 876, October - December, 2013

EFFECT OF PROCESS VARIABLES ON THE PREPARATION OF ARTIFICIAL BONE CEMENTS

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(Submitted: December 28, 2011 ; Revised: November 26, 2012 ; Accepted: December 30, 2012)

Abstract - The present work concerns the preparation of bone cements based on poly(methyl methacrylate) (PMMA), used mainly for prosthesis fixation and cavity filling for correction of human bone failures. A typical bone cement recipe contains methyl methacrylate, which polymerizes *in situ* during cement application. An inherent problem of this reaction is the large amount of heat released during the cement preparation, which may lead to irreparable damage of living tissues. Optimization of PMMA-based bone cement recipes is thus an important step towards safe and reliable clinical usage of these materials. Important process variables related to the reaction temperature profile and the mixing of the recipe constituents were studied in order to allow for the adequate production of bone cements. It is shown that the average molar mass and size of the PMMA particles used in the production of the bone cement, as well as incorporation of radiopaque contrast, co-monomers and fillers into the bone recipe play fundamental roles in the course of the polymerization reaction. Furthermore, the injection vessel geometry may interfere dramatically with the temperature profile and the time for its occurrence. Finally, it has been observed that the morphology of the PMMA particles strongly affects the mixing of the bone cement components.
Keywords: Biomaterials; Bone cement; Mixing; PMMA; Suspension polymerization.

INTRODUCTION

The term bone cement has been frequently used to designate artificial bone materials based on poly (methyl methacrylate) (PMMA) or other acrylate-based polymers. Besides the polymer resin, small amounts of other constituents are added in order to promote the polymerization and to allow for their better clinical use. Due to its excellent optical and mechanical properties, biocompatibility and ease of manipulation, PMMA has been extensively used for manufacturing of artificial bone cements for treatment of osteoporosis. Due to the high initial viscosity of PMMA mixtures, these blends can be manipulated and injected into the body in order to correct failures in porous bone tissues (Vazquez *et al*., 1998).

The first significant application of bone cements was the support of medullary portions of total hip replacements, generally credited to John Charnley in 1958 (Black, 1988). Despite the many small changes introduced into the bone cement recipe since then and its posterior use in many other applications, the basic recipe remains essentially the same as used by Charnley.

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The addition of an X-ray contrast, such as barium sulfate ($BaSO_4$) or zirconium dioxide (ZrO_2), in order to render the final cement radiopaque, was one of the most important modifications of the original bone cement recipes. In a previous work, Santos *et al*. (2006) proposed the *in situ* incorporation of X-ray contrasts during the suspension polymerization performed to produce the PMMA particles. The obtained results showed that the bone cement produced with this PMMA powder is more homogeneous and stronger than the bone cement produced through hand-mixing of the PMMA and $BaSO_4$ particles during the preparation, as usual. Makita *et al.* (2008) showed that radiopacity is increased and strength is reduced by adding increasing concentrations of barium powder to bone cement. The authors suggested that adding barium permits the radiopacity and strength of bone cement to be adjusted in clinical practice. Gomoll *et al.* (2008) replaced the $BaSO_4$ microparticles that are usually present in commercial PMMA cements with $BaSO_4$ nanoparticles and showed that the presence of $BaSO_4$ particles, and the size of these particles, strongly affected the mechanical properties of acrylic bone cement.

A typical PMMA-based bone cement is prepared during its clinical application through free radical bulk polymerization of methyl methacrylate (MMA) monomer, initiated by the decomposition of benzoyl peroxide (BPO) and activated by N,N-dimethyl-p-toluidine (DMPT) (Vazquez *et al*., 1997). The recipe also contains a prescribed amount of $BaSO_4$ or ZrO_2 and PMMA particles, which are used to increase the initial viscosity of the reaction medium and to accelerate the rate of the polymerization reaction, because of the strong and well-known gel effect of MMA polymerizations.

The bone cement preparation is initiated when the recipe constituents are mixed in a reservoir. As soon as the components are mixed, reaction starts and the mixture viscosity and the reaction rate increase quickly due to the gel effect, which is greatly enhanced by the presence of the PMMA powder. When a suitable viscosity (or degree of polymerization) is reached, the mixture is delivered to the patient. Unfortunately, an inherent problem of this reaction is the high amount of heat released during the bone cement preparation, which may cause the reaction temperature to increase above 100 °C and lead to irreparable damage of living tissues (Pascual *et al*., 1996). For this reason, it is necessary to reduce the high temperature peaks during the bone cement preparation.

Meyer *et al*. (1973) verified that the maximum temperature reached during bone cement preparation can be minimized by reducing the operating room temperature. This indicates the importance of heat transfer effects during the bone cement preparation in a real application environment. Haas *et al*. (1975) showed that, by using the minimum acceptable amount of MMA monomer and maximum amount of PMMA particles which do not compromise final properties of the bone cement, the polymerization rate and heat released during the reaction can be minimized. This can be easily explained in terms of the reduction of the reaction rates due to the low MMA concentration in the mixture and partial absorption of the reaction heat by the inert PMMA particles.

Another alternative to reduce the heat released during the bone cement application is to cool the mixture components prior to utilization. Some simulation studies (Maffezzoli, 1997) and experimental investigations (Dipisa *et al*., 1976; Toksvig-Larsen *et al*., 1991) show that this technique can constitute a good alternative to avoid high temperatures during the cement manipulation. However, Meyer *et al*. (1973) did not achieve good temperature control during the bone cement curing process using a pre-cooled prosthesis, which shows that additional investigations on this topic are still required.

The characteristics of the PMMA powder used in the bone cement formulation are also important process variables, related directly to the temperature peak control. Pascual *et al*. (1996) found that it is possible to improve the performance of the curing process and to control the reaction temperature peak through manipulation of the particle size distribution of PMMA. They showed that the use of PMMA beads with an average diameter of 60 μm and a relatively wide particle size distribution (10 - 140 μm) can delay the onset of the gel effect and reduce the maximum temperature by more than 30 °C, when compared to formulations that contain smaller PMMA particles. Liu *et al*. (2003) showed that PMMA powders with different average particle sizes and average molar mass produced bone cements with different properties. More specifically, they observed that using small PMMA particles of lower molar mass led to the production of bone cements with higher molecular masses than the initial beads. These results indicate that the final bone cement performance may depend critically on the initial bone cement formulation and on the properties of the PMMA powder.

The idea of introducing fillers in the formulation of commercial recipes has also attracted the attention of previous research. Nano-sized titania fibers (n-TiO2 fibers) were successfully incorporated into a

commercial brand of bone cement matrix as a reinforcing filler. Enhanced thermal and mechanical properties of these nanocomposites were achieved due to the chemical interaction between the n-TiO2 fibers and the PMMA matrix (Khaled *et al.*, 2011). Hydroxyapatite (HA) has been shown to be an excellent alternative to reinforce polymer resins and to present a highly desirable biocompatibility with the bone tissue (Ogiso *et al*., 1993). Santos *et al*. (2011) synthesized PMMA-HA composites which lead to much better mechanical and reaction performances of test pieces, when compared to the performances of test pieces prepared with standard bone cement formulations. In addition, significantly enhancement of the final mechanical properties of PMMA-based bone cements has been reported after the introduction of HA into typical bone recipes (Castaldini and Cavalini, 1986; Perek and Piliar, 1992; Liebendörfer *et al*., 1995; Vallo *et al*., 1999, Fuentes *et al.*, 2008).

Another point of interest during the manufacture of PMMA bone cements regards the presence of a co-monomer in the recipe. It is interesting that the addition of such substances in the bone recipe has been overlooked in the literature, even though many commercial bone recipe kits include co-polymers in their formulations (Hendriks *et al*., 2004). Co-monomers can be added in small amounts to the reaction medium in order to enhance the polymerization rates and gel-effect, thus accelerating the bone cement curing process. The literature reports that a number of bone cement manufactures utilize high molar mass co-monomers (such as isobornylmethacrylate or n-decyl methacrylate) to reduce the temperature peak in the bone cement preparation (Breusch and Malchau, 2005). The literature also reports the use of an iodine-based compound as a co-monomer in bone cement formulations to provide antimicrobial properties to the cement (Deb *et al.*, 2008). Therefore, the presence of co-monomers in the reaction medium during the production of bone cements should be considered.

From this brief review it is clear that, in order to obtain a PMMA-based bone cement with the desired characteristics, it is necessary to understand and to be able to control the process variables that affect its preparation and, as a consequence, its end-use properties. Although mixing of the recipe components constitutes an important bone cement preparation step, very little information is available about mixing effects on the process performance. Since a considerable amount of PMMA powder particles is necessary to obtain bone cements presenting the desired final properties, the influence of particle properties on the process should be correctly understood. Based on these remarks, an experimental study was carried out in this work to analyze the influence of the PMMA particles characteristics and mixing procedures on the bone cement preparation. In addition, an experimental investigation was also performed to evaluate the influence of the addition of fillers (radiopaque contrast and hydroxyapatite, HA) and comonomers (acrylic acid, AA, and metacrylic acid, MA) on the reaction temperature profile during the bone cement preparation.

MATERIALS AND METHODS

Materials

MMA monomer (polymer grade) was provided by Rhodia with a minimum purity of 99.9%. The suspending agent poly(vinyl alcohol) (PVA) with an average molar mass of 78 kDa and a degree of hydrolysis of 85% was supplied by Vetec Química Fina. The initiator (BPO, 97% pure on a dry basis) was supplied by Fluka. The activator (DMPT) was supplied by Aldrich, with 99% purity. $BaSO_4$ was supplied by Vetec Química Fina (97.5% purity). ZrO_2 was supplied by Spectrum, with 98% purity. Tetrahydrofuran was supplied by Tedia Brazil, with a minimum purity of 99.9%. AA monomer (polymer grade) was provided by Rhodia with a minimum purity of 99.9%. MA monomer (polymer grade) was provided by Hidroquímica with a minimum purity of 99.9%. HA was synthesized by the inverse precipitation method, following Shimoda *et al.* (1990), and supplied by NUCAT/COPPE/UFRJ. MMA was distilled at low pressure. Other chemicals were used as received without additional purification.

Experimental Methodology

PMMA Particles

Suspension polymerization experiments were performed to produce PMMA particles for the preparation of bone cements. Table 1 shows the operational conditions used in each polymerization run. Polymerization reactions were carried out in a stirred jacketed glass reactor. Initially, the reactor was charged with the aqueous PVA solution. After temperature stabilization at 85 °C, a solution of BPO in MMA was added to the reactor. In all runs, stirring conditions were set-up to allow for the production of spherical polymer particles, with the exception of run 4, where production of deformed particles was induced on purpose.

Table 1: Suspension polymerization reaction conditions and polymer properties.

PMMA	MMA (g)	BPO (g)	PVA solution(g)		Stirring (rpm)	Mw×10^{-3} (Dalton)	P.D.I.
			1g/L	2g/L			
1	150	1	450	0.0	800	491	6.10
2	150	2	450	0.0	800	416	6.13
3	150	4	450	0.0	800	261	3.86
4	300	2	0.0	900	1500	486	3.58

Bone Cement Production

Bone cements were produced through free radical bulk polymerization using an initiator-activator system (BPO-DMPT). Bone cement preparations were carried out in test tubes for proper monitoring of temperature profiles. Solid and liquid components were weighed separately and solid materials were mixed manually before addition of the liquid components. Afterwards, the solid and liquid constituents were mixed manually in the test tube for 45-60 s. Immediately after mixing, a thermocouple was placed inside the reaction medium in order to monitor the temperature profile during the reaction. The bone cement reactions performed in the present work are shown in Table 2. The amounts of PMMA (3.0 g), BPO (0.06 g) and DMPT (0.08 g) were kept constant in all runs and one sample of each formulation was analyzed.

Table 2: Experimental plan for the temperature profile tests.

Exp.	PMMA		MMA (g)	$BaSO_4$ (g)	ZrO_2 (g)	HA (g)	AA (g)	MA (g)
	Mw×10^{-3} (Da)	Dp (μm)						
1	416	150-212	2.0	-	-	-	-	-
2	491	<106	2.0	-	-	-	-	-
3	491	300-600	2.0	-	-	-	-	-
4	416	150-212	2.0	-	-	-	-	-
5	261	<106	2.0	-	-	-	-	-
6	261	300-600	2.0	-	-	-	-	-
7	491	150-212	2.0	-	-	-	-	-
8	491	150-212	2.0	0.6	-	-	-	-
9	491	150-212	2.0	-	0.6	-	-	-
10	491	150-212	1.8	-	-	-	0.2	-
11	491	150-212	1.8	-	-	-	-	0.2
12	491	150-212	2.0	-	-	0.6	-	-
13	261	<106	2.0	-	-	-	-	-

- Means zero.

Characterization

Average molar masses of PMMA particles were measured through gel permeation chromatography (GPC). The GPC system was composed of a chromatograph (Waters 600E), three columns (Ultrastyragel) and a refractometer (Waters 2414). The calibration curve was obtained with polystyrene standards with average molar masses ranging from 500 to 3×10^6 Dalton and polydispersity indices (P.D.I.) lower than 1.05. Tetrahydrofuran (Tedia Brazil with a minimum purity of 99.9%) was used as the mobile phase and analyses were carried out at 40 °C. The morphology of the PMMA polymer particles was determined by optical microscopy with a Nikon SMZ 800 stereo microscope and the particles were classified into different ranges of particles size using a sets of sieves in an ATM Co. Sonic Sifter and stored.

Mixing Tests

Mixing tests were performed to evaluate the efficiency of manual mixing of the recipe components. A small amount of purple dye tracer was added to the test tube prior to the addition of the recipe liquid phase. In these experiments, only MMA, PMMA and the dye tracer powder were used. Mixing experiments were carried out in test tubes for the bone cement preparation. PMMA particles and MMA monomer were weighed separately. Then, a small amount of the dye tracer powder was placed on the top of the PMMA layer in the test tube before addition of MMA. The solid and liquid components were then mixed manually in the test tube. A photographic camera was used to collect snapshots of mixing before the addition of the MMA and after 10, 20 and 40 s of manual mixing.

RESULTS AND DISCUSSION

Influence of PMMA on the Temperature Peak

Initially, a fraction of the experimental plan presented in Table 2 was executed in order to verify the influence of both particle size and average molar mass of the PMMA powder on the temperature profile during the bone cement preparation, as shown in Table 3. Figure 1 shows the results obtained in these experiments. It is possible to observe that the temperature profile and the location and magnitude of the temperature peak during the bone cement preparation may be strongly affected by the average molar mass and particles diameters of the PMMA powder. Experiments 1 and 4 also indicate that the experimental procedure is reproducible, allowing for consistent analysis of preparation effects on the temperature profiles.

Table 3: Experimental factorial plan to analyze the effect of Mw and Dp on the reaction temperature peak.

Exp.	Mw × 10^{-3} (Da)	Dp (µm)	Dp normalized	Mw normalized
1	416	150-212	0	0.3478
2	491	<106	-1	+1
3	491	300-600	+1	+1
4	416	150-212	0	0.3478
5	261	<106	-1	-1
6	261	300-600	+1	-1

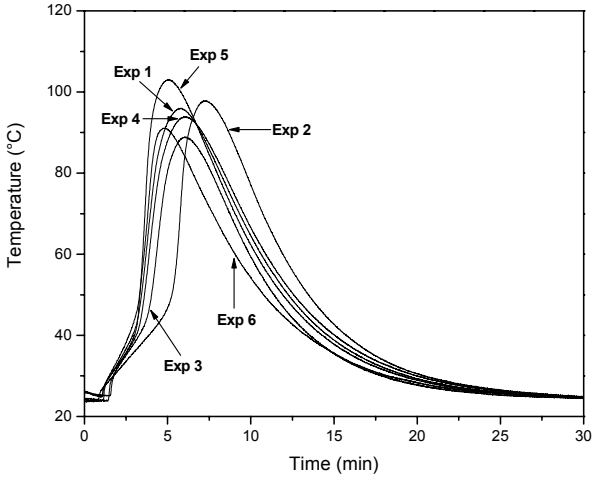


Figure 1: Temperature profiles during bone cement production.

Experiments 2 and 5 and experiments 3 and 6 indicate the influence of the molar mass of the PMMA powder on the obtained results. For both ranges of analyzed particle sizes, the increase of the molar mass led to lower temperature peaks while shifting the peak to longer times. This result may be explained by the fact that the PMMA particles of lower molar mass dissolve more easily in MMA than particles presenting higher molar mass, enhancing the gel effect and leading to higher temperature peaks. One may also note that this effect is more pronounced for smaller sized particles, because small particles may be dissolved in the reaction medium more easily.

Analysis of the effect of particle size may be performed by comparing the pairs of experiments 2 and 3 and experiments 5 and 6. One may note that a consistent temperature difference of at least 10 °C is obtained, regardless of the average molar mass of the particles analyzed. Smaller particles consistently result in higher temperature peaks during the bone cement preparation. This is an interesting result since size distribution is a variable that can be easily controlled in suspension polymerization reactions, through proper manipulation of agitation speed and suspending agent concentration.

Another interesting point regards the location of the temperature peak on the temperature profile during the bone cement production. As presented in Figure 1, experiments 2/5 and 3/6 (variable Mw for constant particle diameter - Dp) and experiments 2/3 and 5/6 (variable Dp for constant Mw) show that decreasing the particle size or increasing the molar mass of the PMMA powder can lead to acceleration of the reaction rates. These results can also be explained in terms of the gel-effect, as explained previously.

The results presented in Table 3 were used to build empirical models with the help of Statistica 6.0 (Statsoft Inc., 2007), in order to understand the influence of both molar mass and particle diameter of the PMMA powder on the temperature profile during the bone cement preparation. The temperature peak can be described as a function of the average molar mass and particle size of the PMMA powder in the form of Equation (1)

$$T_{máx} = a_0 + a_1 \cdot D_p + a_2 \cdot M_w , \quad (1)$$

where the parameters a_0, a_1 and a_2, presented in Table 4 and were obtained through standard least squares regression.

Table 4: Fitted parameters of the temperature peak equation.

$a_0 \pm SD_{a0}$	$a_1 \pm SD_{a1}$	$a_2 \pm SD_{a2}$
95.4 ± 0.5	-5.2 ± 0.6	-1.8 ± 0.6

The negative values of parameters a_1 and a_2 confirm that there is an inverse relationship between the temperature peak and the molar mass and particle size of the PMMA powder, reinforcing the previous observation that particles presenting smaller sizes (for a given Mw) or lower average molar mass (for a given Dp) can be dissolved more easily in MMA, leading to an enhanced gel effect during the bone cement reaction preparation and, therefore, inducing a large temperature peak. It is important to observe that the influence of the particle size on the temperature peak is much more significant than the influence of the average molar mass, which suggests that particle size plays a more important role than molar mass on the magnitude of the peak.

The reaction time when the temperature peak is attained is another important factor, as it also may provide information about the reaction course and,

consequently, may allow for more appropriate manipulation of the bone cement in a real clinical application. Equation (2) and Table 5 present the time of the temperature peak as a function of the average molar mass and particle size and the fitted parameters, respectively

$$t = b_0 + b_1 \cdot D_p + b_2 \cdot M_w . \quad (2)$$

Table 5: Fitted parameters of the temperature peak time equation.

$b_0 \pm SD_{b0}$	$b_1 \pm SD_{b1}$	$b_2 \pm SD_{b2}$
5.7 ± 0.1	-0.3 ± 0.1	0.8 ± 0.1

The positive value obtained for the parameter b_2 confirms a direct relationship between the temperature peak time and the average molar mass, while the negative value of the parameter b_1 shows the inverse relation between the temperature peak time and the particle size, as discussed previously.

The results presented in this section clearly show that the properties of the PMMA particles can strongly affect the temperature profiles during the bone cement preparation. It is important to emphasize, though, that these properties can be easily controlled during the suspension polymerization reactions, allowing for proper design of the bone cement recipe. Although some temperature peaks higher than 90 ºC were obtained and the international standards establish 90 ºC as a maximum temperature for the setting of bone cements, one should consider that the main purpose of this study was evaluate the general effect of process variables on the preparation of artificial bone cements.

Influence of Contrasts

In order to investigate the influence of the radiopaque contrast on the temperature profile during the preparation of the bone cement, experimental runs were performed in the presence of known amounts of contrast (experiments 8/9 in Table 2) and results were compared to those obtained from a blank experiment (experiment 7 in Table 2). Figure 2 shows that addition of either $BaSO_4$ or ZrO_2 to the bone cement recipe caused the reduction of the temperature peak and a shift of the temperature peak towards shorter times. This can be explained by the fact that the fillers are chemically inert, but absorb part of the heat released during the reaction. One must also note that ZrO_2 exerts a more pronounced effect on the temperature profile than $BaSO_4$, which can be explained in terms of the thermal properties of the fillers. It must be pointed out that these radiopaque contrasts have been shown to impart different mechanical properties to the final bone cement pieces, as presented in the open literature (e.g., Hass *et al*., 1975; Bhambri and Gilbertson, 1995; Molino and Topoleski, 1996; Vazquez *et al*., 1997; Ginebra *et al*., 2002; van Hooy-Corstjensa *et al*., 2004).

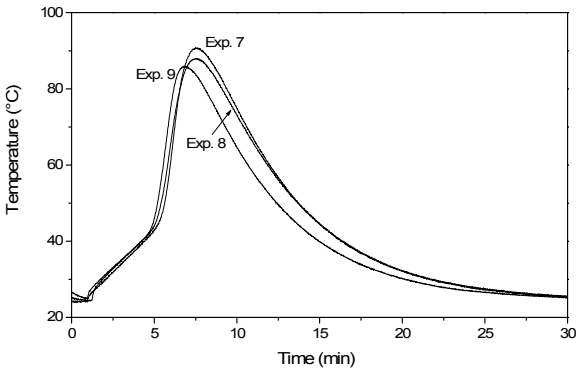


Figure 2: Influence of the radiopaque contrast on the temperature profile.

Influence of Comonomers

It is well known that the addition of comonomers to polymerization reactions may not only provide enhanced end-use properties of polymer resins but may also affect dramatically reaction rates during polymerization (Odian, 2004). Typical comonomers for the bulk polymerization of MMA include AA and MA. For this reason, as shown in Table 2, 10% (w/w) of the MMA was replaced by AA and MA in experiments 10 and 11, respectively. Figure 3 clearly shows that both comonomers analyzed exerted similar influences on the temperature profile during the preparation of the bone cement: the comonomer caused the strong increase of the temperature peak and the acceleration of reaction rates, leading to shorter working times. These results can be explained in terms of the higher reactivities of such monomers, as compared to the bulk reactivity of MMA (Brandrup *et al*., 1999). The observed comonomer effects can be considered advantageous if the controlled addition of comonomer to the recipe can cause the acceleration of the cement preparation and provide enhanced monomer conversions (reducing the residual monomer in the final piece). This certainly is a desirable feature, although the analysis of the temperature profile is not sufficient to guarantee that the residual monomer content of the final bone cement piece will be smaller.

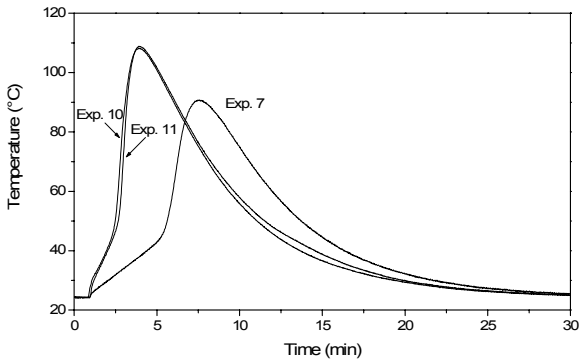


Figure 3: Influence of the co-monomers on the temperature profile.

Influence of Hydroxyapatite

As discussed previously, the introduction of mineral particles in the formulation of bone cement recipes may constitute an excellent alternative to reinforce polymer resins due to the highly desirable biocompatibility of HA with the bone tissue (Ogiso *et al*., 1993). In Table 2, experiment 12 has been designed to include a certain amount of HA in the bone cement recipe. The result for this experimental run is presented in Figure 4.

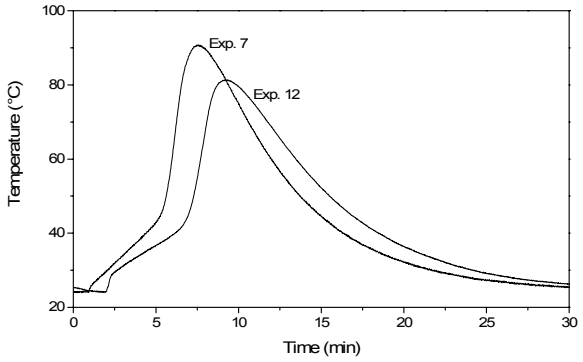


Figure 4: Influence of HA on the temperature profile.

It can be observed that the addition of HA caused a significant decrease of the temperature peak and an increase of the temperature peak time. This is an interesting result, since HA is assumed to be a chemically inert material. Therefore, as observed in the case of adding radiopaque contrasts to the bone cement recipe, sharp temperature effects were not expected. However, it has been reported by others that addition of HA to the cement formulation can cause a decrease of the curing temperature (Giunti *et al*., 1983, Castaldini and Cavallini, 1985, Mongiorgi *et al*., 1993, Serbetci *et al*., 2004), although it should not affect the curing time (Viano *et al*., 2001). The result presented in Figure 4 may suggest that, different from the radiopaque materials, HA may be interacting with MMA during the reaction. It must be emphasized, though, that the introduction of HA into the recipe can also constitute an alternative to control the reaction temperature peak and the peak time during the production of the bone cement.

Influence of Heat Transfer

Due to the highly exothermic features of typical bulk polymerization reactions, heat transfer is an important aspect during the *in-situ* production of artificial bone cements, as addressed in this manuscript. Laboratory controlled simulation of the real clinical production of bone cements is a quite complex task, mainly due to the difficulty of emulating the geometry of the injection system as well as the surgical environment. Both variables can exert a dramatic influence on the heat transfer rates during the polymerization. However, the most important effects related to heat transfer can be analyzed with simple laboratory glassware.

In all experiments discussed so far, bone cement production was performed in glass test tubes. In order to obtain an increased heat transfer area during the reaction, an experimental run was performed in a 50 mL beaker (experiment 13 in Table 2). One can note that the experimental conditions for this run are the same used for experiment 5. The temperature profiles for these experiments are presented in Figure 5.

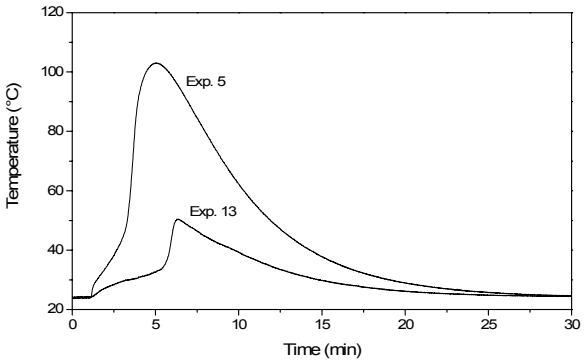


Figure 5: Influence of heat transfer on the temperature profile.

A dramatic temperature drop along the whole reaction can be observed, leading to a reduction of about 50 °C in the temperature peak. However, the temperature peak time was essentially the same, indicating that the gel-effect was not affected by the vessel geometry. This can be regarded as a very important result as it suggests that the geometry of

the injection system can be used to control the production of the bone cement at a clinical site. Therefore, it is possible to conclude that the typical problems related to the reaction temperature profiles can be minimized only through the adequate tuning of the preparation methodology of the bone cement.

Mixing Tests

Mixing of the bone cement recipe components is now analyzed. Mixing is a fundamental operation in many chemical and biological systems and, for the application discussed in this manuscript, mixing plays an important role. It is desirable to understand the effect of particle morphology, more specifically the particle shapes and size on the mixing efficiency of the mixture components. Table 6 shows the set of experimental runs carried out for that sake. Experimental procedures were described in the previous sections.

Table 6: Experimental runs for the mixing tests.

Exp.	MMA (g)	PMMA			Shape
		Type	m (g)	Dp (μm)	
1	1.0	1	1.5	106-150	Spherical
2	1.0	1	1.5	212-300	Spherical
3	1.0	3	1.5	106-150	Spherical
4	1.0	4	1.5	106-150	Irregular

Figures 6 and 7 (related to experimental runs 1 and 2 of Table 6) can be analyzed in order to evaluate the role played by the particle size on the degree of mixing of the recipe components. Figures 6(a) and 7(a), both taken after 10s of mixing, show the notable effect of smaller particles allowing fast homogenization of the mixture. Indeed, even after 40 s of mixing (Figures 6(b) and 7(b)), complete homogenization of the mixture with larger particles had not yet been achieved (note the white particles of PMMA at the test tube wall). This result suggests that the bone cement formulation should have relatively smaller PMMA particles in order to maximize the homogenization of the bone cement mixture. However, a pronounced decrease in the mean size of the PMMA particles may result in very high temperature peaks, as discussed previously.

The effect of the average molar mass on the efficiency of mixing may be determined from the analysis of tests 1 and 3 (Figures 6 and 8, respectively). It can be observed that PMMAs of higher average molar mass provide better homogenization of the recipe components. This intriguing behavior lies in the fact that PMMA particles with lower average molar mass are dissolved more easily in the reaction medium, as discussed previously, resulting in higher viscosities and an enhancement of the gel-effect. Therefore, as is well known from systems presenting a strong gel-effect, mixing becomes a quite challenging task (Odian, 2004). It should be pointed out, though, that utilization of relatively larger particles may not be very interesting for bone cement preparation because partial dissolution may result in a heterogeneous bone cement piece, which is certainly not desired.

Although it has been verified that both the average molar mass and the size of the PMMA particles affect the degree of mixing of the bone cement components, the main influence on the mixing procedure was found to be the shape of the particles (Figure 9). Although there are a considerable number of studies regarding the influence of PMMA particle characteristics on the final properties and also the curing process of the bone cement, very scarce information is available about the role played by the particle morphology (Park and Lakes, 1992). Experimental test 4 was designed to evaluate the mixing performance when non-spherical PMMA particles are used.

(a)

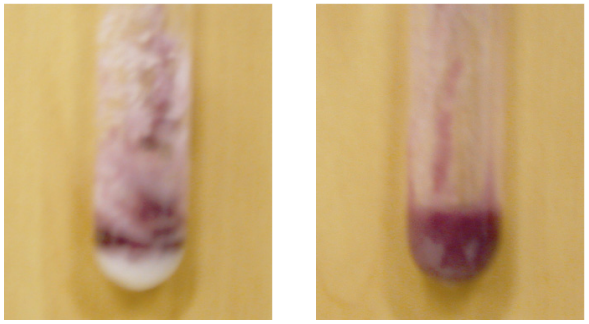
(b)

Figure 6: Mixing test 1: photographs taken after (a) 10s and (b) 40s.

(a)

(b)

Figure 7: Mixing test 2: photographs taken after (a) 10s and (b) 40s.



(a) (b)

Figure 8: Mixing test 3: photographs taken after (a) 10s and (b) 40s.

(a) (b)

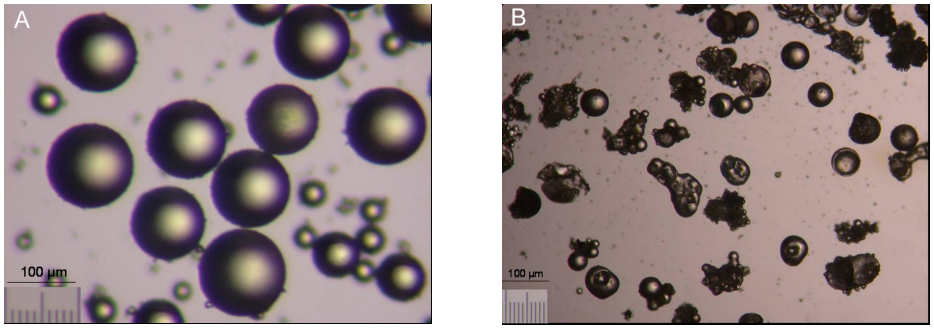
Figure 9: Mixing test 4: photographs taken after (a) 10s and (b) 40s.

Figure 10 shows the optical micrographs of both PMMA 1 and PMMA 4, used in experimental tests 1 and 4, respectively.

A comparison of Figures 6 (spherical particles) and 9 (non-spherical particles) clearly shows that irregular PMMA particles lead to a quite inefficient homogenization of the recipe components. This is a very important result, as it suggests that the manipulation of the bone cement could be strongly affected by the PMMA particle morphology. Despite being quite simple, these tests provide a more adequate assessment of the PMMA particles to be used in the bone cement preparation.

Summary of Observed Effects

Table 7 presents a summary of the variables and the respective effects analyzed in this work. Clearly, the production of artificial bone cements can be affected by a considerable number of variables. Trade-offs are very often found during the manipulation of these variables due to the multi-objective nature of the experimental problem. An unique optimized recipe for bone cement is thus not possible, but the understanding of the individual effects of these variables is certainly mandatory for the production of enhanced bone cement pieces.



(a) (b)

Figure 10: Optical microscopy of PMMA 1 (left) and PMMA 4 (right).

Table 7: Summary of the effect of the variables on the bone cement preparation.

Variables	Increase Mw	Increase Dp	Spherical Shape	Add Contrast	Add Comonomers	Add Hydroxyapatite	Increase Area/Volume Ratio
Temperature peak	↓	↓	-	≈↓	↑	↓	↓
Peak time	↑	↓	-	≈↓	↓	↑	≈↓
Mixing efficiency	↑	↓	↑	-	-	-	-

↑ Increase; ↓ Decrease; ≈ Small effect; - Effect not analyzed.

CONCLUSIONS

A detailed systematic experimental investigation of the preparation of PMMA-based artificial bone cements has been presented. It has been shown that the temperature profile and the location and magnitude of the temperature peak during bone cement preparation may be strongly affected by the average molar mass and particle diameter of the PMMA used. The increase of the molar mass leads to lower temperature peaks while shifting the peak to longer times. This effect is more pronounced for smaller sized particles, because small particles may be easily dissolved in the reaction medium. As far as the presence of contrasts in the reaction medium, the addition of either $BaSO_4$ or ZrO_2 to the bone cement recipe caused a small reduction in the temperature peak as well as a small shift towards shorter times. Co-monomers increased strongly the temperature peak of the reaction. Also noticeable is the fact that the reaction became faster with the addition of comonomers, which would lead to shorter working times during a bone cement clinical application. Regarding the addition of hydroxyapatite, a significant decrease in the temperature peak magnitude and an increase in the temperature peak time were observed. Therefore, the introduction of hydroxyapatite into the recipe may be considered to be another alternative to properly control the reaction temperature peak, as well as the time it occurs during the production of the bone cement. Another interesting result was the effect of a change in the heat transfer area of the mixing vessel. Increasing the area/volume ratio of the mixing vessel caused a dramatic drop in the overall temperature profile. In contrast, the temperature peak time was barely modified, implying that the gel-effect was not affected by the new vessel geometry. Therefore, it is possible to conclude that the typical problems related to the reaction temperature profiles may be minimized only by the adequate tuning of the preparation methodology of the bone cement. Regarding the mixing tests, the important observations are that relatively higher average molar mass and smaller particle sizes promote a better homogenization of the mixture constituents. In addition, it has been shown that irregular PMMA particles lead to a quite inefficient homogenization of the recipe components. This is a very important result, because it suggests that the manipulation of the bone cement could be strongly affected by the PMMA particle morphology.

ACKNOWLEDGEMENTS

The authors thank the CNPq – Conselho Nacional de Desenvolvimento Científico e Tecnológico, FAPERJ – Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro, CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior and FINEP – Financiadora de Estudos e Projetos, for providing scholarships and supporting our work.

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