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PRODUCTION OF BONE CEMENT COMPOSITES: EFFECT OF FILLERS, CO-MONOMER AND PARTICLES PROPERTIES

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Abstract - Artificial bone cements (BCs) based on poly(methyl methacrylate) (PMMA) powders and methyl methacrylate (MMA) liquid monomer also present in their formulation small amounts of other substances, including a chemical initiator compound and radiopaque agents. Because inadequate mixing of the recipe components during the manufacture of the bone cement may compromise the mechanical properties of the final pieces, new techniques to incorporate the fillers into the BC and their effect upon the mechanical properties of BC pieces were investigated in the present study. PMMA powder composites were produced *in-situ* in the reaction vessel by addition of X-ray contrasts to the reacting MMA mixture. It is shown that this can lead to much better mechanical properties of test pieces, when compared to standard bone cement formulations, because enhanced dispersion of the radiopaque agents can be achieved. Moreover, it is shown that the addition of hydroxyapatite (HA) and acrylic acid (AA) to the bone cement recipe can be beneficial for the mechanical performance of the final material. It is also shown that particle morphology can exert a tremendous effect upon the performance of test pieces, indicating that the suspension polymerization step should be carefully controlled when optimization of the bone cement formulation is desired.
Keywords: Biomaterials; Artificial bone cement; Radiopaque contrast; Mixing; PMMA; Suspension polymerization.

INTRODUCTION

Poly(methyl methacrylate) (PMMA) can be produced through standard solution, suspension and emulsion polymerization processes. PMMA is completely amorphous but has high strength and excellent dimensional stability due to the rigid polymer chains. PMMA has exceptional clarity, very good weatherability and good impact resistance, can be machined and is resistant to most chemicals, although it can be attacked by organic solvents (Odian, 2004). Due to the adequate combination of the mentioned properties, together with its good biocompatibility and ease of manipulation, PMMA is very often used in medical applications, which include the fabrication of internals for blood pumps, blood reservoirs and membranes for blood dialyzers and in *vitro* diagnostics (Lee *et al*., 1995). Its optical properties also make PMMA an excellent material for the manufacture of implantable ocular lenses and contact lenses, while its physical and colouring properties make PMMA a good denture material (Park, 1995).

In 1936 it was found that the mixing of ground PMMA powder with liquid monomer resulted in the

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formation of a doughy material (Kühn, 2000). This is due to the partial dissolution of PMMA in its monomer. Besides, when initiator is added to the mixture, polymer chains that constitute the PMMA powder participate in the free radical polymerization reactions, forming entanglements with newly formed chains. This leads to an intimate chemical connection between the new and the previously formed PMMA chains (Hendriks *et al*., 2004). Since then, the term bone cement has been used to designate PMMA and methyl methacrylate (MMA) based mixtures (and mixtures with other acrylate compounds), prepared in the presence of initiators. Due to the high viscosity of bone cement mixtures, these blends can be successfully injected into bone cavities in order to correct structural bone failures (Vazquez *et al*., 1998).

John Charnley was the first physician to use PMMA as an artificial bone tissue in 1958, in surgeries for total hip replacements (Black, 1988). Today, according to the American Academy of Orthopaedic Surgeons (AAOS, 2008), more than 193,000 total hip replacements are performed each year in the United States alone, and similar surgical procedures are performed on other joints, including the knee, shoulder, and elbow. Although small changes have been introduced into the formulation of the basic bone cement material and its usage, since Charnley's pioneering work, bone cement recipes remain essentially the same. The most important change was the addition of X-ray contrasts, like barium sulfate ($BaSO_4$) and zirconium dioxide (ZrO_2), to render the bone cement material radiopaque.

The typical PMMA-based bone cement is prepared in the operating room, during the clinical intervention, through the free radical bulk polymerization of 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), used to provide a radiographic contrast during the clinical application of the BC, and PMMA particles, used to increase the initial viscosity of the reaction medium and to accelerate the polymerization reaction due to the gel effect. Typical commercial bone cement brands contain PMMA particles with mean particles sizes in the range 30-150μm, e.g., Simplex P (34 μm), CMW 1 (44 μm), and Palacos R-40 (55 μm) (Planell *et al*., 1995; Morejón *et al*., 2005; Liu *et al*., 2003). The recipe can also be enhanced by the addition of other inorganic fillers, such as hydroxyapatite (HA), as well as co-monomers (such as acrylic acid, AA), to be discussed later, in order to reinforce the final BC piece mechanically (Ogiso *et al*., 1993), and coloring agents for visualization of the bone cement during the procedure.

The bone cement preparation begins by mixing the recipe components in a vessel (typically a medical bowl). The system viscosity and the reaction rate increase quickly due to the gel effect, which is greatly enhanced by the presence of the PMMA particles. 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 great amount of heat released during the bone cement preparation, which may cause the reaction temperature to increase above 100°C, possibly leading to irreparable damage of living tissues (Pascual *et al*., 1996). However, alternative preparation procedures have been suggested in order to reduce the high temperatures that may be reached during the bone cement preparation, such as the reduction of the operating room temperature (Meyer *et al*., 1973), the manipulation of the MMA / PMMA ratio (Haas *et al*., 1975) and the usage of cold chemicals (Dipisa *et al*., 1976; Toksvig-Larsen *et al*., 1991; Maffezzoli, 1997).

In order to meet clinical requirements, bone recipe components must undergo sterilization procedures prior to application. The most common sterilization procedures used include gamma irradiation (e.g., as used by the Simplex P brand), ethylene oxide gas (e.g., as used by the Palacos R brand), and formaldehyde tablets (e.g., as used by the Sulfixt-60 and Duracem 3 brands) (Harper And Bonfield, 2000). It should be noted that the mechanical properties of the bone cement can be affected by the choice of the sterilization procedure, as reported by Lewis and Mladsi (1998). More specifically, for the case of the Palacos R brand, Lewis and Mladsi (1998) observed that both weight-average molar masses and fatigue performance of the BC were significantly lower when ethylene oxide gas was applied, probably because of the higher operational temperatures and possible oxidative degradation.

Addition of radiopaque agents into bone cement recipes is necessary for clinical reasons (in order to allow for real time monitoring of the medical intervention). However, due to the very different properties of these inorganic compounds and to the poor compatibility with the polymer matrix, the mechanical behavior of the final pieces can be strongly affected by these materials. Van Hooy-Corstjensa *et al*. (2004) verified that it is very

important to obtain a good contrast distribution throughout the polymeric matrix in order to avoid degradation of the mechanical properties. However, the dispersion of inorganic fillers in the polymer matrix is frequently heterogeneous, so that clumps of inorganic radiopaque agents are often present (Van Hooy-Corstjensa *et al.*, 2004) and can initiate the formation of cracks (Bhambri and Gilbertson, 1995). It has been verified that the presence of small particles of $BaSO_4$ in the BC may result in an increase in the fracture propagation resistance promoted by fatigue (Molino and Topoleski, 1996, Ginebra *et al.*, 2002). Furthermore, it has also been shown that the presence of $BaSO_4$ particles may reduce the tensile strength of the bone cement as compared to radiolucent cements (Ginebra *et al*., 2002; Haas *et al*., 1975; Vazquez *et al*., 1997). As a result, the fatigue life of the bone cement can be drastically lowered. This also means that the presence of these inorganic particles contributes to aseptic loosening of the prosthesis (Krause and Mathis, 1988). Contrast particle size may also play a role in the determination of the mechanical properties of the bone cement. As shown by Bellare *et al*. (2005), nanocomposite cement recipes, i.e., produced with nanosized $BaSO_4$ particles, have a fatigue life of over twice that of the typical BC.

Therefore, it is well-established that a better dispersion of the radiopaque agents is of fundamental importance to ensure the desired mechanical properties of BC pieces. In the literature it is clear that the dispersion of these agents tends to be inhomogeneous and thus care should be taken to prevent inadequate mixing of the mixture components. In this scenario, new methods to improve dispersion of the radiopaque agents in the BC mixture are of practical interest.

Regarding the commercial method used to incorporate $BaSO_4$ or ZrO_2 particles into the BC formulation, one can only rely on the open literature provided by the manufacturers. Because of formulation protection by the manufacturer, information is often limited in scope. However, some brands indicate that $BaSO_4$ or ZrO_2 particles are present in the powder in a certain weight fraction (e.g., Simplex®, Orthoset®, Cemfix®, Gentafix®), whereas others either state only that the $BaSO_4$ or ZrO_2 particles are provided "premixed" with the powder in a certain weight fraction (e.g., Concert®) or simply do not provide any detailed information regarding this aspect of the recipe (Medcompare, 2008).

The lack of adherence between the inorganic particles and the polymeric matrix is another problem during bone cement formulation. Due to this incompatibility with the polymeric matrix, the contrast forms a segregated phase and makes mixing of reagents more difficult during the preparation. For this reason, some authors have suggested the use of alternative contrasts, such as iodine (Almén, 1995; Davy *et al.*, 1997; Davenport *et al*., 1999; Ginebra *et al*., 2002; Nakamura *et al*., 2003; Artola *et al.*, 2004; Kjellson *et al.*, 2004; Van Hooy-Corstjensa *et al*., 2004) and/or bismuth (Rawls *et al*., 1996; Deb *et al*., 2002) based compounds. These compounds are chemically linked to specially designed monomers and are thus automatically incorporated into the BC formulation. However, because most commercial BC formulations are still based on $BaSO_4$ (or ZrO_2) radiopaque contrasts, iodine and bismuth based radiopaque compounds are not investigated in the present manuscript.

In order to increase the mechanical strength and improve the final properties of the bone cement, additives like fibers (Woo *et al*., 1974; Pilliar *et al*., 1976; Topoleski *et al*., 1992), metals (Fishbane and Pond, 1977; Topoleski *et al*., 1992) and other polymers (Pourdeyhimi and Wagner, 1989, Yang *et al*., 1997; Vila *et al*., 1999) have been incorporated and tested in some formulations. The addition of mineral particles has been investigated as well. Among these, hydroxyapatite (HA) can be regarded as an excellent alternative material for reinforcement of the bone cement composites, due to its good biocompatibility with the bone tissue (OGISO *et al*., 1993). Significant improvements of bone cement properties have been reported in the literature when HA particles are added to typical bone cement formulations (Castaldini and Cavalini, 1986; Perek and Piliar, 1992; Liebendörfer *et al*., 1995; Vallo *et al*., 1999).

Harper *et al*. (1995) reported that up to 40% (w/w) of HA particles can be incorporated in the formulation of BCs, leading to an enhancement of their mechanical strength (in terms of flexural strength and modulus). Similarly, Castaldini and Cavallini (1986) showed that up to 12.5% may be added to the BC recipe, resulting in an increase in the mechanical resistance of the material. Liebendörfer et al. (1995) investigated the *in vivo* performance of a modified commercial BC formulation by adding 14% (w/w) of HA and verified improvements in biological properties as well as biocompatibility between the BC and biological bone. Perek and Piliar (1992) obtained an increase in the fracture resistance after adding up to 40% (w/w) of HA to the BC recipe. In addition, Lee *et al.* (1997) showed that by adding 50% (w/w) of

HA to the basic BC formulation a better bonding between cement and biological bone is achieved.

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 to the bone recipe has been overlooked in the literature, even though many commercial bone recipe kits include co-polymers in their formulation (Hendriks *et al*., 2004). Co-monomers may be added in small amount to the reaction medium in order to enhance the polymerization rates and the gel effect, thus accelerating the bone cement curing process. Besides, 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). Therefore, because of their particular features, the presence of co-monomers in the reaction medium during the production of bone cements is another point of interest to be considered in the present work.

In a previous work, Santos *et al*. (2006) proposed the *in situ* incorporation of contrast (and other fillers) during the suspension polymerization performed to produce the PMMA particles. The results obtained showed that the bone cement produced with this PMMA powder is more homogeneous and stronger than the bone cement produced from the hand-mixing of the PMMA and $BaSO_4$ particles during the preparation, here called *ex situ* preparation.

The objective of the present study is to carry out an experimental investigation to analyze in detail how the *in situ* contrast ($BaSO_4$ or ZrO_2) incorporation and the addition of other components to the recipe (HA, as a filler, and AA, as a co-monomer) affect the mechanical strength of the final bone cement. Moreover, it is also desirable to evaluate the importance of the shape of the PMMA particles on the final performance of the bone cement material. In order to accomplish these objectives, an experimental strategy has been designed to allow for the manipulation of the radiopaque incorporation method (*ex situ* × *in situ*), the presence of HA and AA in the reaction medium, the average molar mass (MW) and mean particle diameter (DP) of the PMMA powder, and also the shape of these PMMA particles. Different MWs and DPs were tested to allow for a better understanding of their role on the BC mechanical properties investigated. Particles with different morphologies follow the same principle. It is shown that the *in situ* incorporation of contrasts and fillers during the suspension polymerization process exerts a pronounced beneficial effect on the final performance of the bone cement composites. It is also shown that the use of HA and AA in bone cement formulations can significantly improve the properties of the obtained material.

MATERIALS AND METHODS

Chemicals

Monomer MMA (polymer grade) was provided by Rhodia with a minimum purity of 99.9%. The suspending agent poly(vinyl alcohol) (PVA), with a weight-average molar mass of 78kDa 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%. Monomer AA (polymer grade) was provided by Rhodia with a minimum purity of 99.9%. Octanol was supplied by Sigma with a minimum purity of 99%. Absolute ethanol P.A was provided by Vetec with a minimum purity of 99.8%. Hydroxyapatite was synthesized by the inverse precipitation method, following Shimoda *et al*. (1990) and supplied by NUCAT/COPPE/UFRJ. MMA was distilled at reduced pressure. Other chemicals were used as received without additional purification.

PMMA Particle Production and Characterization

Suspension polymerization reactions were performed to produce the PMMA particles used in the BC formulation, as shown in Table 1. Two kinds of suspension polymerization runs were performed: one using pure MMA monomer to produce PMMA powder for the *ex situ* BC formulation (cf. PMMA grades 1, 2 and 5 in Table 1); and another one using a mixture of MMA monomer and either $BaSO_4$ or ZrO_2 to produce a blend of PMMA-radiopaque agent powder for the *in situ* BC formulation (cf. PMMA grades 3, 4, 6 and 7 in Table 1). Radiopaque agents were added to the reactor vessel as a suspension in the pure MMA monomer. Poly(vinyl alcohol) was used as suspension agent and BPO as initiator. After the production of a given batch of PMMA particles, the reactor content was filtered and washed with distilled water repeatedly and afterwards vacuum dried at room temperature. Since the effluent was

found to be limpid and crystalline after each filtration step, the loss of radiopaque agent was considered to be negligible. Finally, particles were classified into different ranges of particles sizes using sets of sieves in an ATM Co. Sonic Sifter and stored.

The conversion level in each experiment presented in Table 2 was determined by taking into account the total amount of MMA added to the reactor and the total amount of dry PMMA particles obtained, assuming total incorporation of radiopaque contrasts, as discussed above. Two conversion values are of particular importance, namely, for PMMA 3, 89.43% (w/w), and PMMA 4, 81.28% (w/w), as these particles are used to produce bone cements by the *in situ* method and are compared to the test pieces produced by the *ex situ* method later on in this paper. Therefore, for PMMA 3 and 4, one can calculate that the weight fractions of incorporated contrasts are, approximately, 0.23 and 0.25.

One may notice that different amounts of the BPO polymerization initiator were used in order to produce the PMMA particles with different average molar masses. As discussed previously, the impact of particle morphology, average molar mass and mean diameters on the mechanical properties of the BC are also investigated in this work.

As shown in Table 2, it is possible to group the PMMA grades obtained into two main groups: in the first one, samples present high weight-average molar mass (Mw), including a pure PMMA grade (PMMA 2), a PMMA grade with *in situ* incorporated $BaSO_4$ (PMMA 3) and a PMMA grade with *in situ* incorporated ZrO_2 (PMMA 4); in the second one, samples present low Mw, including a pure PMMA grade (PMMA 5), a PMMA grade with *in situ* incorporated $BaSO_4$ (PMMA 6) and a PMMA grade with *in situ* incorporated ZrO_2 (PMMA 7). It should be pointed out here that, except for the reaction designed to produce the grade PMMA 1 in Table 1, all suspension polymerizations were conducted with extremely high agitation frequencies in order to produce irregular polymer particles of different sizes. This was done on purpose, in order to observe whether the morphology of the PMMA powder would affect the final performances of the bone cements. The agitation frequency was carefully designed to produce spherical particles for grade PMMA 1, which has the same weight-average molar mass as grade PMMA 2.

Reactions were carried out in a heated stirred tank glass reactor. An aqueous solution of PVA was added to the reactor. After temperature stabilization, a solution of BPO in MMA monomer (which may contain the suspended $BaSO_4$ or ZrO_2 particles) was added to the reactor. Figure 1 shows typical Scanning Electron Microscopy (SEM) analyses of PMMA 3 (left) and PMMA 4 (right), respectively. It can be seen that the surfaces of the PMMA particles are covered by $BaSO_4$ and ZrO_2.

Table 1: Recipes of the suspension polymerization reactions (all reactions performed at 85°C using a straight blade impeller).

PMMA	MMA (g)	BPO (g)	PVA solution(g)		$BaSO_4$ (g)	ZrO_2 (g)	Agitation (rpm)
			1g/L	2g/L			
1	150	1	450	-	-	-	800
2	300	2	-	900	-	-	1500
3	300	2	-	900	80	-	1500
4	300	2	-	900	-	80	1500
5	300	8	-	900	-	-	1500
6	300	8	-	900	80	-	1500
7	300	8	-	900	-	80	1500

- None.

Table 2: Characterization of the PMMA powders.

PMMA	Mw (10^{-3} Da)	Polydispersity (I.P.)	Radiopaque Agent
PMMA 1	491	6.1	none
PMMA 2	486	3.58	none
PMMA 3	515	3.55	$BaSO_4$
PMMA 4	508	4.03	ZrO_2
PMMA 5	135	4.45	none
PMMA 6	230	3.00	$BaSO_4$
PMMA 7	232	2.93	ZrO_2

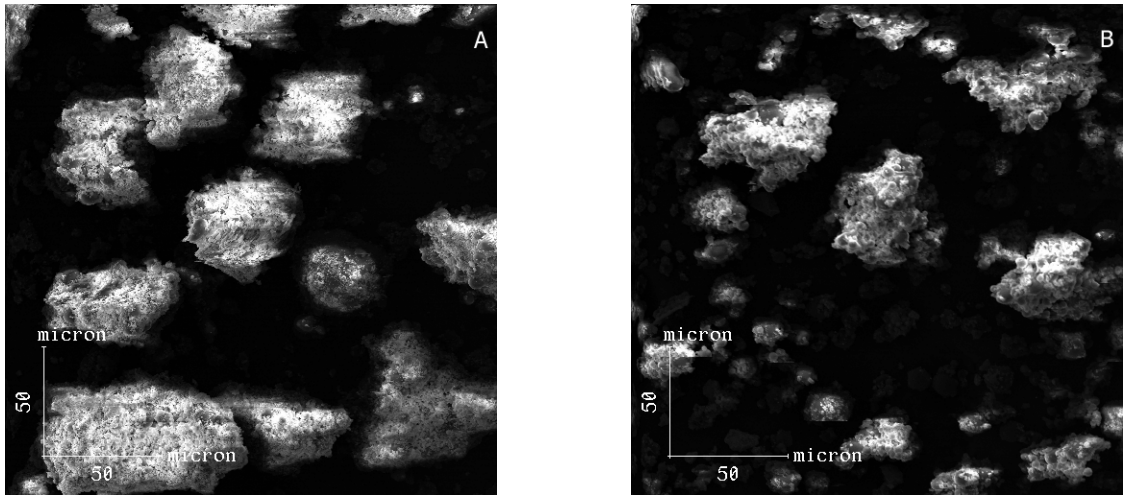

Figure 1: SEM analyses of PMMA 3 (A) and PMMA 4 (B).

Preparation of Bone Cement Test Pieces

Bone cements were produced through free radical bulk polymerization using an initiator (BPO)-activator (DMPT) system. The experimental procedure to obtain the BC test pieces consisted, first, of the preparation of the bone cement mixture and, then, of filling the BC molds. The reactions were carried out in small 50-mL glass vessels. Solid and liquid components were weighed separately. Solid materials were mixed manually before addition of the liquid components. It should be noted here that, if the PMMA powder added to the mixture contained blended radiopaque agents, then the mixing procedure is of the *in situ* type. Otherwise, if PMMA and radiopaque agent powders were added individually to the mixture, then the mixing is of the *ex situ* type, as discussed previously. Depending on the formulation, it is possible in this step to add a filler to the mixture, such as HA, or a second liquid monomer, such as AA. In the case of addition of a second monomer, this would be mixed separately with liquid MMA monomer. After preparation of the solid and liquid mixtures, both were mixed manually in glass vessels for about 45-60s until a homogeneous dough was obtained. Mixing was conducted as normally performed in real surgery rooms. After that, the mixture was carefully transferred to the mold in order to avoid formation of air bubbles and reaction was conducted for 30min. Finally, it is important to stress out that the general characteristics of conversion and temperature dynamics during the bone cement reactions described above are similar to those reported by Santos *et al.* (2006).

Characterization of the Cement Powders and Cured Cements

The weight-average molar mass (Mw) of the polymer samples (either a PMMA powder sample or a BC powder sample) was determined through gel permeation chromatography (GPC). The system was composed of a chromatograph (Waters 600E), three columns (Ultrastyragel) and a refractometer (Waters 2414). The calibration curve was constructed using samples of polystyrene with Mw ranging from 500 to 3×10^6 Dalton and a polydispersity index lower than 1.05. Tetrahydrofuran was used as the mobile phase and the analyses were carried out at 40°C. The morphology of the PMMA powder particles was determined by optical microscopy (Nikon SMZ 800 stereomicroscope) and scanning electron microscopy (JEOL JSM 5300 microscope). The residual MMA content of the cured cement was determined by using a gas chromatograph (Chrompack CP 9000), calibrated using octanol as the internal standard.

After compression tests, three test pieces were randomly selected to undergo evaluation of residual monomer (MMA_R). In order to increase their surface area, the test pieces were frozen with liquid nitrogen for 30s and then carefully smashed to form a powder. This powder was then weighed and delivered to a sealed test tube where an ethanol/octanol solution was added in order to extract the residual monomer content. After 15 days at rest, 0.2 μL samples of this solution were injected into the gas chromatograph, previously calibrated. The relative peaks corresponding to MMA and octanol were then identified to further calculations.

The yield stress or compressive strength (σ_y) and the Young or compressive modulus of elasticity (E) of the cured cement were determined from compressive tests performed on a servohydraulic universal materials testing machine (Instron, model 4204) using cylindrical specimens (diameter and height of 6mm and 12 mm, respectively, in accordance with ASTM 451-86), with the crosshead displacement rate being 20mm/min.

Statistical Methods

The statistical procedure to treat the measurements of mechanical properties (i.e., Young modulus, E, and yield stress, σ_y) simply applied a standard Student t-test to the averages in order to obtain 95% confidence intervals with four degrees of freedom (Pinto and Schwaab, 2007).

RESULTS AND DISCUSSION

The set of experimental runs analyzed in this work is shown in Table 3. The amounts of BPO and DMPT were the same in all runs: 0.075 g and 0.1 g, respectively. In order to represent the different formulations, some abbreviations were adopted, as shown in Table 3. The term "BC" means bone cement, while the subscript abbreviations indicate the added reagents: "H" and "L" indicate high and low Mw, respectively; "D" and "d" indicate the PMMA particle size range, 212-300μm and 75-106μm, respectively; "Ba", "Zr", "AA" e "HA" indicate the addition of barium sulphate, zirconium dioxide, acrylic acid and hydroxyapatite, respectively; the superscript "in" indicates the *in situ* incorporation of contrasts during the suspension polymerization; the subscripts "sph" indicates the spherical shape; the subscript "mod" indicates that a smaller amount of PMMA was used in the bone cement formulation; and the subscript 15d means that the analysis was performed 15 days after the production of the test piece.

The results obtained from the compression tests (to determine final yield stress, σ_y, and Young modulus, E), GPC (to determine weight-average molar masses, Mw, and polydispersion indices, I.P.) and GC analyses (to determine residual monomer content, MMA_R) are also presented in Table 3 and show that the final properties of the bone cement can be strongly affected by the reagents' characteristics, as discussed in the following sections.

Influence of the PMMA Powder

Entries 1-12 in Table 3 present some of the characteristics of the final bone cements that are directly related to the PMMA powder. When one compares pairs of experiments with PMMA powders of distinct size (e.g. Entries 1 and 2), it can be observed that this variable does not exert a significant effect on the final yield stress (σ_y) and Young modulus (E) of the bone cement test pieces in the analyzed range. In all cases, the confidence intervals of the averages overlap each other, indicating that it is not possible to discriminate between the different values with the adopted confidence level (95%). Therefore, particle sizes should be manipulated for control of the thermal responses during bone cement preparations (Santos *et al*., 2006), not for control of the mechanical properties of the bone cement.

Table 3: Experimental conditions for the production of the test pieces and characterization of the bone cements.

Entry #	Test Piece	PMMA	Mw (10^{-3} Da)	MMA (g)	ZrO_2 (g)	PMMA (g)	$BaSO_4$ (g)	HA (g)	AA (g)	σ_y* (MPa)	E* (MPa)	Mw (10^{-3} Da)	I.P.	MMA_R* (w/w %)
1	$BC_{H,d}$	2	486	2.5	-	3.75	-	-	-	81.13±1.39	1975±41.25	260	3.75	3.8102±0.1094
2	$BC_{H,D}$	2	486	2.5	-	3.75	-	-	-	83.63±1.42	1930±151.25	289	5.93	3.7720±0.1694
3	$BC_{H,d,Ba}^{in}$	3	515	2.5	-	3.75		-	-	78.41±1.86	1979±100.00	280	5.53	3.1067±0.2451
4	$BC_{H,D,Ba}^{in}$	3	515	2.5	-	3.75		-	-	79.60±2.86	2036±112.50	303	6.86	3.1799±0.1932
5	$BC_{H,d,Zr}^{in}$	4	508	2.5	3.75		-	-	-	79.07±1.56	1996±86.25	281	7.21	2.9434±0.1045
6	$BC_{H,D,Zr}^{in}$	4	508	2.5	3.75		-	-	-	79.66±1.41	2002±104.00	279	7.79	3.3343±0.1117
7	$BC_{L,d}$	5	135	2.5	-	3.75	-	-	-	92.79±3.22	2109±60.00	100	4.39	1.6155±0.1135
8	$BC_{L,D}$	5	135	2.5	-	3.75	-	-	-	90.83±3.62	2041±163.75	102	4.36	1.4544±0.2185
9	$BC_{L,d,Ba}^{in}$	6	230	2.5	-	3.75		-	-	83.18±1.75	2109±12.50	166	4.86	1.7027±0.1522
10	$BC_{L,D,Ba}^{in}$	6	230	2.5	-	3.75		-	-	83.43±1.70	2084±51.25	206	4.71	1.5719±0.0444
11	$BC_{L,d,Zr}^{in}$	7	232	2.5	3.75		-	-	-	80.47±0.96	2029±53.75	199	5.71	1.4942±0.0770
12	$BC_{L,D,Zr}^{in}$	7	232	2.5	3.75		-	-	-	81.31±1.18	2049±20.00	216	5.39	1.5452±0.0317
13	$BC_{H,d,Ba}$	2	486	2.5	-	2.89	0.86	-	-	71.90±1.51	1928±56.25	354	6.74	2.4172±0.2536
14	$BC_{H,d,Zr}$	2	486	2.5	0.93	2.82	-	-	-	74.35±1.74	1962±70.00	355	7.92	2.8798±0.2153
15	$BC_{H,d,mod}$	2	486	2.5	-	3.00	-	-	-	75.80±1.62	1840±85.00	386	6.55	2.7747±0.2111
16	$BC_{H,d,AA,mod}$	2	486	2.25	-	3.00	-	-	0.25	120.6±4.20	2851±101.25	432	4.61	4.1674±0.2015
17	$BC_{H,d,HA}$	2	486	2.5	-	3.00	-	0.75	-	102.4±1.22	2858±92.50	416	8.73	7.0943±0.1352
18	$BC_{H,d,HA,15d}$**	2	486	2.5	-	3.00	-	0.75	-	123.6±3.25	3116±181.25	--	--	4.9302±0.2473

- None; -- Not measured; * 4 degrees of freedom, confidence level of 95%; ** Analyzed 15 days after the production of the test piece.

When one compares pairs of experiments obtained with PMMA powders of distinct weight-average molar masses (e.g., Entries 1 and 7), it can be observed that test pieces prepared with PMMA grades of lower Mw show higher values of σy and E. It is important to note that the largest differences were obtained for the pair BCH,d / BCL,d (Entries 1 and 7) and the pair BCH,D / BCL,D (Entries 2 and 8), due to the lower Mw of PMMA 5 (compared with PMMA 2, as shown in Table 1). This suggests that the use of a PMMA grade with lower Mw leads to a bone cement with better mechanical properties. This is probably related to the faster solubility of shorter chains in the monomer phase during the reaction, which increases the gel effect, the reaction rates and the size of the newly formed PMMA chains that constitute the polymer matrix. These effects are clearly indicated in Table 3, where one can see the lower contents of residual monomer when PMMA grades of lower Mw are used to prepare the bone cement. Figure 2 illustrates this important result for test pieces prepared with large PMMA particles. It can be seen that MMA conversions are always higher when the bone cements are prepared with the PMMA grades with lower Mw.

The molecular weight analyses performed here concentrated on the molecular weight averages, instead of the full molecular weight distribution, for several reasons. First, the final distributions were always very broad, as one can verify in Table 3, making the final deconvolution (representation of the final MWD as the summation of the MWD of the original PMMA powder and a second MWD curve to be determined) meaningless at times, with computation of multimodal distributions, with modes placed at very distinct molecular weights. Second, the newly formed PMMA chains were subject to strong temperature variations along the batch, due to the almost adiabatic nature of the test piece preparation. As a consequence, deconvolutions performed with the final GPC data could not be unequivocally correlated with the preparation conditions or the original MWD distribution. For these reasons, it was assumed here that the final averages represent the overall system behavior much better than the full deconvoluted MWD.

Figure 3 shows the Mw values of the original PMMA grades and of the respective bone cements prepared with small PMMA particles. It can be observed that smaller differences are observed for bone cements prepared with PMMA grades of low Mw, suggesting that the Mw of the newly formed polymer matrix is indeed larger when the PMMA powder presents lower Mw values. (If one assumes that the Mw of the final bone cement can be computed as the weight-average of the Mw values of the newly formed polymer matrix and of the original polymer powder, Mw values of the matrixes prepared with PMMA grades of low Mw are always larger than the Mw values of the matrixes prepared with PMMA grades of high Mw.)

The effects on the test piece properties caused by the PMMA / MMA ratio and the shape of the PMMA particles are now analyzed. Comparing test pieces BCH,d and BCH,d,mod (Entries 1 and 15), it is possible to conclude that the relative amount of PMMA exerts a pronounced effect on the final properties of the bone cement. The use of smaller amounts of PMMA caused a significant decrease of both σy and E of the final bone cement, as already reported in the literature (Vallo et al., 1998; Belkoff et al., 2002). This is very difficult to explain only in terms of the molecular properties of the bone cement, because the material produced with smaller amounts of PMMA presented higher Mw and lower contents of residual monomer (as also observed by Vallo et al., 1998). Therefore, it may be concluded that the dispersion of the PMMA powder in the polymer matrix is also of fundamental importance for determination of the final properties of the bone cement.

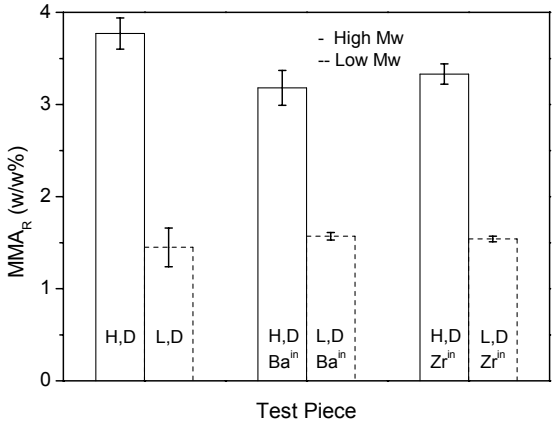

Figure 2: Comparison between the residual monomer contents for test pieces obtained with PMMA grades of high and low Mw.

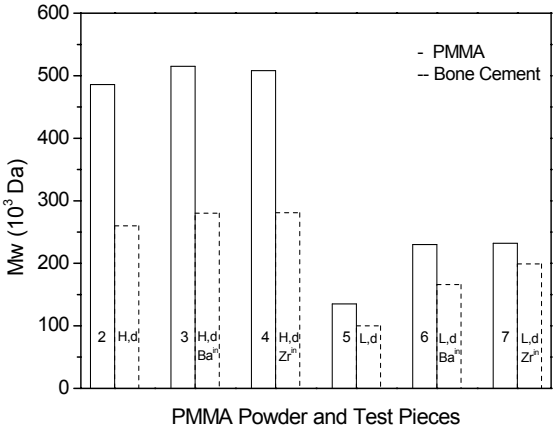

Figure 3: Mw of the PMMA powder and the respective bone cement obtained.

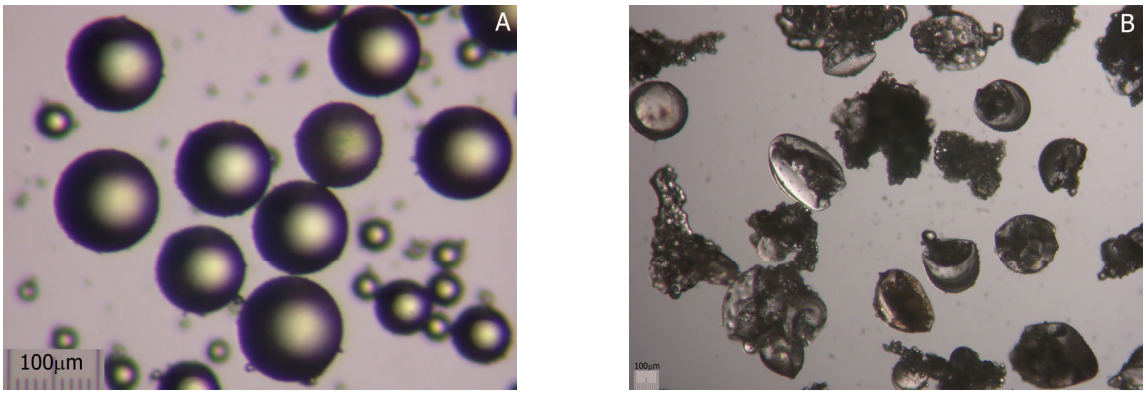

Figure 4: Optical microscopy of (A) PMMA 1 and (B) PMMA 2.

It is important to observe that very little is known about the effect of the morphology of the PMMA particles on the final performance of bone cements. For this reason, two similar formulations, namely, BCH,D and BCH,D,sph (Entries 2 and 19) with PMMA particles of different shapes were analyzed, as shown in Figure 4. The results, presented in Table 3, show very clearly that the use of regular spherical PMMA particles leads to the production of bone cements with improved mechanical properties. The values obtained for both σy and E were much higher when the PMMA particles presented a regular spherical shape. The results are even more impressive when one realizes that sample BCH,D,sph (Entry 19) presented a higher content of residual monomer, suggesting that the morphology of the PMMA particles can affect the final properties of the bone cement very strongly. Therefore, the results presented in Table 3 allow one to conclude that the dispersed PMMA beads exert a tremendous effect on the final performances of the bone cements, which encourages the development of advanced control procedures for the suspension polymerization reactors in which PMMA powders are prepared. The shape of the dispersed PMMA particles certainly affects the distribution of mechanical tensions inside the test piece, which can probably explain the pronounced improvement of the mechanical properties observed here. Therefore, additional investigations should focus on this particular variable in the near future.

Influence of the Contrast Agents

Another important objective of this work was to verify the influence of the *in situ* contrast incorporation on the final mechanical properties of the bone cement, as proposed in a previous work (Santos *et al*., 2006). Entries 1 ($BC_{H,d}$), 3 ($BC_{H,d,Ba}^{in}$), 5 ($BC_{H,d,Zr}^{in}$), 13 ($BC_{H,d,Ba}$) and 14 ($BC_{H,d,Zr}$) in Table 3 show experimental results obtained for test pieces prepared with contrasts incorporated by different techniques. The negative influence of the contrast incorporation on the final properties of the bone cement can be noted when one compares the results obtained for test pieces $BC_{H,d}$, $BC_{H,d,Ba}$ and $BC_{H,d,Zr}$. The incorporation of contrasts caused a significant reduction of σ_y, while E was not significantly affected (probably because of the different elastic properties of the PMMA and of the contrasts). When one compares the results obtained for samples $BC_{H,d,Ba}$ and $BC_{H,d,Zr}$ with the results obtained for samples $BC_{H,d,Ba}^{in}$ and $BC_{H,d,Zr}^{in}$, it can be observed that the *in situ* incorporation of fillers leads to higher σ_y values, while E remains essentially constant. It is important to emphasize that the σ_y values obtained are statistically equivalent to those of the bone cements prepared without contrast ($BC_{H,d}$). Thus, it can be concluded that the *in situ* incorporation of the contrast is very beneficial for the final performance of the mechanical properties of the bone cement, as illustrated in Figure 5.

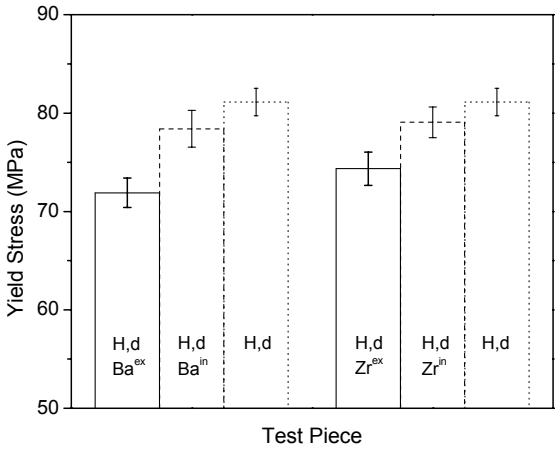

Figure 5: Influence of the *in situ* contrast incorporation on the yield stress of the bone cement.

Table 3 also shows that test pieces prepared with contrast agents present lower residual monomer

contents and higher Mw values (Entries 3, 5, 13 and 14) when compared with the materials prepared without contrasts (e.g., Entry 1) . However, it is important to consider that these differences were due to the smaller PMMA / MMA ratio, as part of the PMMA powder was replaced by contrast in these formulations (cf. Table 3). On the other hand, it is possible to compare the amount of residual monomer for the test pieces produced via the *in situ* incorporation of contrast agents (cf. Entries 3 and 5) with those produced via the *ex situ* technique (cf. Entries 13 and 14). The values of residual monomer are slightly higher for the *in situ* incorporation technique for the case of $BaSO_4$ contrast, but are the same for the case of ZrO_2 contrast. Therefore, one may conclude that the influence of *ex situ* and *in situ* incorporation of contrast agents on the residual monomer contents in the final bone cement pieces is not significant.

Influence of Additives, Curing Time and Comonomer

The influence of the addition of HA and AA in the recipe, as well as the curing time (measured from the beginning of the reaction until the performance of the compression test) on the final mechanical behavior of the bone cement were also investigated. The results are shown in Entries 1 ($BC_{H,d}$), 15 ($BC_{H,d,mod}$), 16 ($BC_{H,d,AA,mod}$), 17 ($BC_{H,d,HA}$) and 18 ($BC_{H,d,HA,15d}$) in Table 3.

The positive influence of both HA and AA on the mechanical properties of the bone cement can be clearly observed. For the case of HA addition, σ_y and E values increased 25% and 45%, respectively (cf. $BC_{H,d} \times BC_{H,d,HA}$), whereas for the case of AA addition, σ_y and E values increased 60% and 55%, respectively (cf. $BC_{H,d,mod} \times BC_{H,d,AA,mod}$). It is important to note that the bone cements with HA and AA showed higher residual monomer contents, when compared to the materials prepared without these components. In spite of this, the modified bone cements presented better mechanical properties and higher Mw. This confirms the positive influence of both HA and AA on the bone cement. One must observe the significant increase of the Mw values when either HA or AA are added to the recipe. This certainly indicates that HA interacts with the reacting MMA monomer and that the properties of the polymer matrix are fundamental for a proper understanding of the performance of bone cement materials.

In order to verify how the mechanical properties of the bone cement vary with time, one formulation ($BC_{H,d,HA,15d}$, Entry 18 in Table 3) was analyzed 15 days after the start of the bone cement preparation reaction. The results obtained for this test piece show that the final mechanical properties of the bone cement become much better after some time, probably due to the reduction of the amount of residual monomer and additional production of polymer (the polymerization reaction continues at lower rates at longer times). This clearly indicates that the proposed ASTM standards are conservative, since the bone cement properties improve significantly with time.

CONCLUSIONS

The results presented here show that the addition of HA and AA to bone cement recipes can be beneficial for improvement of the mechanical performance of the prepared material. GC and GPC analyses indicate that these components take part in the reaction and modify the properties of the polymer matrix formed. It was also observed that the PMMA morphology is a very important process variable and the results indicate that the use of spherical PMMA particles can significantly improve the properties of the final bone cement. Finally, it was shown that it is possible to add the contrast to the bone cement formulation without causing significant degradation of the final mechanical properties if *in situ* contrast incorporation is adopted during the suspension polymerization,, as suggested by SANTOS *et al*. (2006).

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